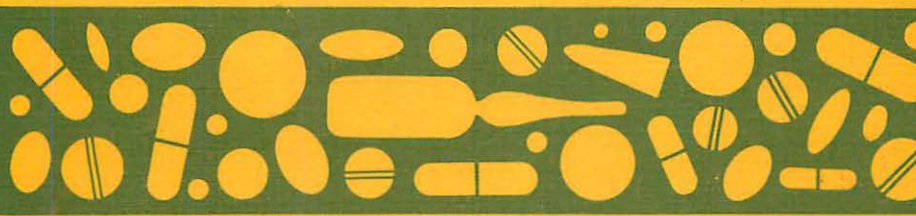
Clinical Pharmacology



D. R. LAURENCE

FOURTH EDITION

Illustrations by Peter Kneebone

CLINICAL PHARMACOLOGY

"Patients may recover in spite of drugs or because of them."

J. H. GADDUM, 1959.

"But know also, man has an inborn craving for medicine . . . the desire to take medicine is one feature which distinguishes man the animal, from his fellow creatures. It is really one of the most serious difficulties with which we have to contend."

WILLIAM OSLER, 1894.

"Morals do not forbid making experiments on one's neighbour or on one's self . . . among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory."

CLAUD BERNARD, 1865.

"I do not want two diseases—one nature-made, one doctor-made."

NAPOLEON BONAPARTE, 1820.

"The ingenuity of man has ever been fond of exerting itself to varied forms and combinations of medicines."

WILLIAM WITHERING, 1785.

"First, do no harm."

HIPPOCRATES, 460–355 B.C.

CLINICAL PHARMACOLOGY

by

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FOURTH EDITION

With some illustrations by Peter Kneebone

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PREFACE

*"For your own satisfaction and for mine, please read this preface."**

This book is particularly intended for medical students in their clinical years.† But it contains many more facts and details than a student either needs or should attempt to learn.

The general aspects of the *how* and *why* of drugs are for the student. The practical details are to help him when he begins to prescribe on his own responsibility after graduating.

Thus the student should read selectively, and I hope it will not be too difficult for him to do so.

In addition I hope that the book may be of use to some more experienced doctors in reminding them of progress or practice in fields with which, perhaps, they are no longer primarily concerned, but which have not lost interest or all importance for them.

Justification. I believe that doctors who understand something of how drugs get into the body, of how they produce their effects, of their fate and of how evidence of therapeutic effect is assessed, will choose drugs more skilfully and use them more successfully than those who do not. They will less often expose patients to the risks of useless therapy and they will also avoid more of the hazards of unwanted effects due to interaction with disease or with other drugs. They will be less likely to mistake the ill-effects of drugs for natural disease and more likely to recognise antagonism or synergism when it unexpectedly arises either from prescribed or from self-medication.

This book represents an attempt to provide pharmacological knowledge that is both interesting and useful to the physician.

Most books of moderate size confine themselves either to discussing the pharmacology of drugs without giving enough information for them to be selected and used effectively, or else they confine themselves to practical therapeutics and ignore the pharmacological background. It is too much to expect the now heavily burdened student to consult and integrate two works, one not always clearly related to clinical practice and the other often as arbitrary and as empirical as a cookery book. This book is offered as a reasonably brief solution to the problem of combining practical clinical utility with some account of pharmacology.

It might be thought that the existence of huge multi-author books on this subject, some of high quality, would make futile a smaller book such as this, for in the available space it is not possible to give a lot of detail. But I believe it is useful to have a book of a size that is easily manageable—

* St. Francis of Sales: preface to *Introduction to the Devout Life* (1609).
† It is assumed that the reader has had teaching in "basic" pharmacology.

that can be compassed by an individual coming to the subject either for the first time or to refresh his general knowledge—and that may help him to use the larger discursive sources more profitably.

How much practical technical detail to include has been difficult to decide. In general, more such detail is provided for therapeutic practices that are complex or potentially dangerous as well as urgent, where there may be no time for consultation with colleagues or search in libraries, e.g. salicylate poisoning, and less, or even none, on therapy that is generally conducted only by specialists or that can wait on such consultation, e.g. anticancer drugs; i.v. oxytocin.

Smaller type has been used here and there for some drugs of lesser therapeutic importance, and for some of the sections giving arbitrary facts that could not reasonably be left out and details of practice only of importance to someone about to use a drug.

The two type sizes do not indicate the author's opinion as to what a student need or need not know. Such a division has not proved practicable.

Use of the book. Students are, or should be, concerned to develop a rational, critical attitude to drug therapy and should therefore chiefly concern themselves with how drugs act and interact in disease and with how evidence of therapeutic effect is obtained and evaluated. They should not allow this to be impeded by attempts to memorise lists of alternative drugs and minor differences between them, or arbitrary practical details, such as dosage or solution strength, which should never be required of them in examinations; the only way to fix these in the mind is by actual prescribing.

The decision to try to include sufficient practical details to enable some drugs to be correctly used has inevitably made substantial parts of the book tedious. In addition, it has been thought necessary to mention numerous drugs of doubtful merit, and what have been aptly called "me-tooers", in order to enable a choice to be made from amongst the huge number of drugs and preparations of drugs thrust at the clinician by a vigorous pharmaceutical industry.

The sensible student will readily see which sections of the book he can, and indeed should, neglect in his general reading, and use them solely for reference when the responsibility of choice and administration becomes his.

Repetition. Readers may notice occasional repetition; this is often deliberate.

The "authority" of a textbook. If a book is to be a useful guide to treatment it must offer clear conclusions and advice. If it is to be of reasonable size alternative courses of action will often have to be omitted, even though they may be satisfactory. What is recommended should be based on sound evidence where this exists, and on an assessment of the opinions of the experienced where it does not. Exceptions to all advice will occur, and part of the clinician's skill lies in knowing when to depart

from an accepted course.* Nor can a textbook take account of all possible modifying factors, e.g. personality, intercurrent disease, metabolic differences.

The status of a textbook as a practical guide has been well expressed in a legal judgement in a case where an accusation of negligent treatment made against a doctor was supported by showing that he had not followed the orthodox treatment as stated in various textbooks. The Judge said that textbook writers were writing of a subject in general and not of a particular patient. A doctor was entitled to use his common sense, his experience, and his judgement as far as they fitted a particular case. "It would be a sorry day for the medical profession if it were to be said that no doctor ought to depart one tittle from that which he saw written in a textbook."† Statements in textbooks were no substitute for the judgement of the physician in charge of the case. "*His Lordship could not follow slavishly the views expressed in textbooks. . .*".† Indeed any sensible author would be horrified at the thought that he was credited with less than the usual human fallibility.

Guide to further reading at the end of each chapter. No attempt has been made to document every statement, but references are provided. These have been largely selected for their interest, and wise students will appreciate that the contact with original minds which such reading affords is instructive, entertaining and even exciting. They will therefore choose an occasional paper on a topic that interests or amuses them and will read it as relaxation from the study of textbooks. The titles of the references, which are chosen from a few of the more accessible English language journals, are supplied to help choice. The foolish student does not realise that the preface is often the most important part of the book, telling the prospective reader whether he will be wasting his time if he proceeds. He will therefore not see this advice, and in any case no amount of exhortation would make him appreciate what he is missing by never looking at original work and seeing how problems are tackled and knowledge obtained.

References to reviews, often short documented editorials, are also given, to enable a student to follow up an interest more easily.

A list of books and journals that cover all the field is given at the end of the book.

Direct quotation is used often in this book because, where a point has been well made by an original observer or thinker, there are excellent reasons for not interposing the mind of another.

Paging. Chapters are paged separately to facilitate revision in this quickly changing field.

* This is why control on claims for a drug by its promoters is properly exercised by government regulating authority (in Britain, the Committee on Safety of Medicines), but limitation of the doctor's freedom to prescribe what he has reason to believe best for his patient should be resisted. The solution to bad doctoring is education, not the imposition of limitations on skilled doctors.

† *Lancet* (1960) i, 593.

Reasons for using non-proprietary drug names instead of the sometimes more familiar proprietary names are given in ch. 5. The index includes an inevitably incomplete range of proprietary names.

It is assumed that the reader will possess a formulary and so the text has not been encumbered with extensive lists of preparations although it is hoped that enough preparations have been mentioned to cover much routine prescribing, and many drugs have been included solely for identification.

D. R. LAURENCE

Note on this edition

UNFORTUNATELY this edition is larger than the previous one. This is chiefly due to the greatly expanded chapter on General Pharmacology. Appreciation of the importance of pharmacokinetics has increased in recent years. It is not suggested that all students and doctors need to remember all the details. But a general comprehension of the subject will, I believe, be useful in handling drug therapy and poisoning.

The chapters dealing with non-medical drug use have also been expanded.

New introductions, the selective β-adrenoceptor blockers, cromoglycate, levodopa etc., inevitably take up additional space without allowing a corresponding amount to be deleted.

Space can be saved by deleting obsolescent drugs, e.g. mercurial diuretics, ganglion-blockers, but it is often difficult to decide when to remove an account of what has been a widely used drug.

Drugs that are used relatively infrequently or only in special circumstances are also a problem, e.g. now that general uses of sulphonamides have been largely replaced by other antimicrobials, the space devoted to them may seem excessive. It is not practicable to give space to drugs proportional to their therapeutic utility. But it still seems worthwhile to explain the rational basis for even uncommonly used drugs, where this is known, e.g. cation-exchange resins.

ACKNOWLEDGEMENTS

I owe a great debt of gratitude to the late Professor Lord Rosenheim who for almost 20 years gave me encouragement and support.

It is not possible, of course, for any individual to cover the whole field of drug therapy from his own knowledge and experience, and I am deeply grateful to all those who have with such good grace given me their time and energy to supply valuable facts and opinions, they principally include:

Dr. B. G. Adams
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Miss P. Waterworth
Dr. Lyal Watson
Prof. O. M. Wrong

Much of any merit this book may be found to have is due to the generosity of those named above in putting their knowledge and practical experience of the use of drugs at my disposal. Responsibility for any errors rests with me.

In addition, permission to quote directly from the writings of some authorities has been generously granted and I thank the authors and their publishers who have given it.

Peter Kneebone's illustrations speak for themselves.

Miss H. Smart has typed and worked on the index assiduously.

Mr. A. S. Knightley has been extremely helpful, as usual.

D. R. LAURENCE

CONTENTS

Tablet size in mg is given in brackets after the drug name.

Chapter 1

DRUG THERAPY

BEFORE treating any patient with drugs* the doctor should have made up his mind on five points:

1. Whether he should interfere with the patient at all and if so—
2. What alteration in the patient's condition he hopes to achieve.
3. That the drug he intends to use is capable of bringing this about.
4. What other effects the drug may have and whether these may be harmful.
5. Whether the likelihood of benefit, and its importance, outweighs the likelihood of damage, and its importance, i.e. to consider *benefit versus risk*, or *efficacy in relation to safety*.

Mere accumulation of factual knowledge from books does not confer an ability to use drugs wisely, although wisdom cannot be attained without such knowledge.

Whenever a drug is given a risk is taken; it is often so small that second thoughts are hardly necessary, but sometimes it is substantial. The doctor must weigh up the likelihood of gain for the patient against the likelihood of loss. There are often insufficient data for a rational decision to be reached, but a decision must still be made and this is one of the greatest difficulties of clinical practice. Its effect on the attitudes of doctors is often not appreciated by those who have never been in this situation. The patient's protection lies in the doctor's knowledge of the drug, his knowledge of the disease, and his experience of both, together with his knowledge of the patient. For instance, in typhoid fever the risk of inducing aplastic anæmia with chloramphenicol is far less than the risk of the patient dying from untreated disease. In less dangerous infections the decision is less easy, and should chloramphenicol be used without mishap in, say, bronchitis, it may leave the patient so sensitised that a second or third course may prove fatal. It is impossible to be sure of the magnitude of such a risk in any individual case.

In some diseases in which drugs will ultimately be needed they may not benefit the patient in the early stages. For example, a victim of early Parkinsonism may be but little inconvenienced by the disease, and the premature use of drugs, whilst perhaps reducing tremor or rigidity, can exact such a price in nausea, languor and constipation that the patient may prefer his untreated state. To attempt to antagonise the side-effects by other drugs is likely to be unsuccessful at worst, and unsatisfactory

* A World Health Organization Scientific Group has defined a drug as "any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient". *Wld. Hlth. Org. techn. Rep. Ser.* (1966). No. 341, p. 7.

at best. Drugs very seldom cancel each other out exactly. It is worth remembering that a feeling of languor which may be merely a slight inconvenience to a manual worker, may disable a man who lives by his intellect.

The most shameful act in therapeutics, apart from killing the patient, is to cause disease in a patient who is but little disabled or who is suffering from a self-limiting disorder. Such **iatrogenic* disease**, induced by misguided treatment, is far from rare.

If the doctor is temperamentally an extremist, he will do less harm by therapeutic nihilism than by optimistically overwhelming his patients with well-intentioned polypharmacy. The latter course is the easier to follow because it gives more immediate satisfaction to the patient, his family and indeed to the doctor himself. All are able to feel cosily that it is clear that the doctor is doing all he can, which usually means a great deal more than is wise. Habitual polypharmacy is sure to blur the outline of rational thought which should precede the use of any drug, and both doctor and patient will be the worse for this.

If in doubt whether or not to give a drug, don't.

In 1917, Sollmann felt able to write "Pharmacology comprises some broad conceptions and generalisations, and some detailed conclusions, of such great and practical importance that every student and practitioner should be absolutely familiar with them. It comprises also a large mass of minute details, which would constitute too great a tax on human memory, but which cannot safely be neglected."†

If the last sentence was true when it was written, it is many times more true now. The selection of useful drugs from the multitude, not only offered to, but thrust upon the doctor by skilful and sometimes misleading advertising, is a matter of great importance. The doctor's aim must be not merely to give the patient what will do him good, but to give him ***only*** what will do him good, or at least more good than harm.

That this provides a real difficulty in clinical practice is shown by the conclusions of two independent panels of experts‡ (in London and in Edinburgh) who were requested by a government committee§ to assess the therapeutic efficacy of proprietary preparations listed in the Monthly Index of Medical Specialities (M.I.M.S.), i.e. prescription preparations. The panels categorised 2,657 preparations thus:

A: therapeutically effective drugs	50%
B: rational combinations	8%
C: not yet classifiable	7%
D: undesirable preparations	35%

* *Iatrogenic* means "physician-caused".

† Sollmann, T. A. (1917). *Manual of Pharmacology*. Philadelphia: Saunders.

‡ Expert: "person having special skill or knowledge". *Oxford English Dictionary*. The word is sometimes used pejoratively, but this is not intended here.

§ Report of the Committee on Enquiry into the Relationship of the Pharmaceutical Industry with the National Health Service, 1965-1967, Appendix 3. London: Her Majesty's Stationery Office. Cmnd. 3410.

Category D included irrational combinations, superseded or obsolete drugs or preparations, ineffective drugs or preparations (including effective drugs in ineffective doses or for administration by ineffective routes).

The two panels agreed on classification of 84% of the total (dermatological preparations were excluded).

Those who have minds that are simple, tidy and inexperienced, may see no reason why the 35% of "undesirable preparations", though largely innocuous, should not have been at once ordered off the market, thus achieving by government regulation what professional education has failed to do. In Britain such a course is unacceptable* and it is currently thought best to eliminate only preparations that constitute a demonstrable physical hazard. However the subject is a big one, it introduces non-pharmacological social considerations, and it cannot be pursued here.

It has been recorded from a large hospital in the U.S.A. that 5% of in-patients suffered *major* toxic reactions consequent to diagnostic or therapeutic measures before or after admission, and it was concluded that iatrogenic disease could be regarded as one of the commonest conditions encountered during the survey.† This has been confirmed.

In England and Wales (population 55 million) the annual average number of notified *fatal* "therapeutic misadventures" from 1959 to 1966 was 174.‡ These figures do not include deaths due to giving the wrong drug (rare), accidents in technique, including surgery (annual average 90) or overdose, usually self-administered but not suicidal (120 in 1966). The total deaths from *all forms* of therapeutic misadventure in 1966 was 334.

Fatal adverse reactions to drugs in one year included:

anticoagulants	11	chiefly bleeding
adrenal steroids	35	chiefly adrenal failure, bowel perforation
chloramphenicol	5	blood disorders
phenylbutazone	17	blood disorders
aspirin	2	gastric erosion

Deaths were also notified as due to insulin, lignocaine, penicillin, gold, phenytoin, monoamine oxidase inhibitors, imipramine and phenothiazine tranquillisers.

These figures are almost certainly underestimates for doctors are understandably reluctant to attribute a patient's death to therapy and they attribute it to disease if it is at all reasonable to do so.

In addition to the fatalities there is the undoubtedly huge body of patients merely made uncomfortable by drugs. The medical profession is contributing significantly to disease, although it can justly be contended that this is far outweighed by the benefits that they purvey. There is still,

* This may have something to do with a natural suspicion of "experts".

† BARR, D. P. (1955). *J. Amer. med. Ass.*, **159**, 1452.

‡ Registrar-General's Statistical Review of England and Wales, 1967. Part 3. Commentary. London: H.M.S.O. Available figures are always several years old.

however, the obligation to strive to obtain the maximum good with the minimum harm.

It is not suggested that all the accidents reported were avoidable; but it is difficult to resist the conclusion that an unnecessarily large number of people suffer nowadays from iatrogenic disease and that a part of it could be avoided by the more thoughtful use of drugs.

New drugs especially should be treated with suspicion. They should not be used widely until properly designed clinical trials have been carried out, especially not in patients with relatively non-serious disease. Patients with recurrent boils have died from chloramphenicol; some with hypertension have committed suicide as a result of rauwolfia-induced depression; others with rheumatoid arthritis have died from agranulocytosis due to phenylbutazone.

Sir Anthony Carlisle, in the first half of the 19th century, said that medicine was "an art founded on conjecture and improved by murder". Although medicine has advanced so rapidly, there is still a ring of truth in that statement to anyone who follows the introduction of new drugs and observes how, after the early enthusiasm, the reports of serious toxic effects begin to appear.

Another cryptic remark of this therapeutic nihilist was "Calomel is poison and digitalis kills people". This derogatory statement is of interest because the latter is one of the few essential drugs in modern therapy. One reason it is essential is that it is potent; therefore it can kill when used ignorantly or carelessly. William Withering in 1785 laid down rules for the use of digitalis which would serve today. Neglect of these rules resulted in needless suffering for patients with heart failure for more than a century until the therapeutic criteria were rediscovered. Any drug that is really worth using can do harm, and *it is an absolute obligation on the doctor to use only drugs about which he has troubled to inform himself.* The following report of a coroner's inquest shows the reality of this:

"... an inquest has been held on a woman who died from internal hæmorrhage due to dicoumarol which had been given for thrombosis in the leg veins. The doctor is reported to have said that he gave the dose recommended in the manufacturer's literature; he confessed his ignorance of the dangerous properties of dicoumarol and complained that these were not mentioned in the instructions for use."*

It may be hoped that such irresponsibility is rarer than the ignorance which contributes to the misuse of drugs, using them where none are needed, inappropriate choice where they are needed, and not only overdosage but inadequate dosage when the doctor is uninformed and does not have clear aims. In addition there is the small but constant death rate from all-too-human carelessness of the kinds shown in the table below.

Effective therapy depends not only on the *correct choice* of drugs but also on their *correct use*. This latter is sometimes forgotten and a drug

* Editorial (1949). *Lancet*, **1**, 698.

EXAMPLES OF FATAL THERAPEUTIC MISADVENTURES DUE TO MISTAKES IN DRUG ADMINISTRATION IN ENGLAND AND WALES, 1954–67*

Drug	*Nature of Misadventure*
Medically administered	
barbitone	given in mistake for sulphasomidine
mersalyl	injected instead of triple antigen
potassium chlorate	given in mistake for sodium chloride
sodium carbonate	given by enema instead of barium sulphate (2 cases)
syrup of chloral	nurse mistook the bottle
chloral hydrate	overdose
adrenaline	injected instead of local anæsthetic (2 cases)
cation-exchange resin	erroneous i.v. injection (hard to believe)
surgical spirit	given i.v. in error
tretamine (anticancer)	given in mistake for Tetracyn (tetracycline)
amethocaine	in error for procaine
mercury	instead of a radio-opaque contrast medium in the subarachnoid space
suxamethonium	i.m. injection of ampicillin mixed with suxamethonium instead of water
Self-administered	
adrenaline & atropine	used as nasal-drops, instead of spray as prescribed
oxalate	taken in belief of medicinal property
camphor & turpentine	in mistake for "medicine"

is condemned as useless when it has been used in a way which absolutely precluded a successful result.

Therapeutic Situation

"It is evident that patients are not treated in a vacuum and that they respond to a variety of subtle forces around them in addition to the specific therapeutic agent under investigation"†.

When a patient is given a drug his responses are the resultant of numerous factors:

1. The pharmacodynamic effect of the drug and interactions with any other drugs the patient may be taking.
2. The physiological state of the end-organ, whether, for instance, it is over- or underactive.
3. The act of medication, including the route of administration and the presence or absence of the doctor.

* Based on tables in Registrar-General's Statistical Review of England and Wales, Part 3. Commentary. London: H.M.S.O.

† SHERMAN, L. J. (1959). *Amer. J. Psychiat.*, **116**, 208.

4. The doctor's mood, personality, attitudes and beliefs.
5. The patient's ditto.
6. What the doctor has told the patient.
7. The patient's past experience of doctors.
8. The patient's estimate of what he has received and of what ought to happen as a result.
9. The social environment, e.g. whether alone, or in company.

Obviously some of the above overlap—the patient's beliefs, for example, being determined by what the doctor tells him as well as by information from other sources.

The relative importance of these factors varies according to the circumstances—an unconscious patient with meningococcal meningitis may be assumed to respond to penicillin only in so far as it affects the invading bacteria, and regardless of whether he and the doctor dislike each other. But a patient sleepless with anxiety because he cannot cope with his family responsibilities may be affected as much by the interaction of his own personality with that of the doctor as by the amylobarbitone prescribed by the latter, and the same applies to appetite suppressants in food addicts.

The physician may consciously use all of the factors listed above in his therapeutic practice. But it is still not enough that a patient gets better, it is essential to know *why* he does so. This is because potent drugs should only be given if their pharmacodynamic effects are needed. If other factors are the effective agents, then any drug given will be a placebo and placebos should be harmless. The double-blind technique in therapeutic trials used with placebo (or dummy) medication represents an attempt to discriminate pharmacodynamic effects from the other aspects of the therapeutic situation.

Placebos* (*1–12*, *18*, *19*, *24*)

Placebos are used for two purposes:

1. *As a control* in scientific evaluation of drugs (see under *therapeutic trials*).

2. *To benefit or please a patient* not by any pharmacological actions, but by psychological means. A placebo is a vehicle for cure by suggestion, and surprisingly often successful, if only temporarily. All treatments carry placebo effect, physiotherapy, psychotherapy, surgery, but it is most easily investigated with drugs, for the active and the inert can often be made to appear identical so that comparisons can be made.

The deliberate use of drugs as placebos is a confession of failure by the doctor. Failures however are sometimes inevitable and an absolute condemnation of the use of placebos on all occasions would be unrealistic for, "to decline to humour an elderly 'chronic' brought up on the bottle is hardly within the bounds of possibility" (*1*).

* Latin, placebo = "I will please".

Placebos are usually given to patients with mild psychological disorders who attribute their symptoms to physical disease. There is no doubt that alleviation can sometimes be achieved but it is often only temporary, and may make any subsequent attempt to face reality more difficult. The patient, not unreasonably, interprets the advice to take medicine as meaning that the doctor admits a physical basis for the symptoms; so that when, later on, an attempt is made to attribute a psychological cause this will not be accepted. Placebos may also be used in patients with chronic incurable diseases when they need a prop to sustain their courage.

Placebos should only be prescribed after a serious attempt to avoid using them has failed and then only for a brief time; the placebo should consist of a substance both innocuous and cheap, unless the patient pays for it himself, when high cost greatly potentiates its effect. Having admitted the legitimacy of their use, however rarely, it is necessary to advise a choice of substances.

"Those who have qualms of conscience about prescribing pharmacologically useless medicines tend to use semi-placebos, such as vitamins, in the vague hope that these may do some good. This is wrong, for thereby the prescriber deceives himself as well as the patient. If deception there must be, says Leslie (*3*), let it be wholehearted, unflinching, and efficient. A placebo medicine should be red, yellow or brown; for blue and green are colours popularly associated with poisons or with external applications. The taste should be bitter but not unpleasant. Capsules should be coloured, and tablets either very small (on the ***multum in parvo*** principle) or impressively large; they should not look like everyday tablets such as aspirin" (*1*). There is some evidence that anxiety symptoms respond particularly to green and depressive symptoms to yellow tablets (*18*).

Harmless placebos are Compound Tincture of Cardamom, B.P. (also contains cochineal, cinnamon, caraway and glycerin), dose 1 to 2 ml. (half teaspoonful) in 15 ml. water (tablespoonful) and Acid (or Alkaline) Gentian Mixture, B.P.C., dose 15 to 30 ml.

The following quotation illustrates some of these points:

". . . a 28-year-old female had had recurrent nausea for several months. . . . A kymographic recording from her stomach revealed the characteristic absence of contractile activity during nausea. After a suitable control period she was given 10 cc. syrup of ipecacuanha directly into the stomach through a Levine tube. Repeatedly on previous occasions this amount of ipecacuanha when swallowed had induced nausea and vomiting. On this occasion, however, not tasting and not knowing what she had been given, she was told that the agent would abolish her nausea; within 30 minutes nausea was gone and small waves of contraction were recorded from the stomach. Sixty minutes later when nausea had recurred with associated gastric hypomotility a second dose of ipecacuanha was introduced into the Levine tube, this time with the reassurance that the nausea would be effectively abolished. Nausea disappeared again in 15 minutes and gastric contractions were resumed. No further nausea was experienced that day" (*2*).

This dramatic demonstration shows that psychological effects may actually reverse pharmacological effects. "It is likely that this mechanism is operative in part in any enthusiastically pursued therapeutic régime. . . . It has even been shown experimentally that the threshold for pain perception may be greatly raised by suggestion" (*2*).

It is of great importance that everyone who administers drugs should be aware that his attitude to the treatment may greatly influence the result. Undue scepticism may prevent a drug from achieving its effect and enthusiasm or confidence may potentiate the pharmacological actions of drugs.

Some individuals are prone to report changes of physical and mental state after taking pharmacologically inert substances, and these are called **placebo-reactors.** Such suggestible people are likely to respond favourably to *any* treatment. They have deceived doctors into making false therapeutic claims and have provided the basis for many therapeutic reputations. Negative reactors, who develop adverse effects when given a placebo, exist, but, fortunately, are fewer.

Some 35% of the physically ill and 40% or more of the mentally ill respond to placebos. Placebo reaction is an inconstant attribute—a person may respond at one time in one situation and not at another time under different conditions. However, there is some consistency in the type of person who specially tends to react to placebos. In one study on medical students (*6*), psychological tests revealed that those who reacted to a placebo tended to be extraverted, sociable, less dominant, less self-confident, more appreciative of their teaching, more aware of their autonomic functions and more neurotic than their colleagues who did not react to a placebo under the particular conditions of the experiment.

Tonics are placebos. They may be defined as substances with which it is hoped to strengthen those so weakened by disease, misery, over-indulgence in play or work, or by physical or mental inadequacy, that they cannot face the stresses of life. The essential feature of this weakness is the absence of any definite recognisable defect for which there is a known remedy. There can be very few doctors who believe that there is any pharmacological basis for a tonic effect. Benefits are attributable to placebo-effects and it is to be hoped that explanation and reassurance will eventually take the place of "bottles of medicine". Many people expect a tonic from their doctor following any illness and they are sceptical and shocked if told that the benefits that they feel are not the result of pharmacological action.

If either the doctor or the patient believes in tonics to such a degree that one has to be prescribed, it may be chosen from those in the B.N.F., e.g. Gentian Mixture with Rhubarb! There are innumerable proprietary tonics, some of which contain highly active drugs including CNS stimulants; these should be avoided. The indiscriminate use of vitamins as tonics is widely advocated by pharmaceutical firms and practised by the gullible. Vitamins A and D can cause serious toxic effects.

There is every reason for the doctor to cultivate techniques for the psychological potentiation of drugs, for his aim is to help the patient, but it is essential that he should be aware of what he is doing and not deceive himself about the physical power of his remedies. Some doctors can be accurately described as having placebo personalities.

Hazards of Life on Drugs

The proportion of the population taking drugs continuously for large portions of their lives increases as tolerable suppressive and prophylactic remedies for chronic or recurrent conditions are developed, hypertension, diabetes, mental diseases, epilepsies, gout, collagen diseases, thrombosis, allergies and various infections.

In some cases the treatment introduces notable hazards into patients' lives and the cure can be worse than the disease if it is not skilfully managed. The dangers may be classified:

1. *dangers of the drug*—these are not markedly increased if therapy lasts years rather than months, except perhaps for addiction, renal damage (analgesic mixtures) and carcinogenesis.

2. *dangers of stopping the drug suddenly*—dramatic illness can follow with anticonvulsants, adrenal steroids, antiparkinsonian drugs.

3. *dangers of intercurrent illness*—these are particularly notable with hypoglycæmics, anticoagulants, adrenal steroids and immunosuppressives.

4. *dangers of interactions with other drugs or diet*—monoamine oxidase inhibitor antidepressants (pethidine, sympathomimetics, cheese etc.): hypotensives (sympathomimetics, including appetite suppressants, tricyclic antidepressants): digitalis (diuretics): hypnotics and tranquillisers (alcohol). See also *drug interactions*.

The patient's protection lies in his physician who should:

1. judge the risks of permanent drug therapy against the likely benefit, and act accordingly.

2. understand the pharmacology of the drug to be used and of other drugs that may be taken if the patient has another illness or accident.

3. ensure that the patient understands what is required of him so that he will not, through ignorance, carelessness or mishap increase the inevitable minimum of risk.

Whether patients take drugs prescribed (*14–16, 20–22, 25*)

This subject has received little attention, and merely asking patients whether they have taken drugs as directed is not likely to provide reliable evidence. Studies in which, as well as asking patients, the tablets returned to the clinic are counted and urine is tested for a marker substance, invisible to the patient, have disclosed that, according to circumstances, 20–60% of patients do not follow the doctor's instructions. Patient "compliance" is evidently a potentially important factor in drug therapy and it has been found capable of affecting the results of a formal therapeutic trial.*

* JOYCE, C. R. B. (1962). *J. chron. Dis.*, **15**, 1025.

It is unlikely that any patient will reliably take more than three drugs without supervision. Even where supervision might be supposed to be completely effective, i.e. in hospital, error rates in drug administration as high as 15 to 25% have been found. These rates can be reduced by simplifying and unifying hospital and ward practice.

Reasons for taking drug history from patients:

1. administration of drugs can cause disease.
2. withdrawal of drugs can cause disease.
3. drugs interact.

As many as 5% of hospital admissions have been found to be due to adverse drug reactions. Drugs are common causes of main symptoms such as rash or jaundice.

Prescribing Costs and Habits (*17, 23, 24*)

Pharmaceutical Services (non-hospital) have comprised about 10% of the National Health Service Expenditure since 1951.

The National Health Service offers opportunities to get information on prescribing habits and costs not previously available.* For instance prescription frequency and cost per prescription is lower for older than for younger doctors. There is no reason to think that the patients of older doctors are worse off as a result. Perhaps age confers a relative immunity both from that occupational disease of the profession, *furor therapeuticus*, and from the belief that what is new and expensive is therefore best.

In 1969 there were 245 million prescriptions in the National Health Service and they cost £110 million. Here are some examples; they give food for thought:

Group	*Millions of prescriptions*	*Cost £ million*
Antacids and antispasmodics	9·2	2·7
Preparations acting on heart	4·5	1·4
Antihypertensives	4·3	6·8
Expectorants & cough suppressants	19·3	3·3
Tranquillisers	15·4	8·5
Antidepressants	5·4	4·4
Hypnotics (barbiturate)	13·1	1·7
Hypnotics (non-barbiturate)	5·9	2·1
Penicillins	14·9	8·1
Tetracyclines	12·9	5·0
Other antibiotics	2·9	2·5
Sulphonamides	2·2	0·8
Adrenal steroids (systemic)	2·1	1·7
Insulin & oral hypoglycaemics	1·5	2·3
Vitamins & vitamin preparations	4·7	1·3

* *Recent N.H.S. Prescribing Trends.* (1964). London: H.M.S.O.

Further food for thought is provided by the following: a survey of over 50,000 patients of 20 general practitioners (*24*) revealed that:

2·8% of patients had been receiving a daily dose of a psychotropic drug for at least one year.
The average time since starting this was 5·2 years.
80% of these long-term consumers were aged over 40 years.
75% of them were women.
The numbers of these patients had increased by 80% in 10 years.
Of 31 patients taking a psychotropic drug in 1957, 24 were still doing so in 1967.

Any suspicion aroused by the above facts that prescriptions are desired by the patients and provided by the doctors for reasons unrelated to the pharmacodynamic effects of the drugs is confirmed by an analysis of patients who received the same preparation for above 6 months, and often for years—"long-repeat patients" (*24*). These people, it was concluded, are unhappy, and their unhappiness manifests itself as unpleasant bodily sensations. The doctor can find no localisable disease, but he goes on trying and makes multiple diagnoses, often psychiatric. However since no satisfactory diagnosis is established, no rational therapy can be provided. The patient continues to complain and the doctor continues to try unsuccessfully. Eventually doctor and patient take refuge uneasily in "long-repeat prescriptions". Further consideration of these patients is beyond the scope of this book. Of course, a proportion of patients taking the same drug for years are doing so for the best reasons, i.e. firm diagnosis for which rational therapy is available, e.g. epilepsy, diabetes, hypertension.

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Chapter 2

CLINICAL PHARMACOLOGY

IT is only over the past sixty years or so in Britain and eighty years on the European mainland that the manifest need to make a special study of the biological effects of the rapidly increasing number of drugs made by organic chemists has led substantial numbers of research workers to devote themselves to pharmacology. So important has this work become that departments of pharmacology have ceased to be subdivisions of physiology, and pharmacology has become an independent discipline with its own attitudes and techniques.

This has been followed by what has aptly been called the "drug explosion" of the past thirty years (*1*). This eruption into therapeutics of thousands of new drugs has led to the appearance of workers specialising in *scientific study of drugs in man*, or *clinical pharmacology*.

The clinical pharmacologist's work is to provide facts that can be used as a basis for improving the treatment of patients, and therapeutic success with drugs is becoming more and more dependent on the user having a knowledge of how they work for both good and ill.

Clinical pharmacology comprises three parts:

1. **Pharmacology:**
   (a) *pharmacodynamics:* investigation of *how* drugs, alone and in combination, affect the body (young, old, well, sick);
   (b) *pharmacokinetics:* absorption, distribution, metabolism, excretion or how the body, well or sick, affects drugs.
2. **Controlled therapeutic trials:** *whether* a drug is useful in the treatment of disease.
3. **Therapeutic auditing:** "operational research on the use of drugs, measurement of the incidence of adverse reactions and assessment of the value of drug therapy"* in the community, e.g. a drug may be found in a controlled trial to abate anxiety, but it does not follow that the drug is the right long-term treatment for patients.

Work in these three categories has long been done well by clinical scientists and physicians, but has largely resulted from the chance availability of a drug having particular interest for them; it has not been systematic. The magnitude of the need for clinical pharmacology, as shown by the disagreements on when and how to use many drugs (tranquillisers; adrenal steroids) and their safety in relation to their benefits (drugs in pregnancy; anti-depressants) now demands the full-time attention of clinical workers whether or not they care to call themselves

* WADE, O. L. (1970). Int. Symp. Clin. Pharmacol. *Arch. Int. Pharmacodyn. Ther.* Brussels. Belgium.

clinical pharmacologists. All that is needed in addition to training in medicine and pharmacology is "enthusiasm, stemming from the knowledge that through the study of drugs, medicine can be changed even more in the next fifty years than it has been in the past fifty" (*2*).

In 1934 the advent of clinical pharmacology was foreshadowed by Sir Thomas Lewis (*8*), one of the founders of modern clinical science, when he wrote of the early investigations of quinidine "these problems were attacked simultaneously, and almost exclusively by clinicians, many of whom, while studying the therapeutic effects, became at the same time their own pharmacologists. Thus from the first the work was co-ordinated and the various problems were quickly solved."

Clinical scientists of all kinds do not differ fundamentally from other biologists, they are set apart only to the extent that there are special difficulties and limitations, ethical and practical, in seeking knowledge from man. Many clinical problems can best be tackled by using animals to fill in the inevitable gaps resulting from the requirements of clinical practice. "Clinical science has the long established right to wander unimpeded into any branch of medical science in search of information directly relevant to the problems of human disease. These excursions into animal physiology, pharmacology, and into all branches of general pathology, are not only legitimate, they are also quite necessary", for "the worker in the allied science is rarely so aware of the precise need of clinical science as is the worker in this field".

"It is essential that those who in studying human patients perceive opportunities for putting questions to the test of animal experimentation should themselves engage in such work; that correlation should not be left to the chance meeting and union of clinical and laboratory studies." Again, writing on his classic investigations into atrial fibrillation, Lewis made the point that the clinical scientist, trying to elucidate a human problem, should not hesitate to pass from one field to another—"the observations began with man; animal experimentation was called in aid; it led to further investigations in man . . . " (*8*).

Pharmacology is the same science whether it is animal or man that is being investigated. The need for it grows rapidly as not only scientists but now the whole community can see its promise of release from distress and death over yet wider fields. The concomitant dangers of drugs (fetal deformities, general toxicity, addiction) only add to the need for the effective and ethical application of science to drug invention, evaluation and use.

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Chapter 3

DEVELOPMENT OF NEW DRUGS*

DOCTORS should have some idea of how the new drugs they are offered are devised or discovered. Drug development is largely an exercise in prediction from animals to man.

Most new drugs are developed in commercial rather than in academic laboratories. These two kinds of laboratory are complementary, having important, though different, approaches, the "organised opportunism" of the industrial and the "knowledge for its own sake" of the academic laboratory. The academic workers are often fired with interest to use the largely empiricalx discoveries of the industrialists as tools to explore fundamental mechanisms. The rational development of new drugs by industry is easier where the fundamental nature of normal and diseased processes, more widely, though not exclusively, studied in academic laboratories, is understood; for example the development of antihistamines depended on knowledge that histamine was released in the body and was a cause of urticaria and hay fever; the application of allopurinol to gout was a deliberate exercise based on knowledge of the synthesis of uric acid in the body. A cure for human cancer is more likely to be found if details of the metabolism of malignant and normal cells are known, than it is by empirically testing on animals tens of thousands of chemicals selected at random or because they are related to existing, inefficient drugs.

Industrial drug development laboratories

"The most frequent purpose of research in the drug industry can be stated simply; it is to discover profitable drugs. For a drug to be profitable, it should be both useful and safe, properties that are determined eventually by the clinician. The task of the pharmacologist is to predict these properties from animal experiments, within the limitations imposed by availability of facilities and staff. This must be done in such a way that the possibility of missing a useful drug is minimised; in other words, the 'screening' programme must be efficient" (*2*).

The great difficulties of the laboratory pharmacologist are to design his animal experiments to yield the maximum information from a relatively few animals and to be relevant to human physiology and disease. It is, for example, particularly difficult to design animal experiments to test drugs for their possible efficacy in human mental disorders, but relatively

* I am specially indebted to the writings of J. R. Vane (2) and G. E. Paget and J. M. Barnes (3) in this chapter.

† Empirical: "based on observation and experiment, not on theory". *Oxford English Dictionary.*

easy to test them for anticoagulant effects because animal and human blood clots by similar mechanisms and because measurement of clotting is easy.

New drugs may be sought by two main approaches:

1. **Rational approach.** Chemicals are made in the light of detailed knowledge of the biological process with which it is wished to interfere, whether this be bacterial or cancer growth or brain metabolism. It commonly takes the form of making slight chemical variants of natural metabolites and presenting these to the cell it is wished to affect "in the hope that the forgeries will upset its utilisation of the true metabolite" (*2*). When, in the far off future, all drugs are developed rationally, prediction of both efficacy and toxicity will be reliable.

Modifications of natural products, hormones and active principles of plants as well as of existing synthetic substances found accidentally, also provide a rational approach. Mere imitation of successful drugs invented by commercial rivals is a prolific source of industrial "me-tooers". Although some of these are undoubtedly improvements, their chief contribution to therapeutics is to confuse and complicate it. Before blaming the drug industry for this it is worth reflecting that if the drugs were not prescribed they would disappear.

2. **Random approach.** This is not really irrational or unscientific, it simply recognises that the "rational" approach to drug discovery, based on knowledge of chemical structure and normal and abnormal biochemistry, is in its infancy. It is based on the principle that the more tests that are made the greater the chance of finding useful activity.

New compounds, made for whatever reason, are put through a battery of tests selected to discover the maximum number of pharmacological effects at the minimum cost.

In big laboratories the rational and random approaches are used together, for they are not mutually exclusive. The chemist and pharmacologist should together decide what compounds ought to be made and they should reach a compromise based on the obvious fact that the more that are made by the chemist the less thoroughly can each be tested by the pharmacologist.

Pharmacological testing (pharmacodynamics and pharmacokinetics)

Naturally, if particular actions are expected of a compound it will be immediately submitted to detailed investigation by appropriate special techniques.

For compounds of which no special actions are expected an empirical screening programme designed to pick out those that are potentially useful and to reject inactive or toxic compounds as efficiently as possible may begin with an "observational test". In this several doses of the compound are given to groups of mice, and trained observers watch their behaviour,

handle them and measure their temperatures, heart and respiratory rates, comparing them with control groups. All changes or lack of changes are recorded on special forms and provide a "profile" of activity

This profile is examined and is compared with the profiles of standard drugs which, with saline control injections, are also fed into the observational test system from time to time to check it for reliability and sensitivity. Of course, observers must always be kept ignorant of what the animals have received.

It is claimed that this kind of test, which is now becoming highly refined, can detect the following types of drug: sedative, hypnotic, tranquilliser, psychomotor stimulant, muscle relaxant, analgesic, convulsant, neuromuscular-blocking, atropine-like, ganglion-blocking, sympathomimetic, antipyretic, vasodilator, acetylcholine-like (*2*).

It is known that some compounds that produce no changes in this observational test, will show effects if tested on animals trained to perform tasks, e.g. to operate a lever to get food; but such tests are expensive in time and so cannot be used as part of the primary screening test.

Any such screening test is a compromise based on the imagined risk of missing useful drugs and the need for simplicity and speed. No one knows whether more valuable drugs have been missed than have been found.

Any compound thought to be of interest in the primary screen is then subjected to more detailed pharmacological and sometimes biochemical study devised in the light of the initial results. This investigation may be done on whole animals with recording of various physiological functions and on isolated tissues ***in vitro***. Several species of animal will be used, generally chosen from mice, rats, cats and dogs, and sometimes guinea pigs and rabbits.

As well as testing the effects of graded single doses, chronic pharmacological studies with regular dosage for days or weeks are sometimes needed, for there are drugs that, as well as acutely altering some bodily functions, also change others more slowly (e.g. some tranquillisers and antihypertensives; oral contraceptives), and many drugs are now given to man for years.

Pharmacokinetic studies should be undertaken in animals; and when correlated with preliminary studies in man they allow selection of the animal species metabolically most akin to man as well as giving explanation of some toxic effects and prediction of dosage schedules.

These studies are integrated with those of the toxicologist to build up a picture of the unwanted as well as of the wanted drug effects. Some information on toxicity will generally have been got during the initial pharmacological testing, and this is extended by the toxicologist's special investigations.

Toxicity testing

The task of the toxicologist is to find out how a compound acts as a poison to animals and to give an opinion on the significance of his data in

relation to risks likely to be run by human beings receiving the drug (*3*). This will remain a nearly impossible task until biochemical explanations of all effects can be got in all cases. The toxicologist is in an unenviable position. When a useful drug is safely introduced he is considered to have done no more than his duty. When an accident occurs he is invited to explain how this failure of prediction came about. When he predicts that a chemical is unsafe for man, his prediction is never tested.

Acute toxicity testing aims first at establishing what is unsuitably called the therapeutic index or ratio (*3*). This concept was devised by Ehrlich as $\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}}$ to give some indication of the safety of antimicrobial drugs. In clinical practice the index is never calculated, for the data are not available in a suitable form, especially for drugs used over long periods. However, the concept embodies a sensible way of thinking about drugs, i.e. *safety in relation to efficacy.*

In a drug development laboratory practical use can be made of a modification of this concept provided it is recognised that, as with all animal data, it cannot be arbitrarily transferred to man. The therapeutic index for animals is nowadays calculated as the ratio LD_{50}/ED_{50}, i.e. the dose that is lethal to 50% of animals (LD_{50}) divided by the dose that is effective in the desired way in 50% of animals (ED_{50}).

But it is more important to discover *how* the compound acts as a poison and this may need histological and biochemical studies with repeated, or chronic, administration.

Subacute and chronic toxicity testing involves giving the compound daily for between one week and the lifetime of the animals, generally rats and dogs. Except for testing for carcinogenesis, little is generally gained by exceeding three months' regular administration at several doses. Duration of the tests and their exact nature will differ widely according to whether a drug may be given once or a few times (general anæsthetic) or continuously for years (anticonvulsant).

Generally a drug is given daily* and the appearance, activity, food intake, growth and reproductive ability in groups of animals on different doses are observed. Biochemical studies (urine, blood, etc.) are often appropriate and histopathological examination of most tissues, but especially blood, bone marrow, liver and kidneys, are done in animals that die as well as in sample animals killed at intervals during the test.

Some adverse effects of drugs on cell division that are liable only to occur or to be recognised long after administration has ceased present particular problems for the toxicologist. This is because both recognition in man and prediction from animals is peculiarly difficult. They include:

1. Carcinogenicity
2. Mutagenicity
3. Teratogenicity
4. Reduction of fertility

There is fairly close association between these effects, e.g. some anti-

* In some laboratories this means 5 days a week!

cancer drugs have all of them. This has not prevented their use in serious disease, but their increasing use as immunosuppressives in diseases with long life expectancy during which the patient may reproduce gives cause for concern. Effects such as these may occur with any type of drug and the use of animal predictive tests is now a routine for teratogenesis and fertility and likely to become so for carcinogenicity and mutagenicity. Unfortunately the validity of the tests in animals remains uncertain.

The detection in man of dramatic effects under the above heads presents relatively little difficulty; but the detection of smaller effects presents almost insuperable problems of population monitoring. In addition, when an effect has been detected there is the problem of ascribing it to its true cause, e.g. whether the association of vaginal adenocarcinoma in girls is or is not causally related to stilboestrol medication of their mothers in pregnancy.* A special feature of carcinogenicity, as shown in this example, (and also of mutagenicity) is that an effect may only be recognised years after the administration of the drug. Not only does this add to the difficulties of causal attribution, but it means that many people have received a toxic dose and, though remaining in good health, may have to be warned that they are at risk of developing drug-induced cancer.

Tests for carcinogenicity ordinarily last for nearly the life span of the animal in the laboratory (e.g. 2 years for rats; 7 years for dogs) and control groups must be kept because spontaneous tumours occur.

Tests for mutagenicity and fertility involve breeding from animals exposed to the drug.

Tests for teratogenicity, or fetal malformation, were not part of the routine of drug development until the thalidomide disaster. The spate of research in animals that followed this event has shown the ease with which fetal abnormalities can be produced with many familiar drugs. When they only occur at high doses it is not easy to decide whether they are due to indirect or non-specific teratogenic effect, e.g. respiratory depression may cause anoxia and this can induce fetal malformations.

The problem of prediction from animal experiments of what new substances will cause fetal damage in man, when there is not even a reliable list of existing drugs that have the effect in man to provide a guide to devising animal tests, will be neither easily nor soon solved. Two illustrations must suffice—it has been found that salicylates are teratogenic in rats and that this effect is enhanced if the pregnant animals are immobilised.† There is no reason to believe salicylates to be significantly teratogenic in man at present. Some adrenal steroids are highly teratogenic in rabbits, but do not appear to be so in man.

It is clear that many common unwanted effects that limit the use of a drug in man cannot be predicted from animals, e.g. malaise, and many cardiovascular and central nervous system symptoms. Nor, at present, can allergic reactions, e.g. some blood disorders and urticaria.

* Editorial (1971). Stilbœstrol and cancer. *Brit. med. J.*, **2**, 593.
† GOLDMAN, A. S., *et al.* (1963). *J. Pharmacol.*, **142**, 351.

The numbers of animals used in toxicity tests cannot approach the numbers of patients that will be exposed to a useful drug for a common disease, and so it is not to be expected that more than the commoner toxic effects will be predicted by empirical tests. Also, in order to get consistent results in these animals, populations with reasonably uniform genetic make up are used and this is just the opposite of what pertains in man.

Species differences are the source of these difficult problems of interpretation. Perhaps the most famous species difference is the lethal hæmorrhagic enteritis following parenteral penicillin in guinea pigs and its negligible toxicity to other species, including man. Another example that almost makes one despair is the hyperplasia of the gums in man due to phenytoin. This effect was not predicted when the drug was introduced. Attempts to produce it since have failed in the common laboratory animals, and have succeeded only in the ferret.

Fortunately such differences of the effect of a drug on the body (pharmacodynamics) are less common than are differences in the effect of the body on a drug (pharmacokinetics) (*9*), but gross differences in rate or path of metabolism may make nonsense of chronic toxicity studies undertaken to predict human toxicity.

Ethics of animal experiments (*16*)

It would be hypocritical for a society that tolerates first the mutilation and later, after short confined lives, the killing of animals for food—let alone chasing them about the fields to their death or driving them towards lines of gunmen for recreation—to shrink from employing them for maintaining health and life in other ways. In order to begin to decide whether a chemical is a drug or merely a chemical, either animal experiments must be done, or substances of totally unknown biological effect must be given to man. Failing either of these, drug therapy must cease to advance. I prefer, though I regret, the first course.

As knowledge of basic mechanisms advances, *in vitro* biochemical preparations may one day allow prediction of what effect a drug will have in intact man.

Conclusion

A dominant feature of the problem of finding new drugs to cure disease is that of predicting from experiments with chemicals on animals what effect these chemicals will have in man, often in situations that cannot be mimicked in the animal laboratory.

As drugs are developed and promoted for long-term use in more and relatively trivial conditions, e.g. minor anxiety or slight hypertension, and affluent societies become less and less willing to tolerate small physical or mental discomforts, demanding relief without even minor inconvenience, drug therapy will increase and the problem of demonstrating not only the efficacy, but the safety of drugs, will grow. Only profound knowledge

of biochemical mechanisms will eliminate risk in the introduction of new drugs, and this is a long way off. In the meantime failures of prediction will continue to occur. Another disaster as horrid as thalidomide may happen although, with growth of adequate systems for reporting possible adverse reactions, it should be on a much smaller scale.

Limited resources of scientific manpower and money will not be used to the best advantage if the public horror over thalidomide is allowed to express itself in governmental regulations requiring a plethora of expensive tests, and toxicity testing is *very* expensive, of dubious meaning for anything other than the animal concerned, for this would prevent industrial laboratories from investigating fundamental mechanisms of drug action, in the knowledge of which alone lies health with safety.

First Clinical Trial of Potential Drugs

The clinician has to satisfy himself that the animal laboratory studies are adequate in kind, quality and extent to justify the risk of administering to man a chemical that has hitherto been tried on animals only. He should not allow himself to be convinced too easily. He should probably only consent to try the chemical on man if there is clear evidence that existing drugs for the purpose are less than perfect and that there is a place for a new one. He should require evidence that the potential drug has been shown in experimental animals to approach perfection more closely in clearly defined respects and that demonstration of low toxicity has been meticulous.* Failing this, trial on man must be a greater gamble than it ought to be.

However, if these criteria are rigidly insisted on then no doubt useful drugs will be missed. This point has been put cogently (*6*): "it is possible to waste too much time in animal studies before testing a drug in man"; though satisfactory both qualitatively and quantitatively in animals, it may be useless in man solely because its duration of action is too short or too long, so that "the practice of studying the physiologic disposition of a drug in man only after it is clearly the drug of choice in animals not only may prove shortsighted and time consuming, but also may result in relegating the best drug for man to the shelf for ever more" (*6*). Despite the undoubted force of this argument, clinical workers may require additional persuasion to try a compound that is not "the drug of choice in animals".

The path of the industrial drug developer is a stony, even if sometimes a highly profitable, one. He risks huge sums of money but the clinician, sympathetic though he should be, must ruthlessly resist any development that he believes will add to the risks of clinical trial. Whilst the clinician must not demand too much, equally he must not allow commercial pressures to affect his judgement of what is best for the sick.

This account of drug development, largely stressing the difficulties and

* Spinks, A. (1962). In *Clinical Trials*. London: Pharmaceutical Press.

the imponderables may be put into perspective by the following figures on the safety of drugs in relation to car driving and to smoking, in Britain in 1967 (*14*).

Deaths due to:

therapeutic use of drugs	43
motor vehicle accidents	7,084
malignant pulmonary neoplasms	28,252

Rational clinical introduction of a potential new drug requires study in *four* successive stages:

1. *Pharmacological study, on normals or patients*, often in the clinical laboratory, to confirm or deny the animal pharmacology.
2. *Wider use on patients* to establish potential therapeutic utility, dosage schedules and some notion of toxicity.
3. *Formal assessment of its therapeutic merits*, compared with those of other remedies, when these exist.
4. *Monitoring for adverse reactions* after general release.

As the number of potential drugs produced increases the problem of who to test them on grows. Clearly there are three main groups, normal volunteers, patient volunteers and, rarely, patient non-volunteers. It is not intended to discuss this matter in detail, but it is relevant that some drug actions can be demonstrated on normals (anticoagulant, anæsthetic, antihypertensive) whereas others cannot (antiparkinsonian, antimicrobial) so that to try the latter on normals to obtain pharmacokinetic data would be to treat man formally as an experimental animal, risking toxicity, however remotely, to obtain information of no benefit to the subject. This is increasingly often done in normal volunteers and raises the question of what constitutes informed consent, especially if the volunteers are prisoners as is the case in some countries, e.g. U.S.A. This procedure may or may not be thought proper.

It is intolerable that a potential new drug should be given to a person who has not been consulted except in the rarest circumstances (advanced mental disease, childhood and in other situations where ability to comprehend is impaired) and here any experiment must have direct therapeutic intent, and not be merely to get, say, metabolic data. If the patient cannot be consulted then his relatives must be.

Considerable problems of ethics arise in testing drugs and it is now usual to require that the ethics of all such projects be subjected to review by an independent committee. The Medical Research Council in Britain requires such approval before making grants for clinical research.

The first two stages of clinical drug development are generally conducted by specialists, but any doctor in hospital or general practice may nowadays find himself concerned with formal clinical evaluation either as a participant or examining reports in order to decide whether to use a drug on his patients.

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Chapter 4

EVALUATION OF DRUG THERAPY

> In your ideas of the powers of remedies do not be too sanguine for you are liable to continued disappointment (Sir Anthony Carlisle, 1824).*

There are two main types of human experiment in the context of this book, pharmacological and therapeutic, and they often overlap.

In the *pharmacological experiment* the individual is the chief subject of a special investigation often using complex measuring techniques (changes in pressure, flow, electrical or chemical activity) and, although the pharmacological data obtained may be useful in advancing drug therapy, they may not have any direct use in therapy of the patient from whom they were obtained. Healthy volunteers are used as well as patient volunteers.

In the *therapeutic experiment* the measurements made on individuals are often simpler and groups of patients treated in different ways provide the basis for comparison of remedies.

Only the therapeutic experiments will be discussed further in this chapter because the doctor may reasonably feel he can dispense with the details of how changes in, say, various vascular beds are detected, until such time as he may take a specialised interest in the subject. But he cannot afford to ignore the principles of formal therapeutic comparison, for such studies provide the basis of his choice of drugs for individual patients, and they enable him to predict the outcome of treatment with less uncertainty. It is useful to know a good therapeutic study from a bad, for the latter are common, and both good and bad are thrust at him by vested interests in the hope that he will accept their verdict. More difficult, some bad studies, previously easily detectable, are now replete with the jargon of the formal therapeutic trial; the terms random allocation, double-blind, statistically significant, and probability, are draped around what on close inspection is seen to be, scientifically, a fraud. Some critics have condemned valid techniques rather than workers who have misused them.

Throughout this book lists of alternative drugs are given without any serious attempt to discriminate between them. The reason for this is that useful discrimination is impossible because "it is not always easy to find clinicians who are prepared to carry out the arduous work of comparing active, but closely similar, drugs. Indeed, even the professional pharmacologist does not often make comparisons on laboratory animals.

"For example, as a result of the activities of the manufacturers, at least thirty antihistamines are now available, and little can be said of their relative merit except that some act for a longer time than others, some

* Davies J. L. (1952). *Westminster Hospital*. London: Murray.

give more drowsiness than others, some have been more thoroughly tried out and some are more expensive.

"It is indeed difficult to see how a comparison could be made without the application by clinicians of more time and energy than would seem to be justified by the knowledge likely to be gained. The position is the same if we consider the antispasmodic drugs, the oral diuretics, the steroids and indeed most groups of substances in which the organic chemist can produce a sufficient modification in the molecule to entitle a firm to patent rights."*

Experimental therapeutics

Pickering has written, ". . . therapeutics is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady and we alter his conditions of life . . . we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain . . . whether the result was merely due to the natural history of the disease . . . or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced improvement, we would experiment with the method, altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them.

"But it has not been followed. Had it been done we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced" (*1*).

There are some who dislike or reject the notion of deliberate experimentation on the sick, feeling that a scientific approach implies an unsympathetic or even a malevolent disposition. They forget that in the past positively harmful treatments have been widely used for many years (bleeding for pneumonia, for example) because of the lack of recognition of the need, as well as lack of knowledge of the techniques, of scientific evaluation of therapy. It has been pointed out that where the worth of a treatment, new or old, is in doubt, there may be a greater obligation to test it critically than to go on prescribing it supported only by habit or wishful thinking (*2*).

The choice before the doctor is not whether he should experiment on his patients, but whether he should do so in a planned or in a haphazard fashion; whether he should try to organise his experience so that it is of value to himself and to others or to follow the notoriously unreliable "clinical impression". The latter is the less ethical course.

Anyone who thinks he can assess the value of any but the most dramatically effective treatments by using them on patients in an uncontrolled

* WAYNE, E. J. (1963). *Practitioner*, **190**, 5.

fashion has the whole history of therapeutics against him. It is given to only a few to test a treatment that dramatically alters disease and whose efficacy is obvious with casual use, and even then details of its use will generally need carefully planned studies, e.g. adrenal steroids in rheumatoid arthritis and asthma, where wrong use may be more dangerous than no use.

Modern scientific techniques uncover the most effective treatments whilst exposing the smallest numbers to the less effective or positively harmful; they save lives, time and money. They are not unethical for they are only properly used where the relative merits of treatments are genuinely unknown.

Some patients find it hard to put their confidence in a doctor who, openly admitting uncertainty, is using two treatments concurrently in order to achieve a true measure of their relative values. They need the emotional security that is provided by a doctor who behaves as though he knows, indeed, who sometimes himself believes he knows, even though they may rightly suspect that there are others of equal authority who take an opposite view.

Though the "statistical therapeutic comparison" or "formal clinical trial", which will be discussed below, is a powerful tool for advancing therapy, it does not suit every occasion. Sometimes, as in malaria, or diabetes, there are clinical or laboratory tests that will rapidly tell whether a treatment is effective, though they may not provide evidence of a marginal difference between effective drugs, and in tuberculous meningitis a single recovery was considered adequate evidence of therapeutic efficacy.

Need for statistics

In order to decide whether patients treated in one way are benefited more than those treated in another, there is no possibility of avoiding the use of numbers. The mere statement by a clinician that patients do better with this or that treatment is due to his having formed an opinion that more patients are helped by the treatment he advocates than by other treatments. The opinion is based on numbers, but having omitted to record exactly how many patients have been treated by different methods and having omitted to ensure that the only variable factor affecting the patient was the treatment in question, only a "clinical impression", instead of facts, can be stated. This is a pity, for progress is delayed when convinced opinions are offered in place of convincing facts. The former, though not necessarily wrong, are unreliable, despite the great assurance with which they are often advanced. This is not to dismiss the anecdotal clinical survey or the case-report, for they tell what *can* happen, which is useful. Also, formal therapeutic trials are commonly done because someone has formed an impression which is thought to deserve testing.

Nearly 100 years ago Francis Galton saw this clearly. "In our general impressions far too great weight is attached to what is marvellous. . . . Experience warns us against it, and the scientific man takes care to base his conclusions upon actual numbers. The human mind is . . . a

most imperfect apparatus for the elaboration of general ideas. . . . General impressions are never to be trusted. Unfortunately when they are of long standing they become fixed rules of life, and assume a prescriptive right not to be questioned. Consequently, those who are not accustomed to original enquiry entertain a hatred and a horror of statistics. They cannot endure the idea of submitting their sacred impressions to cold-blooded verification. But it is the triumph of scientific men to rise superior to such superstitions, to devise tests by which the value of beliefs may be ascertained, and to feel sufficiently masters of themselves to discard contemptuously whatever may be found untrue . . . the frequent incorrectness of notions derived from general impressions may be assumed. . . ."*

Therapeutic trial design

The aims of a therapeutic trial, not all of which can be attempted on any one occasion, are to decide:

1. whether a treatment is of value,
2. how great its value is (compared with other remedies, if such exist),
3. in what types of patients it is of value,
4. what is the best method of applying the treatment, how often, and in what dosage if it is a drug,
5. what are the disadvantages and dangers of the treatment.

Bradford Hill defines the clinical trial as "a carefully, and ethically, designed experiment with the aim of answering some *precisely framed question.* In its most rigorous form it demands *equivalent groups* of patients *concurrently treated* in different ways. These groups are constructed by the *random allocation* of patients to one or other treatment. . . . In principle the method is applicable with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients" (*3*).

Three important points in the above definition may be stressed. *Equivalent groups of patients:* if the treatment groups differ significantly in age, sex, race, duration of disease, severity of disease or in any other possibly relevant factor, it will not be possible to attribute differences in outcome to the treatment under investigation, unless there is some way of eliminating the bias that has entered. The best way of getting equivalent groups is by allotting patients to them by *random allocation.* To allot patients alternately or otherwise systematically is not satisfactory as the physician almost inevitably knows into what treatment group a patient will go whilst engaged in deciding whether the patient should enter the trial, and he may be unconsciously influenced by this if he has strong feelings about either the patient or the value of the respective treatments. With random allocation the treatment group into which the patient goes is only discovered after it has been decided to enter him in the trial.

* GALTON, F. (1879). Generic images. *Proc. roy. Inst.*

Sometimes "it may be considered embarrassing to have recourse to opening a sealed envelope—and still more to tossing a coin" if a decision has to be made in front of the patient, and randomisation can equally easily be achieved by a simple mental trick (*8*).

Treatments must be carried out *concurrently*, partly for the reasons given above and partly because diseases may vary in severity with time, virulence of an organism may change, especially in epidemics, the weather may influence respiratory and cardiac diseases or a hospital may even get a reputation, for good or ill, so that more or less severe cases may be sent to it, and doctors and nurses change.

Before commencing any therapeutic trial it is essential to formulate exactly the question that is to be answered. For example: "Is drug X capable of relieving the pain of osteoarthritis more or less completely, with greater or less side-effects and for a shorter or longer time than Aspirin Soluble Tablets, B.P.?" The question should be as simple as possible, for to try to discover too much can be a cause of failure, and it should be kept in mind throughout the whole process of designing the trial. Failure to set down at the start exactly what it is hoped to discover leads to muddle.

Double-blind technique

The fact that both doctors and patients are subject to bias due to their beliefs and feelings has led to the invention of the double-blind technique. This is a "*control device to prevent bias from influencing results.* On the one hand it rules out the effects of hopes and anxieties of the patient by giving both the drug under investigation and a placebo (dummy) of identical appearance in such a way that the subject (the first 'blind' man) does not know which he is receiving. On the other hand, it also rules out the influence of preconceived hopes of, and unconscious communication by, the investigator or observer by keeping him (the second 'blind' man) ignorant of whether he is prescribing a placebo or an active drug. At the same time, the technique provides another control, a means of comparison with the magnitude of placebo effects.

"The device is both philosophically and practically sound. In addition, perhaps because of the widespread attention it has attracted, or the magic quality it appears to have, the double-blind technique has been assumed to be a complete method of drug evaluation in itself. Indeed, it is often called the double-blind test. Many seem to believe that all that is necessary for a good clinical study is to use it, and, since it is relatively easy to apply, many are exploiting it in just this way. A number of papers emphasise in the very title that this type of control was used, not only as if the use of a control were worthy of special mention, but also as if to warn the reader in advance that a special type of insurance had been taken out to guarantee that the results about to be recounted were beyond reproach" (*9*).

The double-blind technique should be used if possible whenever

evaluation depends on other than strictly objective measurements. There are occasions when it might at first sight seem that criteria of clinical improvement are objective when in fact they are not, for example the range of voluntary joint movement in rheumatoid arthritis has been shown to be greatly influenced by psychological factors, and a moment's thought shows why, for the amount of pain a patient will put up with is influenced by his mental state. Assessment of progress of chest radiographs in pulmonary tuberculosis is also liable to bias, due to enthusiasm or lack of it, and in the classic Medical Research Council chemotherapy trials* it was arranged that the radiologist commenting on the serial films should do so in ignorance of what treatment the patient was having.

Sometimes the double-blind technique is not possible because, for example, side-effects of an active drug reveal which patients are taking it, but it never carries a disadvantage, "only protection against spurious data". It is not, of course, used with drugs fresh from the animal laboratory, whose dose and effects in man are unknown, although the subject may legitimately be kept in ignorance (single-blind) of the time of administration.

Placebo or dummy medication as a control device in therapeutic trials

The foregoing quotation refers to occasions when a dummy or placebo treatment would be used, but this is not invariably necessary or indeed ethical, for it is never permissible to deprive patients of effective therapy for serious disease. In drug trials in, say, epilepsy or tuberculosis, the control groups are patients receiving the best available therapy.

The inert placebo or dummy is useful to:

1. Distinguish the pharmacodynamic effects of a drug from the psychological effects of the act of medication and circumstances surrounding it, e.g. increased interest by the doctor, more frequent visits, etc.
2. Distinguish drug effects from fluctuations in disease that occur with time and other external factors, e.g. in ulcerative colitis, rheumatoid arthritis.
3. Avoid false negative conclusions. For example, a therapeutic trial of a new analgesic should consist of comparison of the new drug with a dummy as well as with a proved active analgesic. If all three treatments give the same result, a likely explanation is that the method used is incapable of distinguishing between an active and an inactive drug and so should be modified; whereas if only the new drug and the dummy are used and give identical results, there are two possible explanations, first that the method used is insensitive and second that the new drug has only placebo-effect, i.e. is pharmacologically inactive at the dose used.

* Medical Research Council (1955). *Brit. med. J.*, **1**, 435.

It was found, for instance, in one trial in which angina pectoris was being treated and the progress of the disease determined by recording the frequency of attacks of pain, that 60% of patients improved over, on average, the first eleven weeks, regardless of whether they were receiving an active drug, a dummy (using double-blind technique) or no treatment at all. This meant that this particular method was less sensitive over this period and improvement genuinely due to a drug was masked, at least partially, until after the eleventh week. This early improvement regardless of drug therapy could partly be attributed to the establishment of a good psychological relationship between patient and physician (*14*).

Controls—within-patient or between-patient

Sometimes in chronic disease it is possible to give a number of drugs to one patient thus conveniently using him as his own control, for example in Parkinsonism, hypertension, anxiety. When this is done it is important to ensure in a small series that each drug both precedes and follows each other drug the same number of times, to avoid the risk of systematic bias as a result of "carry-over" after a drug has ceased to be given. If in an analgesic trial a weak drug always follows a potent drug the weak drug may be dismissed as ineffective because the patient's standard has become influenced by the high degree of relief provided by the potent drug. The weak drug must precede as well as follow both the potent drug and the dummy if error is to be avoided. In addition, persistence of a drug or metabolites and enzyme induction may influence the response to a subsequent drug.

In acute diseases it is plainly impossible to give more than one treatment to one patient and the controls must be other patients.

Hypothesis of no difference, and statistical significance

When it is suspected that treatment A may be superior to treatment B and it is wished to find out the truth it is convenient, and only seemingly eccentric, to set about it by testing the hypothesis that the treatments are equally effective, or ineffective, as the case may be—the "no difference" hypothesis (null hypothesis). Thus, when two groups of patients have been treated (between-patient comparison) or each patient has had a course of each drug (within-patient comparison) and it has been found that improvement has occurred more often with one treatment than with the other, it is necessary to decide how likely it is that this difference is due to a real superiority of one treatment over the other. *A statistical significance test will tell how often a difference of the observed size would occur due to chance (random influences) if there is, in reality, no difference between the treatments.* If the result of the test is that the observed difference is unlikely to have occurred by chance we may choose to believe, or at least to act as though, there is a real superiority of one treatment and to adopt it in preference to the other in our practice. It is up to the clinician to decide what probability level he will accept as a guide to action; the

statistician cannot tell him. A difference may be statistically significant but clinically insignificant.

In clinical practice most agree that if the statistical significance test shows that, the no-difference hypothesis being true, a difference as large as that observed would only occur 5 times if the experiment were repeated 100 times, then this is acceptable as sufficient evidence that the null hypothesis is unlikely to be true, i.e. that there is a real difference between the treatments. This level of probability is generally expressed in therapeutic trials as, the difference was "statistically significant", "significant at the 5% level" or "P* = 0·05". "*Statistical significance*" simply means, "*unlikely to be due to chance*".

If the analysis reveals that, the no-difference hypothesis being true, the observed difference, or greater, would only occur *once* if the experiment were repeated 100 times, the results are generally said to be "statistically highly significant", "significant at the 1% level" or "P = 0·01".

The statistical tests do not prove that a difference is due to one treatment being better than another, or not better than another, as the case may be, they merely provide probabilities. A clinician who would act on the results of an experiment that provided a "statistically significant" result (P = 0·05) where there were good theoretical reasons for expecting that result, might refuse to accept a theoretically improbable conclusion, or one that went against his "experience" unless the difference was "statistically highly significant" (P = 0·01) and this would be reasonable. It is as important not to allow oneself to be bludgeoned by statistics as it is important not to disregard strong evidence. *Statistics may be defined as "a body of methods for making wise decisions in the face of uncertainty"* (*12*). Used properly, it is a tool of great value for promoting efficient therapy.

If an experiment is ill-designed or ill-conducted it cannot be salvaged by statistics. Significance tests can be legitimately applied only to an experiment in which the sole variable that is not subject to chance, or random influence, is the treatment to be tested. Bias in selection, allocation, observation and assessment of patients renders significance tests invalid. The application of such tests to data collected from old case records is more misleading than useful.

Before starting a therapeutic trial it is necessary to decide when it should stop. It is not permissible to use two treatments concurrently and to perform an orthodox significance test at convenient intervals to "see how things are going", or with the intention of stopping the trial as soon as "the results are significant". This is because chance must be the only factor operating in addition to the treatments to be tested, and such a practice introduces the workers' own preconceptions or wishes as a factor in determining when the trial should end. Differences between treated groups naturally fluctuate as the trial proceeds and at one moment a "significant" difference may occur due to chance in most trials. It is essential that this moment should not be watched for and grasped by the

* P = percentage divided by 100 (chance proportion).

workers—to pick it out will lead to a greater number of false positive results, and so to false therapeutic claims.

It is necessary, after deciding in consultation with a statistician what difference it is realistic to seek, having regard to the time, energy and number of patients available, to agree on the number of patients to be treated, to treat them and then to test the results. Then there is less likelihood of hitting on a falsely "significant" difference. This is a **"fixed-sample trial"** and at the end there may be disappointment if, when the results are examined, they just miss the agreed acceptable level of statistical significance. Here, having presented his results, the clinician is entitled to express his opinion on their meaning. It is here too that the results of independent workers ordinarily enable us to decide whether such a difference should be accepted as real. Confirmation by others is a vital process in therapeutic advance. It is *not* legitimate, having just failed (say, $P = 0{\cdot}06$) to reach the agreed level (say, $P = 0{\cdot}05$) to take in a few more patients in the hope that they will bring P down to $0{\cdot}05$ or less, for this is deliberately introducing a bias and not allowing chance and the treatment to be the sole factors involved in the outcome, as they should be.

However, there is a special, somewhat controversial and sophisticated technique—**sequential analysis**—that does allow continuous monitoring of results, and which allows a trial to be stopped as soon as a predetermined significance level is reached. Where there is little difference the trial may be unduly long, so it is not suitable for all occasions. Sequential analysis is specially useful where there are strong ethical reasons for stopping a trial at the earliest moment. For here, a fixed sample trial could result in a needlessly high probability being reached due to too many cases having been decided on the outset, for, naturally, the magnitude of a difference, if any, being uncertain, choice of sample size is made largely in the dark. Where too high a number of cases is chosen in a trial in which grave results for the patient are at stake, then physicians may find themselves completely convinced of the superiority of one treatment before the trial is due to end. In such circumstances they cannot ethically continue to use the less effective treatment and must give all patients what they believe to be best for them, for this is the foundation of the doctor-patient relationship—that each patient must *know* that his doctor will put his patient's interest first, not sacrificing them for possible gain to other patients unless, after consultation, the patient expressly desires this. Fortunately such ethical dilemmas are rare, for physicians, with the history of therapeutics behind them now know that their judgements commonly err. The use of sequential analysis can reduce the likelihood of meeting such difficulties still further.

Number of patients needed (*10*)

A clinician contemplating a fixed-sample therapeutic trial wants to know how many patients should be treated in order to decide whether one treatment is better than another, and he turns to a statistician to help

him. An estimate can only be provided if he will tell the statistician what magnitude of difference he is interested in detecting *and* the risks he will tolerate of accepting a difference where it does not exist, and of missing a difference that does exist. The result of this calculation is commonly a shock to the clinician who may have, a little vaguely, and full of therapeutic enthusiasm, begun by saying that he wants to detect "any" difference, however small, and to be "quite certain" that it is real. What, to the doctor, may seem quite modest requirements may only be realisable with an impossibly large number of patients. A well-conducted trial giving a modest probability that is soon confirmed by other workers is preferable to a mammoth undertaking the aim of which is near certainty and which either breaks down from boredom and other human weakness, or else provides its result after the drug being tested has become obsolete.

It is plain that anyone contemplating a therapeutic comparison should consult a statistician during the planning and not after the trial is over, for the function of the statistician is to help the clinician obtain a reliable result with minimum waste.

An alternative to the classic formal therapeutic comparison described above has been proposed by Jick (*26*) within a routine hospital drug surveillance programme using nurse monitors. The opinions and practice of the physicians providing routine care are monitored to obtain information on the dosage, route, adverse effects, efficacy, etc. of the drugs. The advantage of such a scheme is that the physician is not confined to a rigid pre-planned scheme and his discretion about using known drugs, as well as the "unknown" under test, is unfettered. Such a technique is likely to be specially useful in comparing minor variants of, e.g. hypnotics and analgesics, for which it is already difficult to find skilled workers who are willing to devote time to such useful but unexciting studies.

Some mortal sins of clinical assessment*

1. *Enthusiasm and scepticism*—"a marvellous/useless drug, this".
2. *Change of assessor*—"do the measurements for me Jim/Miss Jones/darling".
3. *Change of time*—"don't worry about the assessment. Go ahead with lunch/X-rays/physiotherapy/your bath".
4. *Squeezing*—"you're much better, aren't you, Miss B?". "Any indigestion yet, Miss B?".
5. *Pride*—"I'm honest. No need for placebo in my trials".
6. *Impurity*—"We're short of cases: she'll have to do". "A few aspirins won't make much difference".
7. *Imbalance*—"Sex/severity/treatment order, doesn't matter".
8. *Error*—"Not quite significant. Let's try sequential analysis".

* By permission from HART, F. D., *et al.* (1972). Measurement in rheumatoid arthritis. *Lancet*, **2**, 28.

Reliability of published therapeutic trials

Ross, in 1951, impressed by the number of articles which extolled some form of therapy but which did not give any acceptable evidence that it was effective, analysed a representative group of 100 medical papers according to one criterion, the use of adequate controls. He concluded that only 27% of published trials showed a definite result. "Other therapies *may* be effective, *but the papers do not show it or the reverse*" (*4*). It has also been observed that authors claim success in psychiatric treatment more often in uncontrolled studies (83%) than they do in studies in which controls have been used (23%), "so that claims for the success of a treatment are closely associated with the absence of the means whereby these claims can be scientifically substantiated" (*17*).

Twenty years later a more detailed study of 141 therapeutic trials suggested that 51% were conducted to a scientifically "acceptable" standard (*30*).

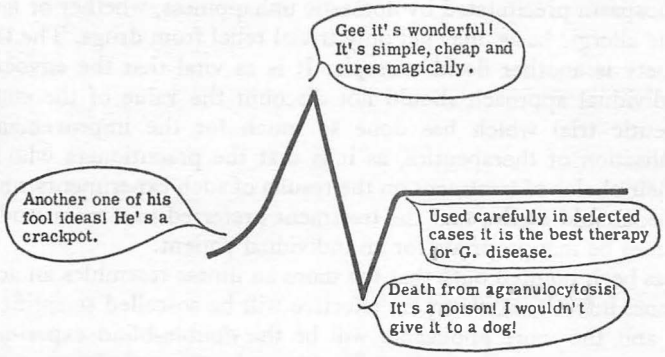

FIG. 1. Oscillations in the development of a drug.*

It is not always easy to decide when a true result has been obtained, even in a superficially well-designed trial (*9*). "Periodically it is observed that the introduction of a new drug is followed by a cluster of favourable reports of its therapeutic value. Later it is often discovered (but not always published) that the agent has no appreciable scientific therapeutic action. Then, as the agent has fallen into disuse, many have assumed that the authors of the favourable reports were either deluded or at least not sufficiently critical of their results. Actually, the favourable reports may have contained strong statistical evidence that the desired physiological change had been achieved. There is little reason to doubt that the results were real enough. The neglected possibility that may explain the later failure of the agent is that the good results were attributable, not to the pharmacological properties of the agent, but to very real and often powerful placebo-effects. In a recent study of inhibition of the

* By courtesy of Dr. Robert H. Williams and the Editor of *J.A.M.A.*

cough reflex Hillis* obtained an effect with placebos as great as that observed with 30 mg. of codeine" (5).

This brief account of some aspects of therapeutic trials may be sufficient to show with what care they must be designed. The possibilities of error are legion. Throughout this book there are references to examples of well-designed trials which show how the same principles are adapted to suit widely different circumstances. The reader is recommended to consult them both for instruction and entertainment and to pursue the subject further in the list of references at the end of the Chapter.

There is, however, danger in relying exclusively on the results of rigorous therapeutic trials designed on "classic" scientific principles. The conclusion that treatment A is better than treatment B, for disease C, may distract attention from the fact that the disease may have multiple ætiology and that "therapeutics" often involves a lot more than prescribing a drug or other regimen. For example bronchospasm due to an antigen-antibody reaction may be completely relieved by orthodox drug therapy, whereas bronchospasm precipitated by domestic unhappiness, whether or no there is a true allergic basis, may get only trivial relief from drugs. The therapy of anxiety is another florid example. It is as vital that the advocates of the individual approach should not discount the value of the statistical therapeutic trial which has done so much for the improvement and rationalisation of therapeutics, as it is that the practitioners who wisely base their choice of treatment on the results of such experiments wherever possible, should realise that the treatment preferred in a mass study may sometimes be inappropriate for an individual patient.

It has been pointed out† that the more an illness resembles an accident (e.g. most infections), the more effective will be so-called scientific treatments and the more applicable will be the double-blind experiment in evaluating treatment: but where illness can be due, wholly or partly, to lack of integration between individual and environment (e.g. anxiety, depression, asthma, eczema, hay fever, ulcerative colitis) the more treatment has to be related to the individual's life history, to enable him to achieve the integration that he could not achieve alone, and then drugs may take second place or may not be needed at all.

This book is not a book of "therapeutics", but of clinical pharmacology and drug therapy which may constitute a negligible part of the therapy of some patients and the determining factor in the outcome for others. The fact that general aspects of therapy will be seldom referred to here does not imply that they are thought to lack importance.

Experimentation on man

Ethics of human experimentation are of grave concern to all who use drugs, especially new drugs, and some aspects have already been mentioned.

Human experiments are of two main kinds, (1) **therapeutic**: those that

* HILLIS, B. R. (1952). *Lancet*, **1**, 1230.
† BALINT, M. (1961). *Lancet*, **1**, 40.

may actually have a therapeutic effect or provide information that can be used to help the subject, and (2) **non-therapeutic**: those that provide information that cannot be of direct use to him. In practice, experiments often do not fall clearly into one or other group and attempts to lay down codes of behaviour based on the assumption that they do have so far failed to achieve their object of allowing medicine to advance whilst certainly preventing abuse.

Some dislike the word "experiment" in relation to man, thinking that its mere use implies a degree of impropriety in what is done. It is better, however, that all should recognise the true meaning of the word. "to ascertain or establish by trial",* that the benefits of modern medicine derive wholly from experimentation and that some risk, however slight, is inseparable from medical advance. The duty of all doctors lies in ensuring that in their desire to help patients in general they should never allow themselves to put the individual who has sought their aid at any disadvantage, for "the scientist or physician has no right to choose martyrs for society".†

Physicians deal with individuals and have sometimes argued against the statistical therapeutic trial that it does not tell what will happen to any one individual who consults them. This is obviously true, but the knowledge gained from such studies that, with a treatment, x% recover, y% improve and z% are unchanged, with details of unwanted effects, provides a better basis for the choice of therapy for individuals than the, often divergent, clinical impressions of the doctor and his colleagues.

It is, of course, only proper to perform a therapeutic trial where the doctor genuinely does not know which treatment is best, and if he is prepared to withdraw individual patients, or to stop the whole trial if at any time he becomes convinced that it is in their interest to do so. A sound guide to conduct is, "no patient should be worse off as a result of the trial than he might have been otherwise in the hands of a reasonable and competent medical man" (*11*).

If it is not known whether one treatment is better than another, then nothing is lost by allotting patients at random to those treatments under test, and it is in everybody's interest that good treatments should be adopted and bad treatments abandoned as soon as possible. It is, of course, more difficult to justify testing a new treatment where existing treatments are fairly good, than where they are bad, and this difficulty is likely to grow. With a new drug the situation is generally clear—its efficacy is unknown—but when a drug has been marketed and used for years without proper scientific evaluation so that unsupported claims surround it, then the difficulties of getting true scientific evaluation are multiplied, for "long years of habitual prescribing based on early and authoritative impressions and optimism confers on a drug qualities of survival which have a high degree of immunity against the disqualifying actions of scientific

* Oxford English Dictionary
† Kety, S. quoted by Beecher (*3a*).

experiment in man" (*15*). Ill-performed scientific tests have the same effect.

The matter will not be pursued further here, but doctors must consider the ethical implications of their acts, the casual use of drugs as much as the planned evaluation, and none can fail to profit by reading some of the references below.

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Chapter 5

DRUG CONTROL, DRUG NAMES

FOLLOWING the thalidomide disaster (1960–62) most countries without a government organisation to supervise the introduction and use of drugs, set one up, and those already having such an organisation overhauled it. In Britain the government set up a control organisation now known as the *Committee on Safety of Medicines* which assesses the safety, efficacy and quality of medicinal products.

It has *sub-committees* that are concerned to:

1. *Review animal data* prior to clinical trial.
2. *Review clinical data* prior to marketing.
3. *Assess pharmaceutical and chemical quality.*
4. *Monitor adverse reactions* in the community.

These sub-committees report to a main committee which makes recommendations to the statutory "licensing authority". Applicants denied a licence may appeal to the "Medicines Commission", some members of which are from the drug industry.

The Committee on Safety of Medicines is chiefly concerned with safety, and does not require that a new drug must be shown therapeutically superior to existing drugs before marketing. This recognises the difficulty of ranking drugs in many fields, e.g. mental disease.

The Committee does not design experiments nor provide facilities for animal or clinical testing of new drugs; it reviews evidence set before it.

The U.S.A. has had a drug supervisory organisation (under the Food and Drug Administration) since 1938 following the death of 107 people from the diethylene glycol solvent of a sulphanilamide "elixir".

Drug Names

Any drug may possibly have names in both of the following classes: *Non-proprietary* and *Proprietary*, in addition to its chemical name.

Non-proprietary name.*

a. Official name. The name used in an official pharmacopœia.

b. Approved name. The name given by the British Pharmacopœial Commission to a drug which is not included in the British Pharmacopœia.

Proprietary name. The name is the property of a pharmaceutical firm which sells, although it may not have made, the drug. For example,

* This is not the same as a "generic" name. "Sulphonamide," "barbiturate" are generic names, i.e. refer to a class or genus of compounds. But "generic" is often misused to mean "non-proprietary".

phenylbutazone = Butazolidin = 4-butyl-3,5-dioxo-1,2-diphenylpyrazolidine: in this book proprietary names have a capital letter.

But a proprietary name may refer to a formulation and not only to a single chemical. *If a non-proprietary name exists it should be used for the sake of:*

1. *Clarity*; because it gives information on the type of drug, e.g. diazepam and nitrazepam are plainly related, but their proprietary names are Valium and Mogadon: nortriptyline and amitriptyline are Allegron and Lentizol.

   There have been cases of prescribers, when one drug has failed, unwittingly changing to another drug of the same group or even to the same drug, thinking that such different names meant different drugs. Multiple names for the same drug are commonly totally uninformative, e.g. imipramine is Tofranil, Dimipressin, Impamin, Praminil, etc. Such occurrences are a criticism of the prescriber, but they are also a criticism of the system that allows such confusion. But in cases where differences in formulation may be critical (see *pharmaceutical formulation and biological availability*) it can be right to specify the source of the preparation, either by naming the manufacturer or by using a proprietary name.
2. *Economy:* drugs sold under non-proprietary names are usually, but not always, cheaper than those sold under proprietary names.
3. *Convenience:* the pharmacist can supply whatever he stocks whereas if a proprietary name is used he is obliged to supply that preparation alone. He may have to send for the preparation named although he has an equivalent in stock. But hospitals commonly allow substitution so that drugs can be bought in bulk. Mixtures of drugs are sometimes given non-proprietary names, e.g. co-trimoxazole for Bactrim and Septrin, but most are not, no doubt largely because the details of the mixture are liable to be changed by the manufacturer, whether for medical or for commercial reasons, so that the official specification would be liable quickly to become incorrect. No prescriber can be expected to write out the ingredients, so proprietary names are used in the many cases where there is no non-proprietary name.

The difficulties of nomenclature are shown by the following. A dispenser "received a written slip from the theatre sister asking for 1 gram of procaine. Thinking procaine and Percaine to be similar substances, she used crystals from a bottle of Percaine and labelled the solution procaine. Giving evidence before the coroner she said that she had heard of Percaine but had never dealt with it in the pure drug form; she was so convinced that procaine and Percaine were identical that she did not consult any book." The patient into whom the drug was injected had seven convulsions in less than 15 minutes and died. In 1940 the *Lancet* expressed the hope that the manufacturers of Percaine would sell their product here under the name by which it was known in the United States: Nuper-

caine. The makers retorted, with some justice, that the trade mark Percaine was registered in 1918, whereas procaine was not adopted by the B.P. until 1932, so that it was for the B.P. to make a change if one was necessary. The B.P. commission considered the matter "but it was not then thought possible to take any action". Later, in 1942, the makers of Percaine discarded this trade-name and substituted Nupercaine. Reporting this co-operative action, the *Lancet* added "it would be a blessing to both prescribers and dispensers of local anæsthetics if makers of procaine would relegate their brand names to second place and market their products as procaine (Smith) or procaine (Jones)". The necessity for some such system as this was emphasised in the following year when a woman died as a result of the newly named Nupercaine being confused with Novocaine (procaine). The proposed solution would be a great relief to the medical profession. Unfortunately it is unacceptable to commercial pharmaceutical firms, although it is applied to insulin without apparent serious economic effect on the manufacturers. It is unlikely that the commonsense system of one name for one drug will be achieved in the near future as it seems to be impossible to reconcile uniformity with commercial enterprise at present.

The pharmaceutical industry regards freedom to market under brand names and to advertise or, as it calls the latter, to "effectively (bring) to the notice of the medical profession",* as two of the essentials of the "process of discovery in a vigorous competitive environment".*

Industry resents criticism of these activities for, rightly knowing itself to have contributed immensely to the relief of human suffering, it believes that it knows what is best for the community, particularly as much criticism has undoubtedly been made from frankly political motives. As a result the reasonable protests by doctors who simply want to practise rational medicine undistracted by a hubbub of names and claims are unregarded.

The present situation is that industry spends a lot of money promoting its many names for the same article, and the community, as represented by the Department of Health, spends a smaller sum, trying to persuade doctors to forget the brand names and to use non-proprietary names.† The ordinary doctor who prescribes for his ordinary patients is the target of both sides.

Whatever the theoretical pros and cons, one thing is plain, that until non-proprietary names approach in brevity and euphony those coined by the drug firms, the fight for their general use is a losing one. If one of the chief purposes of a drug name is that it should be used by doctors when prescribing, then provision of such non-proprietary names as methallenœstril for Vallestril, bromodiphenhydramine for Ambodryl, di-iodohydroxyquinoline for Floraquin, defeats this purpose.

The search for proprietary names is a "major problem" for drug

* Annual Report, 1963–64. Assoc. Brit. Pharm. Ind.
† *Prescribers J.*, 1964, **3**, 102.

firms increasing, as they are, their output of new preparations. One well-known firm *averages* thirty new preparations a year, another warning of the urgent necessity for the doctor to cultivate eclecticism, which he can do only on a foundation of knowledge of drugs and of criteria for their clinical assessment. The bleak outlook for practising doctors is shown by the following. One firm (in the U.S.A.) has "commissioned an I.B.M. machine to produce a dictionary of forty-two thousand nonsense words of an appropriate scientific look and sound". An official said "Thinking up names has been driving us cuckoo around here . . . proper chemical names are hopeless for trade purposes, of course. . . . We manufacture what are known as ethical drugs, sold on prescription. Doctors are the market we shoot for. A good trade name carries a lot of weight with doctors . . . they're more apt to write a prescription for a drug whose name is short, and easy to spell and pronounce, but has an impressive medical ring. . . . We believe there are enough brand new words in this dictionary to keep us going for years. . . . We don't yet know what proportion of names is unpronounceable. . . how many are obscene, either in English or in other languages, and how many are objectionable on grounds of good taste: 'Godamycin' would be a mild example." The names which "look and sound medically seductive" are being picked out. "Words that survive scrutiny will go into a stock-pile and await the inexorable proliferation of new drugs."*

Perhaps the doctors have themselves to blame for this prospect which is made more appalling by the news that "no other industry has a faster rate of innovation and product obsolescence."†

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* *New Yorker*, July 14, 1956.

¶ Annual Report, 1963–64. Assoc. Brit. Pharm. Ind.

Chapter 6

GENERAL PHARMACOLOGY

Pharmacology can conveniently be divided into two branches:

1. **Pharmacodynamics*** (studies of the biological and therapeutic effects of drugs).
2. **Pharmacokinetics*** (studies of the absorption, distribution, metabolism and excretion of drugs).

The distinction can be put crudely thus—pharmacodynamics is what drugs do to the body: pharmacokinetics is what the body does to drugs. Knowledge of both is essential if drugs are to be used to the best advantage.

It is self-evident that pharmacodynamic knowledge is essential and it is becoming progressively more evident that pharmacokinetic information is necessary if the desired amount and duration of pharmacodynamic effect is to be achieved.

Naturally, no physician can be expected to know detailed facts of pharmacokinetics, half-life, pK_a, protein binding, routes of metabolism, etc. of all the drugs he uses. But an outline knowledge of principles† and of their practical application is valuable to him when, for example, treatment seems to be going wrong, in cases of poisoning and when a patient has diseased organs of metabolism (liver) and of excretion (kidney). General knowledge of the many factors that modify choice and use of drugs enables him to ask himself the right questions, without which he cannot hope to produce the right answers.

Pharmacodynamics (*12*, *28* and refs. throughout book)

Little can profitably be written here of the mode of action of drugs, for though much is known of drug effects, the way in which they occur is often complicated and obscure. The importance of studying mechanisms of action is that better understanding leads not only to more intelligent use in medicine but also gives leads towards the development of better drugs.

The molecules in the patient or in the infecting micro-organism with which drug molecules react include:

(a) *Specific receptors.* Many drugs produce their effects by combining with imagined receptors which are a convenient and indeed necessary concept for developing and discussing hypotheses of drug action.

* The terms are thus defined in The World Health Org. Tech. Rep. 446. on *Clinical pharmacology: scope, organisation and training.*

† A principle is "a fundamental truth as basis for reasoning", or a "general law as guide to action". *Oxford English Dictionary.*

"To most of the modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly claim to have seen her, although one day he may do so."*

(b) *Non-specific receptors*, e.g. plasma proteins, which act as a store for the drug.

(c) *Enzymes*, e.g. MAO inhibitors, anticholinesterases, allopurinol.

(d) *Metabolic processes* of wide variety, e.g. sulphonamides, antibiotics, insulin, thiazide diuretics, probenecid.

Drugs also act by:

(e) *Physico-chemical properties*, e.g. volatile anæsthetics (including lipid solubility, molecular volume and vapour pressure) and osmotic diuretics and purgatives.

(f) *Direct chemical interaction*, e.g. chelating agents, antacids.

One important type of action is that called "competition" or "competitive antagonism". It is of three kinds, (1) for a chemical substrate, e.g. sulphonamides, (2) for a specific receptor, e.g. adrenoceptor blockers, and (3) for an enzyme, e.g. reversal of anticholinesterase effect by oximes.

Generally substances that act by competition are comparatively inactive themselves (though they may have some agonist action, e.g. nalorphine), so that when they occupy receptors they exclude more active substances, thus antagonising the effects of these active substances.

The effect of a competitive antagonist may be reversed by increasing the amount of agonist present so that there is relatively more agonist to "compete" for unoccupied receptors. But some competitive antagonists are irreversible (e.g. some anticholinesterases and some adrenoreceptor blockers).

In the laboratory, drug antagonism is considered to be competitive when the log-dose-response curves of agonist, given alone, and with antagonist, are parallel; which is not the case with physiological antagonism. Drugs acting by competition usually, but not always, have a chemical resemblance to the drug with which they compete.

Pharmacokinetics

(5, 7–11, 13–15, 20–23, 37, 38, 40, 43–49)

In addition to a knowledge of how drugs act in the body, it is necessary to consider how the drug itself is affected by the complex properties and functions of the body; absorption from the point of administration, transport in the blood, distribution at the site of action and in the tissues, how the body changes the drug (metabolism), and elimination from the body. These depend on the physico-chemical properties of the drug such as *molecular weight*, *chemical stability in the body* and *degree of ionisation*. Aspects of pharmacokinetics will be considered in the following pages.

* DE JONGH, D. K. (1964). In *Molecular Pharmacology*. Ed. Ariens, E. J. Vol. 1. New York: Academic Press.

Conclusion

Already it can be said that a physician with knowledge of chemistry and physiology is less likely to find himself surprised at some of the results of his prescribing, e.g. MAO inhibitors. His handling of patients poisoned with salicylate, barbiturates or pethidine will be more skilled; and it is impossible to doubt that an anaesthetist well trained in the basic medical sciences will handle his gases and liquids more successfully, particularly in patients with diseased organs of absorption, metabolism and excretion.

Those who ignore the principles of pharmacology, the study of how drugs enter the body, how they produce effects within it and how they are eliminated, and try to practise drug therapy by remembering an apparently arbitrary list of actions cannot provide the standard of care that patients now have a right to expect.

Technical incompetence in the modern doctor is inexcusable, and it is worth adding that technical competence and a humane approach are not incompatibles as has sometimes been suggested.

There follow sections of general pharmacological importance.

Selectivity of Drug Action (*28*)

The more selective drugs are, the better; unselective drugs are liable to have too numerous actions for convenience. Chlorpromazine is an example of an unselective drug interfering with numerous enzyme processes. On the other hand some anticholinesterases are highly selective for the enzyme cholinesterase, but the enzyme being ubiquitous, they also produce too-various effects.

That drugs were selective in their effects had been obvious from their first use, but it was not until 1899 that Paul Ehrlich began to develop new selective drugs scientifically in the laboratory (see *chemotherapy*). In 1901 this principle, i.e. *selective toxicity* was first applied to agriculture, when it was shown that an oatfield could be cleared of the weed yellow charlock by a spray of copper sulphate. The vigorous exploitation of this principle in food production (weedkillers, insecticides) for economic reasons is now causing anxiety.

Individual Variation: General

That individuals respond differently to drugs is a matter of everyday experience. Leaving out allergy and idiosyncrasy, it is clear that despite this, the differences are not so great that many effects and doses cannot be reasonably predicted for large groups. To any one drug there are a few people who are naturally intolerant and who will show the expected pharmacological effect at very low dose, and there are a few who will only begin to show it at a very high dose, the extremes of the Gaussian continuous distribution curve. It is important to remember this, not only because of the danger of the intolerant individuals but because, before abandoning a drug as useless, it is important to consider whether an

adequate dose has, in fact, been given. To make a decision it may be necessary to measure the plasma concentration.

Unfortunately, data on the therapeutic range of plasma concentration of most drugs are lacking, and even where this is known the facilities for measuring plasma concentration are seldom available for monitoring routine therapy. The physician making decisions on dosage and on withdrawal of a drug is thus often under a considerable handicap for, although he may be using dosage in the recommended range, plasma concentrations commonly vary by a factor of 5 and often more. In some cases it may be necessary to use the maximum tolerated dose, that is, to increase the dose until unwanted effects appear and then to reduce it slightly (e.g. Parkinsonism, epilepsy) to ensure that a therapeutic effect is not being missed.

Not many drugs are like penicillin, a drug that is so non-toxic (excepting allergy) to man that dosage can be arbitrarily fixed so high that it will give plasma concentrations well above the lethal dose (LD) of the infecting organism despite any individual variations in absorption, distribution and elimination.

Factors affecting the response of an individual to a dose of a drug are legion; they include: race, sex, diet, size, metabolic rate, environmental and body temperature, mental state and expectations, route of administration, pharmaceutical formulation, state of the gut or circulation, whether or not the drug is protein-bound, the rate and paths of biotransformation and excretion (largely genetically determined) and whether the relevant organs are healthy, the presence of other drugs, etc. Indeed it is a matter of surprise that the results of drug therapy are as reliable and as good as they often are.

Individual Variation: Heredity: Pharmacogenetics

(*7*, *21*, *26*, *92*)

All pharmacological responses must be affected by heredity, for they depend on biochemical and biophysical factors that are controlled by genes. Heredity is thus an important determinant of that familiar concept "individual variation".

Just as the appearance of our faces differs, our sites of action, and particularly our capacity to metabolise drugs differ; all the elements are nearly always present, but they vary in size, shape and amount. For instance it has been found that *identical twins* with identical heredity from the same fertilised ovum metabolise drugs at identical rates, and that *non-identical twins* with different heredity from different fertilised ova metabolise drugs at different rates.

Kalow points out that there are two kinds of individual variation; the familiar *continuous variation* as expressed in a Gaussian continuous distribution curve, e.g. for height, weight or metabolic rate, and *discontinuous variation*, in which differences of response occur in discrete steps, e.g. ability to inactivate isoniazid or suxamethonium or to taste phenylthiourea, with regard to which individuals can be put into one of

two groups: here, fine gradations do not occur, and they cannot be placed along a continuous distribution curve.

Continuous variation is generally the result of *multifactorial* inheritance and discontinuous variation the result of *monofactorial* inheritance. Drugs can thus be used as tools to demonstrate the presence or absence of particular genes.

Inherited factors causing different responses to drugs are commonly biochemical, but can also be anatomical, e.g. occurrence of glaucoma due to mydriatics in patients with a shallow anterior eye chamber.

Kalow (*21*) classifies some clinical drug responses thus:

(a) **Heritable factors recognised by use of drugs, etc.**

1. Defective plasma cholinesterase resulting in prolonged action of suxamethonium.
2. Slow and rapid acetylation (isoniazid, sulphonamides, hydrallazine, phenelzine).
3. Haemolytic reaction to primaquine.
4. Malignant hyperthermia.
5. Inability to hydroxylate phenytoin, with ability to hydroxylate other drugs retained.
6. Resistance to coumarin anticoagulants: this also occurs in rats and has practical importance as these drugs are used as rat poisons.
7. Ability to taste phenylthiourea.
8. Resistance to vitamin D, leading to rickets.
9. Characteristic-smelling urine after eating asparagus (methyl-mercaptan is formed).
10. Red urine after eating beetroot: this has led to erroneous diagnosis of haemoglobinuria.
11. Inability to smell cyanide.

(b) **Hereditary defects or diseases, with altered drug response**

1. Hereditary methæmoglobinaemia, in which the abnormal hæmoglobin forms more readily with drugs, e.g. nitrites.
2. Porphyria.
3. Gout and diabetes induced by thiazide diuretics is probably an example.
4. Shallow anterior chamber of eye so that, when the pupil is dilated, the iris blocks the outflow of aqueous humour and angle-closure glaucoma results.
5. Rise of intraocular pressure with adrenal steroid: mechanism obscure.
6. The eyes of mongols are more sensitive to mydriatics than normal.

(c) **Racial differences in response to drugs**

These may be differences in the mean of the Gaussian normal distribution shown as a somewhat greater or lesser tolerance to drugs, e.g. slower

alcohol elimination in Eskimos and N. American Indians, or there may be a greater or lesser occurrence of discrete abnormalities, e.g. primaquine sensitivity in American Negroes.

The mydriatic response to sympathomimetics is related to iris colour. Light eyes (common in Caucasians), dilate more than dark eyes (commoner in Negroes). Whether this is due to enzyme differences or to the fact that the Negro iris is both thicker and more heavily pigmented is uncertain.

Atropine has less effect on the eye and causes less *initial* reduction of heart rate (vagal stimulation) in Negroes than in Caucasians.

Much of the above is interesting rather than important but it is likely that many clinically important genetic differences in the response to drugs remain to be discovered.

Bacterial resistance to drugs is genetically determined and is of great clinical importance.

Insect resistance to insecticides is also genetically controlled.

Utility for pharmacogenetics may be found in predicting drug reactions due to homozygosity for a rare gene by observing small deviations from normal metabolism in those, commoner, subjects who are heterozygous for that gene.

Once a genetic difference, e.g. an enzyme defect, is understood, it will be possible to predict what will happen when drugs of particular chemical groups are administered. But whether patients should be screened routinely for such differences in drug response, e.g. isoniazid, suxamethonium, is a matter of economics and logistics.

ASPECTS OF PHARMACOKINETICS

(5, 7, 8–10, 11, 13–15, 20, 22, 23, 37, 40, 43–49, 94)

See also routes of administration: dosage: accumulation.

The ability of a drug to cross lipoprotein cell membranes is fundamental to its clinical use, for it is a major factor in determining whether it can be taken orally for systemic effect, whether, after entering the blood it will enter the brain and other tissues, and whether, after entering the glomerular filtrate it will be reabsorbed or excreted in the urine. Drugs that are reabsorbed in the kidney must be metabolised to non-lipid soluble substances if they are to be excreted. Highly lipid soluble substances that are not metabolised persist in the body indefinitely (unless they are volatile and excreted through the lungs) and are not suitable for use as drugs.

Drugs pass across lipoprotein cell membranes by three principal means:

1. **Diffusion:** drug must be lipid soluble and unionised.
2. **Filtration:** drug passes through pores in cell membrane.
3. **Active transport:** drug is transferred across cells by active energy-requiring processes.

Diffusion is the most important means by which drugs enter the body

and are distributed within it. It is dependent on the drug being *lipid soluble** (high lipid/water partition coefficient).

Unionised drug is lipid soluble and diffusible.
Ionised drug is lipid insoluble and non-diffusible.
Ionisation is pH dependent.

Most drugs are weak organic acids and bases (electrolytes) and in aqueous solution they are ionised to different degrees depending on the pH.

There is a wide range of pH in the gut (pH 1·0 in the stomach: 6·8 in the upper, and 7·6 in the lower, small intestine). But the pH inside the body is maintained within a limited range, pH 7·4 ± 0·04, so that only drugs that are substantially unionised within this range will be widely distributed. Urinary pH can vary between 4·6 and 8·2 and so it affects the amount of drugs reabsorbed in the renal tubule by passive diffusion. Now the proportion of drug that is ionised and unionised depends not only on pH but also on the dissociation (or ionisation) constant of the drug (K_a). This is usually expressed as the pK_a, i.e. the negative logarithm of K_a.†

The importance of this is shown by the fact that when the pH of a solution is the same as the pK_a of the drug then the drug is 50% ionised (non-lipid soluble) and 50% unionised (lipid soluble). Aspirin and phenobarbitone are acids and so by raising the pH of a solution (making it more alkaline) the drugs will become more ionised and so less lipid soluble. Thus aspirin and phenobarbitone are better absorbed from the stomach than from the intestine, though this is not of clinical importance because the drug leaves the stomach so soon and stays much longer in the intestine. However pH can be of considerable importance in renal excretion, and alkalinising the urine can result in substantially increased urinary elimination in cases of poisoning by aspirin ($pK_a = 3·5$) and by phenobarbitone ($pK_a = 7·24$). However other barbiturates have a higher pK_a (7·7 to 8·0) than phenobarbitone so that at blood pH (7·4) they are highly unionised and more lipid soluble. Attempts to raise the pH of the urine to levels that would increase the ionisation to about 50% (i.e. $pH = pK_a$) would require administration of amounts of bicarbonate that could raise blood pH to levels that would endanger life before a useful effect appeared (see also *drug interactions* and *poisoning*).

The above is made more complex by the effects of differences in pH and in drug concentration on either side of membranes, e.g. stomach (pH 1·0): plasma (pH 7·4).

Filtration through pores in the cell membrane is of little practical importance, for the pores are small and will only pass substances of a size

* Whilst ionised drug is non-lipid soluble, unionised differs in the extent of its solubility in lipids, e.g. barbitone and thiopentone are equally unionised at the same pH, but the thiopentone is much more lipid soluble, which accounts for its speedy action when given i.v. Barbitone enters the brain relatively slowly, which is acceptable for a hypnotic, but not for a general anæsthetic.

† Just as pH is the negative logarithm of H, the hydrogen ion concentration.

of less than three carbon atoms long (mol.wt. 100), e.g. urea (mol.wt. 60) (glucose has a mol.wt. of 180). But the glomerulus has holes ten or more times that size and nearly all free drug (not bound to plasma protein), indeed anything smaller than albumin (mol.wt. 69,000) passes into the glomerular filtrate.

Active transport mechanisms are important with a few drugs. The substance forms a complex with a carrier enzyme and is passed across the cell, e.g. penicillin excretion: iron and methyldopa absorption.

Absorption

Drugs taken orally pass across cell membranes as described above. Absorption from the gut is modified by presence of food and motility and can be significantly impaired in malabsorption syndromes. If injected i.m. or s.c. the above principles also apply but large molecules are transported by lymph before entering the blood. Local blood flow and physical activity also affect absorption from i.m. or s.c. injection.

Distribution

The body can be considered as a group of compartments of varying accessibility to drugs. Plainly a drug that does not reach its site of action in sufficient amounts is useless. Some considerations on drug distribution follow.

Once a drug is in the blood its distribution is chiefly influenced by its lipid solubility, its pK_a, the pH of body fluids, the extent of protein binding and differences in regional blood flow. These factors are relatively independent of genetic factors and so distribution is less variable than metabolism which is greatly influenced by genetic factors.

Capillaries are permeable to both water soluble and lipid soluble drugs. Therefore, a water soluble drug (streptomycin), given by injection because it will not be absorbed from the gut, will be distributed in the extracellular space only, it will not readily pass into cerebrospinal fluid or into other body cavities. Lipid soluble drugs (volatile anæsthetics) are rapidly distributed throughout the intra and extracellular spaces.

Selective distribution of drugs results from protein binding in the blood (very many drugs, including penicillins, phenylbutazone, imipramine, etc.) and in the tissues (mepacrine), and highly lipid soluble drugs are sequestered in fat.

Drugs that are not bound to proteins and that are confined to the extracellular space can be used to measure its volume (bromide, inulin).

Drugs that are virtually entirely bound to plasma protein can be given i.v. and the dilution allows the measurement of the plasma volume. Albumen labelled with Evans blue is commonly used.

If the packed cell volume is known, the blood volume can be calculated.

It is often unimportant for the clinician to have special knowledge of the details of distribution of drugs that he uses and facts of distribution are implicit in the prescribing rules for drugs, but there are two organs

which can usefully be mentioned separately, the **brain** (and cerebrospinal fluid, CSF) and the **fetus** (and placenta).

The general principles mentioned above (diffusion, active transport) apply to the brain. Drugs that are well absorbed from the gut because they are lipid soluble (unionised) will enter brain and CSF readily. Drugs that are not well absorbed because they are water soluble (ionised) (e.g. neostigmine, tubocurarine, streptomycin) will not enter. Dopamine does not enter the brain from the blood and this is why its precursor levodopa is used in Parkinsonism. If the meninges are inflamed any drug will enter the CSF. For drugs and the fetus see later.

Plasma protein and tissue binding (see also *drug interactions*)

Plasma protein binding. Many drugs have a substantial physicochemical affinity for plasma protein (chiefly albumen) and are carried in the blood in two forms, free (pharmacologically active, diffusible and available for metabolism and excretion), and bound (pharmacologically inert, and not diffusible nor available for metabolism or excretion).

The protein-binding is generally weak* so that, as the concentration of free drug in the plasma falls, drug is quickly released from the protein. Thus, protein-binding can be regarded as a drug storage mechanism.

When a drug that has a high affinity for plasma protein enters the blood in small amounts most of it will become protein bound. As the concentration in blood rises, the protein-binding sites will become saturated so that any further increase must be in the free form. Thus, the *proportion* of protein-bound drug, which is at first high, will diminish. Then, as free drug is eliminated and the *total* blood concentration falls, the *proportion* protein-bound will increase. Thus, *figures on protein-binding of drugs are only useful if they are measured at plasma concentrations that are used in therapeutics.* This has practical importance for therapy, e.g. phenylbutazone, at ordinary therapeutic doses, is 98% protein bound. If the dose is increased in an attempt to get a greater effect, the result is to increase the free drug level (reducing the *percentage* of total drug that is protein bound) which causes increased rate of metabolism. There is no greater therapeutic effect, but there is increased risk of toxicity and the total plasma concentration tends to remain stationary, despite the higher dose.

Another aspect of practical importance is the control of antimicrobial therapy. Total plasma concentration figures (free plus bound drug) without knowledge of proportion protein bound can give a misleading impression, for only the free drug will diffuse into tissues and other body fluids and provide biological activity. Thus the total concentration of sulphonamides in the blood is higher than that in cerebrospinal fluid,

* Strong protein binding is a big disadvantage in a drug as in the case of some iodine-containing radiodiagnostic agents and clioquinol which render the measurement of plasma protein-bound iodine misleading for months.

for there is little protein in the CSF and the CSF concentration equilibrates with the free drug in the plasma. Also, claims that, e.g. one penicillin gives higher total plasma concentrations than another, are meaningless for therapeutics unless it is known what proportion is free and what proportion is bound.

But in the control of therapy in individual cases, measurement of total concentrations is ordinarily adequate since percent of protein binding is relatively constant and little influenced by individual genetic factors (unlike metabolism which is greatly influenced). Protein binding *in vivo* must be taken into account when relating plasma concentration to *in vitro* inhibitory concentration in control of antimicrobial therapy.

When two drugs that both have an affinity for the same binding site are given, they will compete and concentrations of free drug will alter. Alteration of the plasma concentration of one drug by another drug is a source of clinically important drug interactions. The fact that two drugs are highly protein-bound does not allow the assumption that they will displace each other, for there are many binding sites, e.g. for organic anions and salicylate as many as 5 sites with high, and 20 sites with low, affinity. But for any one drug there is commonly one or perhaps two important sites. Also, small chemical changes in the drug can cause big changes in affinity for protein so that generalisations to a group of drugs (sulphonamides, barbiturates) from a single member are unlikely to be valid. In general, drugs highly bound to protein tend, as may be expected, to persist in the body longer than members of the same series that are less bound, to have a lower therapeutic activity (free drug), to be less effectively distributed and less amenable to dialysis in poisoning.

The plasma protein binding of penicillins provides an example of a series (*8*)**:**

benzylpenicillin	60%
phenoxymethylpenicillin	80%
ampicillin	25%
methicillin	40%
cloxacillin	95%

and so do the sulphonamides:

sulphadimidine	30% (rapidly excreted)
sulphadiazine	50% (rapidly excreted)
sulphadimethoxine	95% (slowly excreted)
sulphamethoxypyridazine	85% (slowly excreted)

and the barbiturates:

barbitone	5%
phenobarbitone	20%
pentobarbitone	37%
thiopentone	65%

Some other examples of plasma protein binding:

salicylate	50 to 80%
warfarin	95%
phenylbutazone	98%
indomethacin	90%
pethidine	40%

Disease states, e.g. hypoalbuminæmia, with reduced protein binding capacity, and **multiple drug therapy** leading to competition for binding sites, can be significant factors in unexpected excessive response due to unusually high free drug concentrations.

Carrier proteins, natural hormones and drugs. Special globulins provide binding sites for some natural hormones, transcortin for adrenal steroids and thyroxine-binding globulin. The amount of these globulins increases with œstrogen administration (the dose in oral contraceptives is marginal in this respect) and pregnancy, so that *total* plasma hormone concentration rises due to increased binding. But the concentration of free hormone remains under the usual physiological control so that the raised *total* concentration has no clinical significance except that it may mislead, e.g. a patient on an œstrogen may have a protein-bound iodine level in the range of thyrotoxicosis whilst remaining euthyroid.

The amount of these globulins decreases with androgen and adrenal steroid therapy so that the protein-bound iodine level may be misleadingly low.

Phenytoin and salicylates can displace thyroxine from its carrier protein so that protein-bound iodine level may drop into the range characteristic of myxœdema.

Antirheumatics (phenylbutazone) displace hydrocortisone (cortisol) from transcortin. Whether this contributes to the antirheumatic effect is uncertain.

Tissue binding. Some drugs have an affinity for particular constituents of tissue, and may be concentrated there. Where this is extreme, plasma concentrations may not give a simple relationship with pharmacological effect. Examples of selective tissue binding include: chlorpromazine in brain: mepacrine in liver: digoxin and digitoxin in kidney, liver and heart: tetracyclines and heavy metals in bone and teeth: chloroquine in retina and liver: calcium in collagen: arsenic in keratin.

Storage in fat occurs with substances of high lipid solubility (thiopentone, DDT, phenoxybenzamine, some œstrogens). But fat has a poor blood supply and in the case of thiopentone it is redistribution into the muscles, which have a good blood supply, that is of greater importance in the brevity of action of a single anæsthetic dose.

Plasma concentration of drugs and pharmacological effect

To know the time course of concentration of drug at the site of action in any tissue would plainly be useful both in planning routine dosage

schedules and in monitoring therapy in individuals. But such information can be hard or impossible to get, e.g. concentration in brain, renal tubule cell, etc.

The blood is the principal vehicle for distributing drugs to the various pharmacokinetic compartments of the body and the concentration of drug in blood (or plasma)* is likely to be related to, though not necessarily the same as, concentration in these compartments (see *distribution*, above).

Because of this relationship and of the easy accessibility for sampling, plasma concentrations are being increasingly used as a guide during clinical use of drugs.

The relationship of plasma concentration to tissue concentration (and so to pharmacological effect) is closest with drugs which are themselves the sole pharmacologically active substance and whose action is reversible.

The relationship is poor, or non-existent with, (1) drugs, e.g. methyldopa, which are not themselves active, i.e. are converted to active metabolites, and (2) drugs that act irreversibly. Brodie has aptly named these "hit and run" drugs, because their effects persist long after the drug has left the tissues. They destroy or inactivate target tissue (enzyme, receptor) and replacement occurs over days or weeks: examples include reserpine, MAO inhibitors, some anticholinesterases.

Thus, despite the multiplicity of factors concerned in the distribution of drugs (plasma protein and tissue binding, diffusion, sequestration in fat depots, conversion to metabolites of varying activity), the plasma concentration often correlates well with pharmacological effect on the target site which is commonly in another distributive compartment. Measurement of "steady-state" (a self-explanatory term) plasma concentrations is being used increasingly, not only to work out dosage schedules but also to monitor therapy. In the case of antimicrobials where the minimum inhibitory concentration for the infecting organism is known, but the tissues infected are relatively avascular (e.g. osteomyelitis, necrosis, fibrosis, pus), then the tissue concentration may lag substantially behind the plasma concentration and this should be borne in mind when concentrations are interpreted.

Plasma concentrations are specially useful where the drug may have to be taken to near toxic doses, e.g. lithium, digoxin, where there is great individual variation and no frequent and easily measured response, (e.g. antidepressants), where a potentially toxic drug is being used in the presence of renal failure (e.g. streptomycin); and in some cases of poisoning (e.g. salicylate, barbiturate).

The difficulties before the physician lacking pharmacokinetic data are illustrated by a study of the antidepressant, nortriptyline, in which it was found that the optimum response was at intermediate plasma concentrations. The lack of benefit at low concentrations was expected; the lack at

* Plasma concentrations are usually the same as those in whole blood; but some substances are concentrated in erythrocytes, e.g. mercury, so that blood and plasma concentrations can differ.

high concentrations may be explicable by a developing blockage of the adrenergic receptor, so that the therapeutic effect of the drug (to raise monoamine concentrations at the central receptor by preventing reuptake of this transmitter into the releasing neurone) is countered.

The increased drug metabolism that results from enzyme induction does not always reduce the effect of drugs. If the effect of a drug is due to an active metabolite and the parent compound is inert, enzyme induction increases the formation of this active metabolite; thus there may be increased effect, with lower plasma concentration of the parent drug.

Metabolism

To be useful, a drug must not only enter the body reliably and reach the site of action but it must also be eliminated in a reasonable time. Some drugs, especially those that are relatively lipid insoluble and ionised are excreted unchanged by the kidney. Volatile anæsthetics are highly lipid soluble and, because of their volatility, present a special case of pulmonary elimination. But, in general, drugs that are highly lipid soluble and un-ionised will be reabsorbed by diffusion from the glomerular filtrate and would remain in the body indefinitely unless altered. To be eliminated, these highly lipid soluble drugs must be converted into lipid insoluble and ionised metabolites.

Brodie (*11*) illustrates the situation by estimating the rate of disappearance of drugs from the body if there were no drug metabolising enzymes. "For simplicity, let us assume that a drug is evenly distributed throughout body water. If the compound has a low lipid solubility, about five hours would elapse before half the substance is lost from the body; if the drug is also secreted by the tubules, this time will be shortened to as little as one hour. However, if the drug is lipid-soluble, the excretion rate will be drastically reduced by back diffusion into plasma from the tubular segment where the urine is concentrated. About 30 days would elapse before half the drug leaves the body. This extended duration might be a therapeutic advantage with an antibacterial agent but would be of doubtful value with an anæsthetic agent. If a drug (for example, mepacrine or thiopentone) is also reversibly localised in tissues its half-life would be about 100 years—considerably longer than those of the physician and patient combined!" (see also *half-life*).

Brodie suggests that since drug metabolising enzymes "are not the usual enzymes of intermediate metabolism (they) were developed in evolution to permit the organism to dispose of lipid-soluble substances—hydrocarbons, alkaloids, terpenes, sterols—ingested in food".*

"Of course, it is not conceivable that nature should have prepared, in advance, a specific microsomal enzyme for the oxidation of every existing or yet-to-be synthesised foreign substance; this would require an endless number of such enzymes". And it is fortunate that drug metabolising

* Fish lose lipid-soluble substances through the gills. They do not need such effective metabolising enzymes and they have not got them.

enzymes are extremely non-specific, attacking types of molecule rather than specific compounds. If such metabolism does not occur, lipid-soluble substances, except volatile anæsthetics, once inside the body "would be doomed to remain there for days, weeks, and, in many cases, even for months". The use in industry and agriculture of substances that are metabolised little or not at all presents an environmental hazard that is currently causing anxiety.

Drug metabolism occurs chiefly in the liver and is of two kinds:

1. *Conversion to pharmacologically inactive substances.*
2. *Conversion to pharmacologically active substances*, e.g. cortisone prednisone, phenacetin, imipramine, phenylbutazone, chloral, cyclophosphamide, oraganophosphorous insecticides.

In liver disease, therefore, drugs may have effects greater than expected or less than expected.

The amount and kind of drug-metabolising enzymes are genetically determined (see *pharmacogenetics*) and the rate of drug metabolism varies greatly between individuals, e.g. by a factor of ten times for dicoumarol and more for some antidepressants. Thus, therapeutic trials conducted with a single fixed dose are liable to mislead. Generally, even if a trial is to be conducted double-blind, it is practicable to allow for individual dosage adjustment.

Monovular twins have identical rates of drug metabolism whereas binovular twins differ as much as expected.

Suxamethonium provides a striking example of a genetic difference with which "disaster may strike if the unlucky patient and the careless doctor happen to coincide" (*11*).

Drugs are principally metabolised by enzymes in hepatic microsomes (a fraction of the cell endoplasmic reticulum), but also to a less extent by enzymes elsewhere in the cell and in the blood.

Two main kinds of chemical change occur:

1. **Non-synthetic:** the molecule is changed by oxidation, reduction, hydrolysis.
2. **Synthetic:** the molecule is conjugated with other substances, glucuronic acid (glucuronidation), acetic acid (acetylation), sulphate (ethereal sulphate formation).

Phenazone (antipyrine) is used as an experimental model for investigation of drug metabolism because only 10% is plasma protein bound, none is excreted unchanged and it is almost exclusively hydroxylated by hepatic microsomal enzymes, its half-life is 13 hours, and the rate of metabolism is genetically controlled (*7*).

Enzyme induction. Some chemicals, when administered over a few days or more induce an increase in microsomal drug metabolising enzyme activity (chiefly hepatic, but also extrahepatic) which is accompanied by increase in amino acid uptake and in total cell protein. That induction of

enzymes (which are proteins) is due to increased synthesis is suggested by the fact that inhibitors of protein synthesis, e.g. actinomycin D, prevent enzyme induction.

The time for onset and offset of induction depends on the half-life of the enzyme, but significant induction generally occurs over a few days and it passes off over 2 to 3 weeks following withdrawal of the inducer.

It is not known why some substances induce metabolising enzymes and why some do not. Inducing substances share two properties, they are lipid soluble and they are substrates, though sometimes only slight (e.g. DDT), for the enzymes.

Thus, a drug or environmental chemical can stimulate its own metabolism and, since these enzymes are non-specific, the rate of metabolism of other substances, including some normal constituents of the body.

Drugs known to induce enzymes to a clinically important extent include: hypnotics, anticonvulsants, antirheumatics. It would not be useful to try to provide a list as it would quickly be misleadingly out of date. However, such a list would include: phenobarbitone, phenylbutazone, phenytoin, primidone, carbamazepine, glutethimide, meprobamate. Other chemicals that induce enzymes include caffeine, ethyl alcohol, DDT, carcinogenic hydrocarbons and tobacco smoking. Penicillin induces penicillinase production in staphylococci.

Normal body constituents known to be affected by enzyme induction include: adrenal steroids, male and female sex hormones, calciferol, bilirubin.

Examples of the quantitative aspect in man are few, but in one study (7) 2 weeks administration of phenobarbitone reduced the half-life of a single dose of phenazone (antipyrine) from $12{\cdot}7 \pm 3{\cdot}3$ hours to $8{\cdot}0 \pm 1{\cdot}5$ hours, a reduction of 30% which, for many drugs could be clinically significant.

Enzyme induction can explain some drug interactions, and it also contributes to development of tolerance.

Response to enzyme inducers is genetically controlled, and slow metabolisers respond more than rapid metabolisers, presumably because the slow metaboliser has greater capacity for increase. Studies in monovular twins living together and apart indicate that enzyme inducers in the diet or environment are not of great practical importance. But subjects occupationally exposed to chemicals e.g. DDT (the most widely distributed man-made substance) could be significantly affected.

For enzyme induction as a source of *drug interactions* see under that heading.

Enzyme induction as therapy. Phenobarbitone stimulates hepatic glucuronyl transferase, the enzyme that conjugates bilirubin and it also increases bile flow. Given to pregnant women for 7 to 14 days before labour (it enters the fetus), phenobarbitone reduces the incidence of severe hyperbilirubinæmia in the neonate.* This is enhanced by also giving the drug to the infant at birth. It is probably worth using pheno-

* The water-soluble glucuronide is more readily excreted than bilirubin itself.

barbitone where hyperbilirubinæmia is expected, e.g. in rhesus hæmolytic disease (in which, although it probably will not eliminate the need for exchange transfusion it may reduce the need for repeated exchanges), and where induction of labour before term is planned. Ethanol has also been used for the same purpose (for 3 hours to 3 days before labour).

Possible risks to the infant include enchanced metabolism of steroid hormones and coagulation defect. Early protein feeding also lowers plasma bilirubin concentration, and barbiturates can reduce the infant's sucking capacity. As with so many ingenious notions, a careful evaluation of benefits and risks is needed.

Phototherapy (exposure of infants to day or to artificial light) also reduces hyperbilirubinæmia. It was introduced following the casual observation that serum specimens awaiting assay for bilirubin lost up to 30% of activity in one hour. The mechanism is not known. It is not enzyme induction.

Patients with familial unconjugated hyperbilirubinæmia (Gilbert's syndrome) and a degree of icterus that is socially embarrassing can be helped by phenobarbitone (30 to 60 mg orally t.d.s). If sleepiness is troublesome, the non-hypnotic barbiturate, phetharbital, can be used. Alternatively, glutethimide (500 mg orally) can be given at night. Chronic intrahepatic cholestasis may also respond.

Enzyme inhibition. See under *drug interaction.*

Excretion

Renal excretion. The following factors are important:

1. Extent of plasma protein binding of drug.
2. Glomerular filtration rate.
3. Amount of back diffusion from filtrate (influenced by urine pH).
4. Active renal tubular reabsorption.
5. Active renal tubular secretion.

See also under *pharmacokinetics* (for passage of drugs across lipoprotein membranes), *drugs and the kidney* and *drug interactions.*

Pulmonary excretion: see volatile anæsthetics.

Biliary excretion. Many drugs in the blood enter the bile, pass into the intestine, are reabsorbed (enterohepatic cycle) so that the stay of the drug in the blood is prolonged. They leave the body eventually in the urine. Others are ionised at intestinal pH and being insoluble in lipid remain in the gut.

Good entry into bile is important in treating infections of the biliary tract, including typhoid carriers. The following drugs reach substantial concentrations in bile: penicillins, tetracyclines, erythromycin, novobiocin, rifampicin. Sulphonamides and chloramphenicol enter bile poorly.

Milk. Unionised lipid soluble drug diffuses easily from blood into milk, but since the pH of blood and milk differ (blood 7·4, milk 7·0) the *total* concentrations of drug will not be the same in both fluids. Since

drugs in the milk are seldom of practical clinical importance the matter will not be pursued in detail here, but those with sufficient interest may care to engage in predictive exercises based on knowledge of whether the drug is an acid or base, it pK_a and the pH of blood and milk. For others, the following notes are provided.

It is probably generally true that if the mother needs drug therapy for serious disease, e.g. chloramphenicol for infection or imipramine for depression, she will not breast feed for reasons unconnected with the possible effect of the drug on the baby. Reliable data for human milk are scarce. *Streptomycin*, small amounts in milk, should not interfere with baby: *penicillin*, moderate amount in milk, may sensitise baby (see also below): *chloramphenicol*, concentration in milk 50% that in mother's blood, potentially hazardous to neonate, which has defective conjugating capacity: *tetracyclines*, small amounts appear in milk, probably bound to calcium and clinically insignificant: *isoniazid*, appears in same concentration as in mother's plasma: *adrenal steroids*, probably insignificant in milk: *barbiturates*, *alcohol*, *antihistamines*, *salicylates*, *chloral*, *narcotic analgesics*, *phenylbutazone*, *imipramine*, in ordinary doses have not been seen to have any important effect on the baby: *phenothiazine tranquillisers* appear in the milk, probably in clinically unimportant amounts: enough *diazepam* may enter the milk to affect the baby: *senna* has no effect on the baby, but other purgatives may have some effect, though slight: *ergot* preparations as used in migraine may affect the infant dangerously: *bromide* in toxic doses to mother, may affect the baby: *oral anticoagulants* appear in the milk and can dangerously affect the infant: in the unlikely event of breast feeding being essential the baby could be protected by 1 mg of a synthetic vit. K analogue per day: heparin is inactive orally: *antithyroid* drugs affect the baby.

It has been necessary to put a limit on the antibiotic content of cow's milk for sale (they are injected directly into the udder as well as i.m.) because cases of drug allergy have occurred in man, particularly from penicillin in milk. It is desirable that veterinary antibiotic preparations should contain one suitable marker substance to increase ease of detection of contamination by a range of antibiotics. If a cow, or a woman, eats garlic, onions or other strongly flavoured substances her milk may be flavoured; the possibility of encouraging infants with flavoured breast milk remains unexploited at present.

DRUGS AND THE KIDNEY

Chemicals damage the kidney by:

1. Direct biochemical effect.
2. Indirect biochemical effect.
3. Immunological effect.

The kidney is peculiarly vulnerable to *direct chemical injury* because it receives the peak plasma concentrations of all substances entering the

blood and because the process of concentrating the glomerular filtrate (200 l/day) into urine (1·5 l/day) inevitably means that renal tubule cells are exposed to much higher concentrations of chemicals than are other cells in the body. An important factor is the counter current mechanism,* both passive exchanger and active multiplier. This requires hypertonicity in the renal medulla, the maintenance of which is ensured by selective low blood flow with its inevitable accompaniment, low oxygen tension. In addition to being concentrated in the urine by reabsorption of water, substances pass across the tubule cells by both simple diffusion and active transport mechanisms. Thus renal cells are exposed to high concentrations of chemicals in both blood and urine.

Substances that can cause renal damage include:

Heavy metals (Hg, Au, Fe, Pb)
Antimicrobials (neomycin, kanamycin, colistin, amphotericin, sulphonamides)
X-ray contrast media (chiefly biliary agents)
Analgesics (phenacetin etc.)
Anticonvulsants (troxidone, paramethadione)
Solvents (carbon tetrachloride, ethylene glycol)

Some drugs cause renal damage by *indirect biochemical mechanisms*, e.g. uricosurics may cause precipitation of uric acid in the tubule, and damage can result from the hypercalcæmia of calciferol overdose as well as from severe electrolyte depletion (Na, K) due to excessive use of diuretics and purgatives.

The capillary endothelium is also vulnerable to drug-induced *immunological injury*.

A drug may cause damage by more than one of the above three mechanisms (e.g. sulphonamides).

Prescribing for patients with renal failure

Drugs may:

1. exacerbate renal disease,
2. be potentiated by accumulation due to failure of renal excretion.

Any drug that can cause renal damage will carry the first hazard. Tetracyclines cause an increase in protein catabolism and in the presence of renal failure a brisk rise in blood urea may occur, so that they are best avoided. Adrenal steroids can have the same effect.

Hospitalised patients with a serum nitrogen concentration above 40 mg/100 ml have been found to have an adverse reaction rate $2\frac{1}{2}$ times those whose concentration was below 20 mg/100 ml.

* The most easily comprehended countercurrent exchange mechanism (in this case for heat) is that in wading birds whereby the veins carrying cold blood from the feet pass closely alongside the arteries carrying warm blood from the body and heat exchange takes place. The result is that the feet receive blood below body temperature (which does not matter) and the, often very cold, blood from the feet is warmed before it enters the body so that internal body temperature is more easily maintained. The principle is the same for concentrating urine.

Problems of safety arise especially in patients with renal failure who must be treated with drugs that are potentially toxic and which are wholly or largely eliminated by the kidney. A knowledge of, or at least access to sources of, pharmacokinetic data is essential for safe therapy of such patients.

The importance of the matter is shown by the following data on antimicrobials *:

	Half-life in serum (hrs)	
Drug	*normal*	*oliguria*
Penicillin G	0·5	7–11
Cephaloridine	1·5	20–23
Tetracycline	8·5	57–108
Kanamycin	3·0	72–96
Streptomycin	2·5	52–100
Colistin	1·5–2·7	72–96

Relation of half-life of drug to renal failure. The best guide is creatinine clearance. If the creatinine clearance, i.e. the volume of plasma cleared of creatinine (or of free drug) by glomerular filtration, per min, is halved, then the half-life of the drug (or of creatinine) is doubled, if the clearance is only 25%, then drug half-life is quadrupled and so on. Kunin (*16*) suggests that only where creatinine clearance is less than 25% (blood creatinine and urea raised) is it necessary to reduce dosage of antimicrobials cleared by the kidney. He also usefully classifies antimicrobials thus:

1. *Drugs eliminated only by the kidney*, e.g. tetracyclines (but not doxycycline or chlortetracycline), streptomycin, polymyxins (including colistin), kanamycin, gentamicin, vancomycin, amphotericin B, sulphonamides. *Ordinary doses will accumulate in patients whose renal function is less than 25% of normal* (raised creatinine and urea concentrations in the blood).

2. *Drugs eliminated by non-renal mechanisms*, e.g. chlortetracycline, doxycycline, erythromycin, fusidic acid, chloramphenicol, novobiocin, isoniazid, nalidixic acid. Metabolites of these will accumulate in renal failure, but they do not seem to be toxic.

3. *Drugs intermediate between 1 and 2 above.* e.g. penicillins, cephalosporins, lincomycin, nitrofurantoin, co-trimoxazole, PAS.

It is clear that measurement of plasma concentrations will be useful when treating infections in patients with renal failure. But these facilities are not always available, and for short courses, arbitrarily reduced dosage schedules can be used safely. Maintenance dosage of the drugs in group 1 (above) should be reduced to about 25% of the normal and of the less toxic members of group 3 to about 50%. Priming, or loading doses, will obviously not require to be changed.

* KUNIN, C. M. *et al.* (1959). *Arch. intern. Med.* **104,** 1030.

Nitrofurantoin is so likely to produce peripheral neuropathy, that, although it is in group 3 (above) it should be avoided.

Further points of importance are:

1. *Sodium and potassium-containing drugs*, e.g. gastric antacids, potassium citrate etc. should be avoided and the composition of all effervescent preparations should be examined before prescribing them.

2. *Aluminium hydroxide* may be used as gastric antacid.

3. *Digoxin* will be potentiated, but not digitoxin, because the latter is inactivated in the liver: it is important to avoid doses that cause vomiting, for this will cause electrolyte upset.

4. *Hypotensives:* adrenergic neurone blockers accumulate and may be potentiated (excessive reduction in blood pressure reduces renal blood flow and may exacerbate renal failure), but then may also lose their effect. Methyldopa, thiazides and hydrallazine may be preferable.

5. *Diuretics:* ethacrynic acid accumulates (deafness) and so does mercury: where the glomerular filtration rate is low, most of the water and sodium will have been reabsorbed in the proximal renal tubule so that diuretics acting principally on the distal tubule (thiazides) are less effective. Frusemide acts on both proximal and distal tubule and so is the diuretic of choice in renal failure.

6. *Uricosuric agents* are ineffective in the presence of renal failure, but allopurinol, which blocks uric acid synthesis, is a useful alternative in gout, especially if the gout is the cause of the renal failure.

7. *Sedation* should be by drugs that are metabolised in the liver: chloral derivatives, nitrazepam, barbiturates (other than phenobarbitone and barbitone). Phenothiazine tranquillisers and antiemetics may accumulate.

8. *Anticonvulsants:* phenytoin and diazepam may be used.

DRUGS AND THE LIVER (*17*, *50*)

Many drugs are metabolised by the hepatic microsomal enzymes. The metabolites may be pharmacologically active (e.g. of cortisone, chloral, phenylbutazone, cyclophosphamide) or inactive (many drugs). Therefore when there is liver damage drugs may become either more or less effective. See also *enzyme induction.*

Drugs may also interfere with hepatic function, and Sherlock (*17*) classifies them thus:

1. **Interference with bilirubin metabolism.** This is of clinical importance in the newborn whose bilirubin conjugating microsomal enzymes are relatively underdeveloped so that either increased hæmolysis or bilirubin displacement from plasma albumin (by sulphonamides, synthetic vit K) can cause elevated free plasma concentration leading to kernicterus.

Novobiocin inhibits bilirubin conjugation.

Cholecystographic media compete with conjugated bilirubin for excretion.

C-17-substituted testosterone derivatives interfere with bilirubin excretion into the hepatic canaliculi and cause a cholestatic (obstructive type) jaundice, though the block is biochemical not mechanical. Drugs in this class include androgenic and anabolic steroids, oestrogens and progestogens (e.g. methyl testosterone, norethandrolone, methandienone, norethynodrel, mestranol) including those used as oral contraceptives. Androgens that are active only by injection, e.g. testosterone propionate, nandrolone esters, are not of this group and do not cause jaundice. Recovery ordinarily occurs on stopping the drug.

2. **Direct liver cell (hepatocellular) injury** occurs with carbon tetrachloride (renal damage too), tetracyclines (high i.v. doses), tannic acid (as used in barium enemas to make the barium stick to the mucous membrane), dicophane (DDT), arsenicals, iron, anti-cancer drugs, chloroform.

3. **Allergy or hypersensitivity.**

(a) *Hepatitis-like reaction*, which unfortunately is indistinguishable from acute virus hepatitis (infective hepatitis). It occurs with hydrazine MAO inhibitors, and other hydrazines such as isoniazid, pyrazinamide and ethionamide; halothane may cause it, also chloroform. It is unrelated to dose though it may be more frequent after multiple exposure. It may occur up to 3 weeks after stopping the drug. Mortality is high, about 20%.

(b) *Cholestatic injury*, i.e. the picture is of obstructive jaundice, though the block may be biochemical rather than mechanical [see 1 above].

It can be a direct pharmacological effect, i.e. dose-related, and all receiving the drug get the effect if enough is given, as with some steroids (1 above); there may also be a genetic predisposition. It can also be allergic, e.g. phenothiazine tranquillisers, when it is unrelated to dose and generally occurs within the first month of therapy. Recovery is usual. Direct cell injury can occur simultaneously.

(c) *Generalised drug allergies* may also involve the liver so that liver damage may occur with a wide range of drugs including penicillin, sulphonamides, PAS, erythromycin estolate and triacetyloleandomycin.

The reaction is usually cholestatic, but may be hepatocellular.

Morphine and the liver (*50*)

Even a small dose of morphine (8 mg) may induce characteristic EEG changes in a patient who has a history of hepatic encephalopathy though it will not do so in a patient with similar hepatic function who has no such history. This probably results from abnormal cerebral metabolism in such patients rather than from failure to metabolise the morphine in the liver, though disease of the liver can prolong its action. Larger doses of morphine are dangerous (coma) and it should be specially avoided in hepatic patients with a history of encephalopathy or with jaundice, ascites or gastrointestinal bleeding. Pethidine is safer than morphine.

Prescribing in hepatic disease

It is specially important that all drugs should be prescribed only if there are clear indications and the physician knows and is prepared to deal with any adverse effects. In severe liver disease brain metabolism is also abnormal (see above).

Some of the background is given above but the following notes may be added. **Antidepressants**: tricyclics are safer than MAO inhibitors.

For **sedation**: in encephalopathy of acute hepatic necrosis all sedatives are extremely dangerous (deeper coma) and mechanical restraint is the lesser evil. Otherwise the least hazardous drug is diazepam (Valium) orally; or in restlessness or convulsions, i.v. (5 mg) slowly (over 10 min) and repeated in 30 min and then up to 4-hrly: there is some risk of respiratory depression in severe cases.

For **pain**: avoid morphine; use paracetamol, codeine or pethidine, initially in low doses. For **cardiac glycosides** see ch. 19.

For **diuresis**, where hepatic cirrhosis is the cause of fluid retention, use sodium restriction and standard diuretics with spironolactone if necessary; proceed cautiously because of risk of electrolyte disturbance and precipitation of encephalopathy (monitor blood electrolytes frequently, even daily); hypokalæmia is dangerous; it is associated with extra-cellular alkalosis and a rise in blood ammonium, so give K and Cl.

Adrenal steroid therapy: some steroids are inactive until converted by the liver to an active form, e.g. cortisone to hydrocortisone: prednisone to prednisolone. These may thus be less effective in the presence of severe hepatic disease. But active steroids are metabolised to inactive compounds by the liver and so may be potentiated; lower than usual doses of these may suffice.

Antimicrobial therapy: ordinary doses are generally safe.

DRUG INTERACTIONS (*2, 3, 6, 51, 52, 87*)

Drug interactions may be desired or undesired. They are deliberately sought when sodium aminosalicylate and isoniazid are given together in the treatment of tuberculosis or when nalorphine is given to reverse respiratory depression due to morphine. On the other hand, "every time a physician adds to the number of drugs a patient is taking he may devise a novel combination that has a special risk."*

Although dramatic and unintended interactions attract most attention and are the principal subject of this chapter they should not distract attention from the many therapeutically useful interactions that are the basis of rational polypharmacy. These useful interactions are referred to throughout the book wherever it is relevant to do so and can be classified similarly.

It is salutary to be reminded that "when a patient receiving one kind of tablet is given another in addition, he sometimes hesitates, thinking that

* DOLLERY, C. T. in ref (2).

the second may 'interfere' with the first. A similar, though more sophisticated, notion should induce some thoughtful hesitation among prescribers. They should certainly not share the enthusiasm for combined preparations still shown by many drug firms—an enthusiasm which often goes far beyond the sparse pharmacological data available on such combinations".*

Doctors provide generous opportunity for the occurrence of interactions. In one hospital study, the average number of drugs per patient stay was six and the maximum was 21; the pharmacy stocked 2,000 preparations, amongst which the possible combinations were $6{\cdot}4 \times 10^{19}$!†

In a second hospital study above 40% of patients receiving drugs were taking six or more. The incidence of unwanted effects (not all of them were drug interactions, of course) in this group was about seven times that amongst patients taking less than six drugs.‡

In a third study the number of additional drugs given to hospital patients receiving methicillin (for staphylococcal infection) was counted. All received at least one other antibiotic and one (with nocardiasis) received 10; the average was 4. The total number of drugs received averaged 14, with a range from 6 to 32.

The patient who had 32 drugs was in hospital 48 days. They included adrenaline, metaraminol, theophylline, warfarin, vit K, chloral, codeine, atropine, diphenhydramine, pentobarbitone, chlordiazepoxide, calcium gluconate, morphine, nalorphine, aspirin, magnesia, neostigmine, dextropropoxyphene, digitalis, procainamide, chlorothiazide, mercaptomerin, ammonium chloride, mannitol, benzylpenicillin, methicillin, oxacillin, streptomycin, chloramphenicol and colistin; the diagnoses are not stated, nor the fate of the patient (53).

This list includes at least two interactions that were desired (warfarin, vit K: morphine, nalorphine) but which were sought because of the excessive action of the main therapeutic agents.

Some knowledge of the *pharmacological basis* of how one drug may change the action of another will be useful in obtaining those interactions that are wanted, as well as in preventing and recognising those that are not, for the numbers of drugs and of facts are already too great for it to be possible to remember them.

Drug interactions are of two principal kinds:

1. *Both drugs act on the target site of clinical effect*, exerting synergism, potentiation or antagonism, e.g. alcohol/barbiturate: morphine/nalorphine: streptomycin/isoniazid. In this type of interaction, the drugs have the same kind of agonist effect or are physiological or pharmacological antagonists.

2. *The drugs interact remotely from the target site of clinical effect* to alter plasma (and other tissue) concentrations so that the amount of drug at the target site of clinical effect or the sensitivity of the target site is

* Editorial (1962). *Lancet*, **2**, 818.
† Dollery, C. T. Personal communication.
‡ Wade, O.L. in ref. (1).

altered, e.g. enzyme induction (phenylbutazone/anticoagulant), competition for plasma protein binding sites (phenylbutazone/anticoagulant): thiazide diuretic/digoxin.

Drugs can interact at any stage from when they are mixed with other drugs or with substances used in pharmaceutical formulation to their final excretion either unchanged or as metabolites.

Interactions are exceedingly varied in kind, and in the following categorisation there has been some sacrifice of scientific precision in favour of simplicity, e.g. class 3(b).

Drug interactions occur—

1. *Outside the body:* formulation, or mixing by giver.
2. *At site of entry:* before, or at point of, absorption.
3. *Inside the body:* after absorption.
   (a) *at transit and storage sites:* non-specific receptors.
   (b) *at site of action or nearby:* specific receptors, enzymes, parasites, etc.
   (c) *by interference with biotransformation:* metabolism.
   (d) *at exit:* excretion.

That one drug can be shown measurably to alter the disposition or effect of another drug does not mean that the interaction is necessarily of clinical importance.

The examples that follow are all potentially important in therapy, and the term interaction has for convenience, been extended to include stability in solution and interaction with food and with natural substances in the body.

Interactions Outside the Body

(a) **Pharmaceutical interaction:** the preparation becomes disgusting or the ingredients separate. This is rare since doctors nowadays wisely confine their prescribing to preparations whose detailed constitution has been devised by pharmacists; the subject will not be considered further.

(b) **Chemical interaction:** is rare for the same reason. A case in which the interaction was between drug and pharmaceutical diluent has occurred. In 1968 in several Australian cities there was an outbreak of neurological disorder in epileptics. Initially, posterior fossa tumour was often suspected, but the clinical picture was compatible with anticonvulsant intoxication. The only drug being taken by all the patients (in Brisbane there were 51) was phenytoin, and they got better when phenytoin dosage was reduced. It was at first difficult to understand why patients, most of whom had not altered their dosage, should suddenly develop toxic effects. In most of the cases who could be investigated the blood level of phenytoin was found to be above the therapeutic range.

The affected patients were all taking the same brand of phenytoin. It was therefore possible that the currently used capsules might have acci-

dentally been filled with too much phenytoin or that the previously used capsules might have contained too little phenytoin. Samples were investigated and both were found to have the correct total amount of drug.

Enquiries revealed that some months before the first cases appeared the manufacturer had changed the diluting substance from a calcium compound to lactose. Patients were therefore treated alternately with the two types of capsule each containing the same total of phenytoin, but different diluents. Substantially higher blood levels occurred with the lactose diluent. Probably the phenytoin was interacting with the calcium diluent to form an insoluble complex so that absorption was reduced.

Some patients suffered, but there were others who became better controlled, showing that they had previously been treated inadequately. (See also *Pharmaceutical formulation and therapeutic efficacy*).

Examples

Thiopentone and suxamethonium interact chemically and should not be put in the same syringe.

Protamine zinc insulin contains excess of protamine which interacts with soluble insulin if this is drawn up in the same syringe.

Intravenous fluids

Intravenous fluids offer special scope for interactions (incompatibilities) when drugs are added to the reservoir. A principal factor causing interaction is change of pH. The concentration of drug in a mixture is also relevant to its stability, e.g. the more concentrated a solution of ampicillin, the greater its instability.

Drugs are commonly weak organic acids or bases. They are often insoluble, and to make them soluble it is necessary to prepare salts. Plainly the mixing of solutions of salts can result in precipitation or instability.

General advice

1. Do not add drugs to blood, amino acid solutions or to fat emulsions.

2. In the absence of special knowledge a drug should only be added to simple solutions (dextrose, sodium chloride, or a mixture of these). Sodium chloride (0·9%) is usually slightly acid (pH 5–6) due to dissolved CO_2. Dextrose (5%) is acid (pH 4–4·5) due to some breakdown to acid products resulting from heat sterilising and storage. The solutions have very little buffering capacity and pH readily changes with added drugs.

3. Interaction may occur without visible change in the solution, though if the infusion is to be brief absence of visible change during the course of the infusion gives ground for optimism that acceptable activity is retained.

4. All mixtures should be made immediately before use; do not make up a supply for the whole weekend on Friday night.

5. Single drug additions to simple solutions are likely to be safe; two or more are likely to interact.

6. The pharmacy or drug firm package inserts should be consulted wherever possible, for what you are using is not simply a drug, it is a preparation containing drug, stabiliser, preservative etc., all of which may be a source of interaction.

7. The examples given here apply to mixing a drug in the infusion reservoir. Where the drug is injected over a few minutes into the tubing near the patient and flushed in there is little time for interaction to occur.

Some examples

1. **Retention of major (about 90%) activity of antibiotics*** in simple dextrose (5%) and sodium chloride (0·9%) solutions:

penicillins retain a major proportion of activity for about 16 hrs (except methicillin 5 hrs). But ampicillin is stable in saline up to 24 hrs, though only about 1 hr in dextrose. Penicillins become less stable with increasing alkalinity, e.g. in presence of sodium bicarbonate.
cephalosporins retain major activity up to 24 hrs.
tetracyclines: about 10 hrs (they chelate with Ca, e.g. in Ringer-lactate infusion).
erythromycin: in dextrose, 4 hrs: in sodium chloride, 24 hrs.

2. **Heparin** can generally be added to infusions but is incompatible with hydrocortisone, tetracyclines, gentamicin, etc. and sympathomimetics.

3. **Noradrenaline** (4 mg in 1 litre, i.e. 4 mcg/ml) in dextrose or dextrose saline retains its potency (above 80%) for about 5 hrs; in blood or sodium chloride (0·9%) it is rapidly oxidised and this may be reduced by adding ascorbic acid (10 mg/litre).

4. **Other sympathomimetics,** also aminophylline, vit B complex and vit C are liable to interact with a wide range of drugs.

5. **Insulin** is stable in dextrose and sodium chloride solutions though about 20% is lost by binding to reservoir and tubing.

It is convenient to mention here the local thrombophlebitis that is a complication of i.v. infusions. Its frequency increases with the duration of the infusion, the acidity of the fluid (due to manufacturing requirements most i.v. infusion fluids are acid) and the amount of obstruction and damage to the vein caused by the catheter or needle. Protection lies in giving brief infusions into large veins, and in changing the site daily, if possible, where they must be prolonged. However, occasionally it is vital to maintain an infusion for days at one site. In such cases thrombophlebitis can be reduced by buffering the solutions, if practicable, or by adding 10 mg. hydrocortisone per litre (though this can reduce stability of penicillins). Where large volumes are being used for several days the

* Formulations differ, data are incomplete, there are many variables (pH, temp, concentration, etc.) and any data given by good drug firms about their preparations take precedence.

total dose of the steroid can significantly suppress endogenous hydrocortisone production.

Heparin, in doses that do not produce generalised reduction in coagulation, is probably ineffective in preventing local thrombophlebitis.

Interactions at Site of Entry, before Absorption

The complex environment of the gut offers extensive opportunities for drugs to interfere with each other as well as with gut physiology.

(a) **Gut motility.** Plainly, decreased motility (e.g. by anticholinergics) will increase the total absorption of drugs that are ordinarily slowly and incompletely absorbed (e.g. digoxin, tetracycline) and purgatives may decrease absorption by speeding passage. Decreased motility will also allow drugs to remain longer in the acid gastric environment with the results mentioned in the next paragraph.

(b) **pH of gut contents.** Changes in pH, by altering ionization and so solubility in lipids, can alter the rate of absorption.

Antacids raise gastric pH so that acidic drugs are more ionised, less soluble in lipids and so more slowly absorbed (e.g. oral anticoagulants, some sulphonamides, nitrofurantoin, salicylate, phenylbutazone). This effect has been shown to be sufficient to abolish the hypnotic effect of a dose of pentobarbitone, although ultimately the whole dose was absorbed (*3*).

When used in ordinary therapy these effects of antacids are probably of little practical importance, for an oral dose has soon (30 mins) substantially passed into the intestine where the absorbing area is much greater than that of the stomach and pH effects are trivial.

Benzylpenicillin is labile in acid and antacids can protect it. Phenoxymethylpenicillin is more stable in acid and is to be preferred for oral use.

(c) **Direct interaction in the gut.** Tetracyclines chelate with metals and in the presence of calcium, magnesium and aluminium-containing antacids absorption may be seriously reduced. Milk contains sufficient calcium for it to be necessary to avoid it as a major article of diet when taking tetracyclines. Iron, even in small amounts, seriously reduces tetracycline absorption.

Cholestyramine interferes with absorption of thyroxine and perhaps other drugs. Iron absorption is enhanced by ascorbic acid and reduced by carbonates, tetracyclines and desferrioxamine. Liquid paraffin reduces absorption of fat-soluble vitamins.

(d) **Alterations in gut flora** may affect drug responses. Antimicrobials can reduce vit K synthesis by gut flora and so potentiate oral anticoagulants.

(e) **Interference with absorptive mechanisms.** *Phenobarbitone* significantly reduces absorption of griseofulvin, but the mechanism is uncertain.

Monoamine oxidase inhibition in gut mucosa allows increased absorption

of tyramine (from foods) and other sympathomimetics that are substrates for MAO.

(f) **Other than in the gut.**

(i) See *hyaluronidase.*

(ii) *Vasoconstrictors* (noradrenaline, felypressin) are added to local anæsthetics to delay absorption and so usefully to prolong anæsthesia.

Interactions Inside the Body, after Absorption

(a) **Transit and storage sites.** Drugs sometimes interact directly in the plasma or tissues, e.g. protamine with heparin: desferrioxamine with iron: dimercaprol with arsenic. More important in clinical practice is the result of administering a drug with a high affinity for plasma protein (non-specific receptors) to a patient who is already taking another drug with a high protein affinity. When this is done, there is **competition for protein binding sites.**

If the second drug displaces the first, the proportion of the total blood level of the first drug that is free and available to act pharmacologically, to be metabolised and to be excreted will rise and there may be a substantial immediate increase in effect. If the first drug is more than 95% protein bound it is only necessary to displace a little to double the concentration of free drug.

Fluctuations in control of anticoagulant and oral hypoglycæmic therapy can be due to these factors, particularly if the interfering drug is given in varying amounts or intermittently. Unfortunately, because there are numerous protein binding sites, and because drugs have different affinities for these sites, the knowledge that a drug binds heavily with plasma protein (phenylbutazone and imipramine are both above 90% bound) is not, of itself, sufficient to allow prediction of clinically important interactions. In addition, small chemical differences between members of a series may be accompanied by big differences in protein binding so that generalisation to a group of drugs from knowledge of a single member is unlikely to be valid.

Some clinically important protein-binding interactions include:

clofibrate, a *chloral metabolite* (trichloracetic acid), *aspirin* (salicylate), *phenylbutazone*, *oxyphenbutazone* and *indomethacin* all displace and so potentiate warfarin and phenindione.

sulphonamides, *dicoumarol* and *salicylate* potentiate tolbutamide and methotrexate.

sulphonamides and *vit K* displace bilirubin and can cause kernicterus in the newborn.

Displacement by competition for tissue proteins other than blood also occurs, e.g. a 4-aminoquinoline antimalarial (mepacrine) prevents the tissue uptake of an 8-aminoquinoline antimalarial (pamaquine) causing serious toxicity from the latter. However other members of these two groups may be safely used together (e.g. chloroquine, primaquine)

though there is some variation in blood levels due to competition. This illustrates the statement made above that generalisations cannot be made from one drug to another of the same series.

The complexity of considerations involved in this type of interaction can be illustrated; when chloral hydrate was given to subjects taking warfarin it was found that there was greater anticoagulant effect with lower total plasma concentration of warfarin. At first sight this might surprise. The explanation suggested is that a metabolite of chloral (trichloracetic acid) displaces warfarin from plasma albumin, causing higher free drug concentration relative to bound drug, so that there is more of the active drug not only to produce its pharmacological effect, but also to be metabolised and to be excreted. The result is potentiation of warfarin effect with shortened half-life (50 hrs reduced to 30 hrs) and lower total plasma concentration (*10*). It is uncertain how important this interaction is in clinical practice.

(b) **Site of action and nearby.** This imprecise heading includes interactions at specific receptors: There are numerous examples of competition for specific receptors and use is made of, for example, selective antagonists to acetylcholine (atropine-like drugs) and to catecholamines (α and β adrenoceptor blockers) in therapeutics. Strictly, interaction with the agonist administered as drugs is sought only in cases of overdose (cholinergic drugs including anticholinesterases, and adrenergic or sympathomimetic drugs).

Examples, some of which are more complicated than the classic tissue receptor competition, but which involve competition, include:

α-adrenoceptor block against monoamine oxidase/cheese interaction.
nalorphine against morphine.
anticholinesterase against curare.
atropine against cholinergic drugs.
atropine against anticholinesterases.
pralidoxime against anticholinesterases.

This heading includes **other interactions of considerable variety.** The following list shows something of the range of possibilities:

indirectly acting sympathomimetics, e.g. most appetite suppressants, and tricyclic antidepressives antagonise hypotensives.

indirectly acting sympathomimetics are potentiated by monoamine oxidase inhibitors.

levodopa induces hypertension in presence of a monoamine oxidase inhibitor.

catecholamines that are substrates for monoamine oxidase (phenylephrine, orciprenaline, tyramine in foods), when taken orally after a monoamine oxidase inhibitor, are readily absorbed instead of being destroyed in the gut wall and so are greatly potentiated.

tricyclic antidepressants potentiate catecholamines.

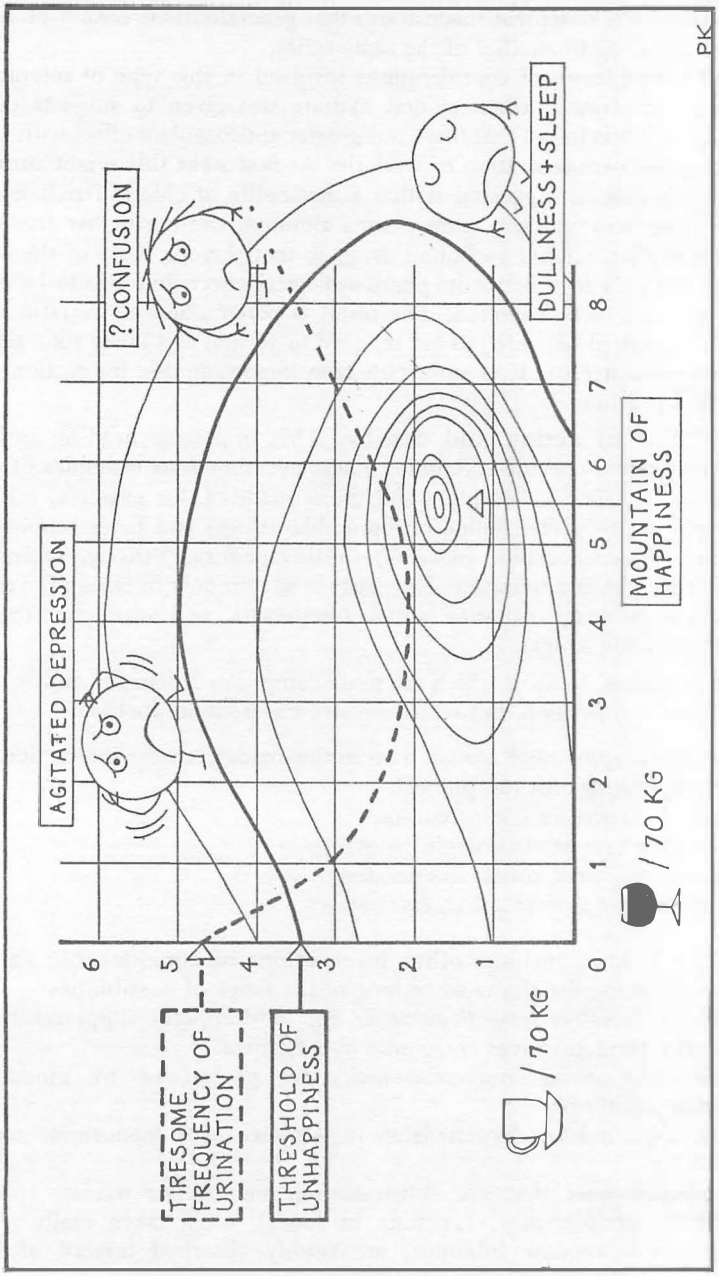
AGITATED DEPRESSION
?CONFUSION
DULLNESS + SLEEP
TIRESOME FREQUENCY OF URINATION
THRESHOLD OF UNHAPPINESS
MOUNTAIN OF HAPPINESS
/ 70 KG
/ 70 KG
0 1 2 3 4 5 6 7 8
1 2 3 4 5 6
PK

FIG. 2. **Interaction of two drugs: wine and coffee.** Diagram based on imaginary data representing some interactions between wine, and coffee taken 45 mins later. The dose of wine is plotted along the West-East axis, and that of coffee along the South-North axis, so that each point in the combined-dose field uniquely represents a particular combination of doses. In such a diagram the intensity of an effect for each such combination can be plotted along a third axis, upwards out of the plane of the paper, and these points then form a combined-dose/response surface.

This surface can be described in two dimensions by contour lines, like those which join points of equal height on maps. In this diagram these lines join points representing dose combinations that produce effects of equal intensity; the lines are called isobols (Greek, *isos:* equal; *bolos:* effect), and the diagram an isobologram. The continuous lines are isobols for different intensities of happiness, determined by a rating scale. The level of happiness in the SW corner (no alcohol, no coffee) is the 'usual' or control level. When the dose of wine alone or of coffee alone becomes large, happiness decreases, and this is shown by the line labelled threshold of unhappiness. The convexity of this line towards the NE indicates that coffee and wine reduce the tendency of the other to cause unhappiness (antagonism). The concentric isobols (which meet neither axis) in the SE quadrant represent higher levels of happiness than can be produced by either wine or coffee alone, and only occur when both are taken. The imaginary data show that happiness is most intense after about 6 glasses of wine followed by 2 or 3 cups of coffee—other things being equal.

The broken isobol represents a different effect, frequency of urination, at one level of intensity only, tiresomeness. When coffee is taken alone the frequency of urination can become tiresome. But when both are taken, frequency may increase, but it is not noticed as tiresome due to increased dullness (line turns to NE and peters out). The concavity of the first (W) part of this line indicates that there is potentiation. Note also that the mountain of happiness lies to one side of this isobol; happiness would be decreased by tiresomely frequent urination.

I am greatly indebted to Dr. Andrew Herxheimer for this ingenious figure and legend. D.R.L.

Such studies are complex but should be made if it is desired to develop combinations of drugs. The approach can be used for any effect, whether the euphoria of barbiturate/amphetamine combinations or for antibacterials. The details of such studies may not concern a busy physician but the principles deserve his notice.

aminophylline potentiates β-adrenergic effects: a cardiac risk in treating asthma.

neomycin and *streptomycin* have neuromuscular blocking activity and potentiate curare.

thiazide diuretics potentiate curare probably by inducing hypokalæmia.

(c) **Biotransformation (metabolism)**

(i) *Enzyme induction* (stimulation) (see above). Many drugs which are substrates for drug metabolising enzymes can induce an increase in synthesis of these enzymes with the result that the rate of metabolism of the inducing drug and of other drugs is increased. Since chlorinated hydrocarbon insecticides (DDT group), alcohol, some hypnotics, anticonvulsants, antidiabetics, antirheumatics, griseofulvin, and probably a wide variety of substances in the environment, including food additives, are enzyme inducers, enzyme induction can be considered a contributory factor to the normally encountered individual variation, i.e. much of the population is induced to varying degrees.

However, there are specially important situations in which a potent inducer is administered to a person who is being treated with a drug the action of which requires to be precisely controlled. A major example of this is oral anticoagulant therapy and it can be illustrated as follows—a patient is admitted to hospital with venous thromboembolism and treatment with an oral anticoagulant (e.g. warfarin) is commenced. A hypnotic (barbiturate, dichloralphenazone, glutethimide, etc.) is prescribed routinely because the ward is noisy and only the hardiest patients manage to sleep. Within a few days the hypnotic has induced the liver enzymes sufficiently to increase the rate of metabolism of the warfarin and the patient is stabilised on warfarin at an abnormally high rate of metabolism. When the patient returns to his peaceful home and no longer needs a hypnotic, the enzyme induction passes off over two to three weeks, the warfarin metabolism returns to a normal rate and the patient is now taking too much and may bleed. Conversely, a patient stabilised on warfarin at home, who enters hospital and begins to take a hypnotic that induces drug metabolising enzymes, may become underdosed.

If, at the same time, the patient also takes aspirin in large doses the situation may be complicated by competition for plasma protein binding sites, by risk of gastric erosion and by interference with prothrombin metabolism, all increasing the risk of bleeding.

It is a relief to know that nitrazepam is a useful hypnotic that does not significantly induce drug metabolising enzymes or otherwise interfere with anticoagulant therapy. It is also preferable in patients taking tricyclic antidepressants, plasma concentrations of which are lowered by barbiturate enzyme induction.

Enzyme induction by alcohol is a likely explanation of the tolerance shown by alcoholics to barbiturates, hydrocarbon anæsthetics and to tolbutamide. Barbiturate can cause relapse in steroid-treated asthma.

In treating epilepsy, enzyme induction can have practical importance. Both phenobarbitone and phenytoin are inducers, but as each is anticonvulsant this is of little practical importance when they are used together. However, if phenytoin is used alone and non-anticonvulsant inducers e.g. hypnotics or antirheumatics, are given, the result may be an additional and dangerous lowering of phenytoin blood and tissue levels.

Deliberate induction of enzymes can be exploited in therapeutics (see *drug metabolism*).

(ii) *Enzyme inhibition and competition.* Drugs that depress metabolising enzymes (chiefly drugs that interfere with liver function, e.g. alcohol) will potentiate other drugs whose intensity and duration of action are dependent on these enzymes. Interactions are seldom due to competition as in the case of specific drug receptors, for the enzymes are not specific for particular substrates and they are ordinarily in ample supply.

Examples of clinically important interactions are:

phenytoin metabolism is inhibited by coumarin* (but not by indandione) anticoagulants, by isoniazid (with slow inactivators only), by phenylbutazone, methylphenidate, disulfiram, sulphaphenazole (but not sulphadiazine), so that phenytoin intoxication may occur.

tolbutamide metabolism is inhibited, so that hypoglycæmia may occur, by phenylbutazone, by coumarin* (but not by indandione) anticoagulants, and by chloramphenicol.

purine analogues such as azathioprine and 6-mercaptopurine are metabolised by xanthine oxidase so that allopurinol (a xanthine oxidase inhibitor), which is used in gout to block the part played by xanthine oxidase in the synthesis of uric acid, can potentiate these toxic drugs.

alcohol metabolism is blocked, with accumulation of the unpleasant intermediary acetaldehyde, by disulfiram and to a less extent by sulphonylurea antidiabetics and metronidazole.

monoamine oxidase inhibitors (MAOI) are not selective for MAO and they also interfere with metabolism of narcotic analgesics, especially pethidine, barbiturates, anticholinergics and tricyclic antidepressants.

anticholinesterases, which see.

chloramphenicol depresses enzymes that metabolise warfarin, tolbutamide and chlorpropamide.

(d) **At site of exit from the body:** the clinically important interactions occur in the kidney.

(i) *Interference with passive diffusion.* Drugs that are soluble in lipids are reabsorbed from the glomerular filtrate by diffusing across the renal tubular cell membranes. Most drugs are weak electrolytes and the degree of solubility in lipids depends on the proportion of drug that is ionised (lipid insoluble) or unionised (lipid soluble). The degree of ionisation is affected by pH. The pH of the urine can be easily raised (by

* In the case of coumarins the interaction is *competition* for the same metabolic paths so that *both* drugs are potentiated as neither is fully metabolised. With enzyme *inhibition* only one drug is potentiated.

sodium bicarbonate) or lowered (by ascorbic acid). Thus the amount of drug that remains in the tubule lumen and is excreted in the urine can be influenced by the physician. *pH influences on renal excretion are only of practical importance with drugs:*

1. *that are excreted unchanged in the urine, and*
2. *whose ionisation constant is such that important changes in ionisation will occur over the range of pH that is obtainable in the urine.*

Changes in excretion sufficiently large to be useful in the treatment of poisoning can only be obtained over a limited range of dissociation constant (expressed as the pK_a, see *aspects of pharmacokinetics*). The ranges of pK_a which allows *useful* changes in excretion by altering urine pH are for bases pK_a 7·5 to 10·5 and for acids 7·5 to 3·00.

In the case of barbiturates, alkalinisation of the urine to its maximum pH, combined with diuresis, can usefully increase renal excretion of the longer acting compounds only. Alkalinisation is also clinically useful in salicylate poisoning. With pethidine and amphetamine, excretion is enhanced by urinary acidification but this is unlikely to be necessary in the treatment of poisoning though it can be used to increase the ease of detection of the drugs in the urine of "sportsmen" or of suspected addicts who deny taking the drugs. Reliable chemical identification allows the investigator the psychologically satisfying experience of accusing others of falsehood out of a sense of personal duty.

(ii) *Interference with active transport.* Organic acids are passed from the blood into the urine by active transport across the renal tubular epithelium. The bulk of penicillin is excreted in this way. Probenecid is an organic acid and competes with penicillin for this transport system so that penicillin excretion is reduced. The excretion of other organic acids can be reduced, e.g. some iodinated radio-diagnostic agents, para-aminohippuric acid (used for testing renal tubular secretory capacity) and PAS. Salicylates block the uricosuric effect of probenecid.

(iii) *Interference with glomerular filtration* may occur, e.g. aspirin may delay excretion of a radiodiagnostic agent, but more work is needed to define the importance of this.

DRUG COMBINATIONS (see also under *chemotherapy*)

This section refers to *combinations of drugs in a single pharmaceutical formulation.* It does not refer to concomitant drug therapy, e.g. in infections and in cancer, where several drugs are given separately to obtain increased therapeutic effect or range, or to treat more than one disease.

Combinations should not be prescribed unless there is good reason to consider that the patient needs *all* the drugs in the preparation, that the doses are appropriate and will not need to be adjusted separately.

Advantages of fixed-dose drug combinations

1. *Convenience* to the patient.
2. *Reliability of administration:* the patient has to remember one preparation only.

3. *Reliability and enhancement of therapeutic response*, where the drugs are synergistic, have a narrow dose range and, usually, a similar time-course of effect: e.g. oral contraceptives; isoniazid plus PAS; co-trimoxazole (Septrin, Bactrim); thiazide plus reserpine; Aspirin, Phenacetin and Codeine Tabs have sanction of time rather than of clinical science.

4. *Minimisation of unwanted effects* (*a*) *by including antidotes:* the combination of one tablet of potassium with a thiazide diuretic has obvious theoretical advantage. However, hypokalæmia is a less important disadvantage of thiazides used as antihypertensives than when used to produce fluid loss in œdema. In the latter case amounts of K larger than those generally included in the combined preparation are likely to be needed.

Combinations of oral broad spectrum antimicrobials with a fungicide are unnecessary for routine therapy but may be useful in patients specially at risk from superinfection (those taking immunosuppressives: the very old).

Narcotic plus narcotic antagonist combinations have not been shown to be safer than the narcotic alone, and the combination of analeptics or emetics with barbiturates to prevent death from acts of self-poisoning is an example of an ingenious idea that has not proved useful in practice.

(*b*) *By combining drugs that have the same therapeutic effect but different adverse effects* so that there is synergism for therapeutic but not for adverse effects, e.g. thiazide plus reserpine: Aspirin, Phenacetin and Codeine Tabs.

Disadvantages of fixed-dose drug combinations

1. *Impracticability of providing individual multi-drug preparations* because of the amount of labour and the complex pharmaceutical technology required (see sections on pharmaceutical formulation and interactions).

2. *Dosage of one drug cannot be altered without altering that of others.* Drugs with a wide range of dosage that must be adjusted to suit the patient's response (adrenergic neurone blockers) are best not combined with a drug for the same disease with a narrow dose range (thiazide, reserpine). Adrenocortical steroids should *never* be combined in one tablet with other drugs.

3. *Time course of drug action often demands different intervals* between administration.

4. *Irregularity of administration*, e.g. in response to a symptom, pain, cough, maybe desirable for some drugs, but not for others.

5. *Confusion of therapeutic aims:* routine use of combinations of iron with folic acid and cyanocobalamin are hazardous as they may delay diagnosis of pernicious anæmia. The fact that iron plus a little folic acid is properly used in pregnancy for routine anæmia prophylaxis simply confirms that combinations must be rationally thought out and adjusted to meet particular needs.

Combinations of antimicrobial drugs may be essential for particular situations, but they should be specially critically considered before prescribing.

Conclusions

A great many marketed combinations are open to criticism, some are positively desirable and some have the sanction of time alone. Occasionally, an advantage can be justified in theory but may be insignificant in practice. Some combinations are marketed to fulfil a commercial rather than a medical need.

Before prescribing a combination the doctor should pause to consider whether any of the ingredients is unnecessary; if it is, the combination should not be prescribed. It can never be justifiable to give a patient a drug he does not need in order to provide him with one that he does need. The fact that doctors sometimes prescribe combinations in ignorance of the exact ingredients, which are commonly not indicated by the name, and are then surprised to find the patient is taking an undesired drug provides a sad criticism of the medical profession, as does the fact that some of the available combinations are prescribed at all.

DOSAGE: ACCUMULATION (*39*, *88*)

The clinician, unlike the pharmacologist, is usually concerned with the individual, and not with groups. He is therefore less concerned with the shapes of the classical dose-response curves, since for him individual variation is all-important.

Sometimes in therapeutics *graded responses* are required; for instance, it may be desired to reduce, but not to abolish, intestinal motility or consciousness, and the dose of a drug may have to be adjusted accurately. Sometimes a *total response* is required, for instance in chemotherapy, in which dosage is less individual, for the drug is aimed at the microbe rather than at the patient. The intention is that the dose should be supramaximal and should exceed the effective dose for all the parasites. At other times, where the therapeutic potential of the drug is limited by low efficacy or by unwanted effects occurring at a dose below the therapeutic, the *maximum tolerated dose* is used. Examples will be found throughout the book.

In most cases the **dosage schedule**, i.e. amount of drug and the interval between doses, is determined most accurately if the pharmacokinetics (absorption, distribution, elimination) of the drug is known. Sometimes the initial dose is the same as that to be given throughout the course of therapy (most antimicrobials), sometimes a priming or loading dose is needed (some antimicrobials, digitalis) and at other times the dose is adjusted in the light of clinical response (hypertension). Increasingly it is being appreciated that drug therapy can be improved if plasma concentrations are measured, especially when the clinical condition does not change rapidly in response to changes in dosage (e.g. epilepsy, depression)

and to help explore and remedy unexpected failure or toxicity. The concentration in the plasma is commonly, though not always, related to that at the site of action. Consideration of the planning of antibacterial therapy shows well the utility of measurement of blood (or urine or cerebrospinal fluid) concentrations after different amounts, by different routes, under different conditions (before or after food) in the presence and in the absence of disease, including disease of the organs of metabolism (liver) and excretion (kidney).

Plainly it is impossible for a clinician to know and to think out the implications of all the pharmacokinetic factors of the drugs he uses. But there is one measurement that can be conveniently remembered and that is useful in thinking about drugs. This is the **half-life** ($t_{\frac{1}{2}}$).

Like so many laboratory measures on patients, the half-life requires interpretation, as it is influenced not only by every aspect of pharmacokinetics but by genetic factors and by disease (e.g. of organs of metabolism and excretion). Despite this, it is a useful concept.

The $t_{\frac{1}{2}}$, as the term suggests, means the time in which a measure (concentration, effect) declines by one half. It can be measured in three principal ways, of which the **plasma** $t_{\frac{1}{2}}$ is the most usual as it is generally the most informative and also the most convenient technically.

1. **plasma half-life:** the time in which the plasma concentration falls by one half.

2. **biological or elimination half-life:** the time in which the total amount of drug in the body after equilibration of plasma with other compartments (fat, muscle, etc.) is halved.

3. **biological effect half-life:** the time in which the pharmacological effect of the drug, and of any active metabolites, has declined by one half (this term is not in general use, but is introduced here as it expresses a useful concept).

Obviously the clinician is chiefly concerned with duration and magnitude of biological effect. Sometimes the *biological effect* $t_{\frac{1}{2}}$ can be provided with reasonable accuracy e.g. with drugs that act competitively on receptors, (α- or β-adrenoceptor blockers). Often it cannot be provided, e.g. with antibiotics, where the determining factor is the sensitivity of the infecting organism, and so the biological effect $t_{\frac{1}{2}}$ varies with each infection.

The *biological* $t_{\frac{1}{2}}$ is not easily obtained, except with radio-isotopes, for which total amount in the body is relatively easily measured. Although it is often similar to the plasma $t_{\frac{1}{2}}$, it may differ, e.g. some drugs are unevenly distributed as a result of concentration in fat or binding to tissue proteins, sites that are not necessarily related to those where the pharmacological effect is manifested.

The *plasma* $t_{\frac{1}{2}}$ is often closely related to the concentration at the site of biological (pharmacological) effect, is comparatively easily measured and is a resultant of the numerous and variable processes discussed in this chapter. It is influenced by route of administration, diffusion into tissues, plasma protein and tissue binding, metabolism and renal excretion, which

are subject to individual variation. Despite this, knowledge of the half-life intelligently interpreted gives a general guide to dosage schedules, to prediction of duration of effect and to the handling of cases of overdose.

Defects of the plasma $t_{\frac{1}{2}}$ as a guide include uneven drug distribution and storage and the formation of active metabolites, (which may not be measured) e.g. vit D has a plasma $t_{\frac{1}{2}}$ of mins-hrs, but its biological effect $t_{\frac{1}{2}}$ is about six weeks and is due to storage of active metabolites. For some drugs effect persists after disappearance of the drug from the plasma, e.g. reserpine, MAOI (see "hit and run" drugs).

Another relevant factor is whether the plasma $t_{\frac{1}{2}}$ is measured after a single isolated dose, when it is greatly affected by distribution into the various body compartments, or whether it is measured during continuous, steady-state, administration when there is established equilibrium between plasma and other body compartments.

Thus half-lives must always be considered in the light of knowledge of:

1. Whether the drug is metabolised or eliminated unchanged; metabolism shows great individual variation (genetical) whereas the physicochemical factors on which elimination of non-metabolised drugs depend are relatively constant.
2. Whether the drug is itself active or is converted to an active metabolite.
3. Whether the drug has irreversible action (see "hit and run" drugs).
4. Presence of disease of the organs of metabolism or excretion.

Half lives are given in the text where they are known and seem particularly relevant. A few are listed below so that they can be pondered in relation to clinical practice. Data from different sources often vary greatly, but the following are probably reasonably accurate.

Plasma half-life of some drugs

digoxin	48 hrs	tolbutamide	5 hrs
digitoxin	212 hrs	insulin	40 mins
paracetamol	4 hrs	hydrocortisone	1·7 hrs
aspirin	4 hrs	glyceryltrinitrate	35 mins
phenylbutazone	60 hrs	benzylpenicillin	30 mins
lignocaine	20 mins	ampicillin	1 hr
caffeine	4 hrs	tubocurarine	12 mins

Drug accumulation: some theory

In order to understand how a steady state of plasma concentration can be achieved quickly and maintained, it is necessary to consider how drugs accumulate in the body. From the moment a drug enters the body its elimination begins and for most drugs the rate of elimination is high for high plasma concentrations and low for low concentrations; but in either

case the $t_{\frac{1}{2}}$ is constant (*exponential or first-order kinetics*). It is generally true that if a drug is repeatedly given at intervals of its half-life, it will reach a steady state (in fact, fluctuating between the maximum concentration produced by the first dose and twice that concentration) after the fourth dose. Quicker attainment of a steady state is achieved by giving a priming dose sufficient to achieve the effective level followed by half that dose at half-life intervals.

But with some substances elimination is constant regardless of plasma concentration, e.g. alcohol 10 ml/hr (*zero-order kinetics*) and $t_{\frac{1}{2}}$ varies with the amount in the body.

Butler* has illustrated the difference in ***half-life*** that may result from three factors, ***distribution, renal excretion and protein binding*** for a drug that is not metabolised, thus:

* Butler, T. C. (1958). *Fed. Proc.*, **17**, 1158.

1. *A substance distributed in total body water* and
   (a) reabsorbed by renal tubule in the same proportion as water—half-life 24 days.
   (b) not reabsorbed by the tubule—half-life 280 min.
   (c) secreted at maximal rate by tubule—half life 50 min.
2. *A substance distributed in extracellular water only* and secreted at maximal rate by the tubule—half-life 15 min.
3. *A substance heavily bound to plasma albumin and to tissues*, with resulting low free plasma concentration, and reabsorbed by tubules in proportion to water—half-life 93 years.
4. *A substance as in* (3) *but with maximal tubule secretion*—half-life 49 days.

Clearly, with substances that are also metabolised the half-lives are greatly shortened, and, in fact, drug metabolism is a major factor affecting the half-life.

It can be stated generally that with a drug that is *quickly* absorbed and *slowly* excreted (long half-life) a dose that is sufficient to give an almost immediate therapeutic concentration will, if repeated daily result in toxicity due to accumulation of the drug. Equally, a dose that is sufficient to *maintain* indefinitely a steady therapeutic concentration, will if given from the outset, fail to provide a therapeutic level for some days. For example, if a drug having a half-life of 48 hours is taken 12 hourly each dose will enter the body in which most of the previous 2 or 3 doses still remain so that the drug will accumulate in the body in a stepwise fashion, eventually reaching a plateau (after many days) when percentage daily elimination balances the dose taken.

Thus a standard dose of such a drug will provide, if high, immediate therapeutic effect followed by toxicity, or, if low, delayed therapeutic effect with safety. Neither of these arrangements is acceptable in therapeutics.

The solution has been found in giving a single substantial **priming or loading dose** followed by a lower regular maintenance dose, and this is

necessary where the half-life of a drug is more than a few hours. These dose regimens can be quickly worked out if details of pharmacokinetics are known.

With a drug that is *quickly* absorbed and *quickly* excreted (short half-life) the dose that provides a therapeutic level is also used for maintenance. However, with the most rapidly excreted drugs blood levels will fluctuate more than in the case of those more slowly excreted.

Unfortunately, even where he is capable of doing such arithmetic, the physician has not available the data on ideal plasma concentration, on absorption, metabolism and excretion for the particular drug preparation in the individual patient before him that would be necessary to devise dosage schedules. The above theory has to be put into practice empirically. Also, it is neither convenient nor necessary to administer drugs at half-life intervals. But the attainment and maintenance of therapeutic concentrations is influenced by the factors determining the half-life at whatever intervals the drug is given.

Accumulation occurs with drugs having a long half-life that are also given frequently, and the reason is described above. Digoxin, digitoxin, thyroxine, lithium and bromide are all notorious for accumulation. It is obvious that any drug will accumulate in the body if it is prescribed too frequently, i.e. without regard to its half-life, or if metabolism or excretion are blocked, e.g. penicillin in presence of probenecid, and disease of liver or kidney.

Some examples: Digoxin, morphine, penicillin and sulphonamides provide examples. *Digoxin* is quickly absorbed and slowly excreted (half-life 48 hrs). For quick action a *loading or priming dose* (see Ch. 19) is necessary to get the plasma concentration into the therapeutic range. Once there, as it is slowly eliminated, quite a small daily maintenance dose (0·25 to 1·0 mg.) is sufficient to keep it there. If the priming dose were repeated daily accumulation would be rapid and toxicity would soon result. If the maintenance dose were used from the outset, the therapeutic response would be delayed for days.

The useful duration of action of *morphine* is about 4 hrs. and the same dose is used repeatedly, because it has a short half-life and most of the drug has left the body by the time the next dose is needed. If morphine were given hourly (which would be ridiculous), it too would, of course, accumulate.

Benzylpenicillin (half-life 30 min) is so non-toxic that a dose that will raise the blood level several times higher than that expected to kill all the organisms is given at once and the same dose is repeated about 6 hrly for maintenance. If such relatively enormous doses could not be given, the drug would have to be given inconveniently often or by continuous infusion.

Sulphonamides, on the other hand, are comparatively toxic, and unduly high blood levels must be avoided, yet they must be above the minimum inhibitory concentration for the infecting organism. With those that are

rapidly absorbed and rapidly excreted (half-lives about 5–15 hrs.) a loading dose is given followed by about half that amount 4 to 8 hrly, for maintenance. With those that are rapidly absorbed and slowly excreted (half-lives about 40 to 60 hrs.) a loading dose is followed by about half that amount 24 hourly.

The choice of sulphamethoxazole for combination with trimethoprim in the antibacterial co-trimoxazole is because the half-lives of the two substances are similar (about 10 hrs.), but differential excretion can occur in renal disease and this may lead to development of bacterial resistance because the ratio of drugs is altered from the optimum.

Drugs that are very rapidly metabolised must be given by constant i.v. infusion to maintain a steady state, e.g. noradrenaline, oxytocin.

Calculation of dose

In animal work it is usual to calculate dose according to *weight*, although there is evidence that surface area may be more appropriate, perhaps because the *surface area* is directly proportional to the metabolic rate.

In clinical practice the dose of most drugs is chosen in the light of experience, with little regard to variations in the size of patients, e.g. digitalis, diuretics, analgesics. For drugs whose dosage needs calculating (in adults or children), the best correlation is with surface area, though the same results are got by calculating dose on body weight to the 0·7 power. Fig. 3 relates body weight to percentage of adult dose on this basis, and its use is recommended where a calculation has to be made and only the adult dose is known.

For *infants* there is no reliable formula and if the proper dose of a drug is not known it must be ascertained (*42*), because the risk of intolerance is substantial. This is largely because the mechanisms of metabolism and excretion of drugs are not fully developed in infants. In any case, for all patients, size is only one of many factors determining response. The *aged* are also liable to be intolerant and lower doses should be used.

Drug dosage can be of five main kinds:

1. *Fixed dose.* The effect that is desired can be obtained at well below the toxic dose (many mydriatics, diuretics, analgesics, oral contraceptives, antimicrobials) and enough drug can be given to render individual variation in pharmacokinetics clinically insignificant.

2. *Variable dose with crude adjustments.* Here fine adjustments make comparatively insignificant differences and the therapeutic end-point may be hard to measure (depression, anxiety), may change only slowly (thyrotoxicosis, epilepsy), or may be limited by pathophysiological factors (diuretics, analgesics, allopurinol, adrenal steroids for suppressing disease).

3. *Variable dose with fine adjustments.* Here a vital function (blood pressure, blood sugar) which often changes rapidly in response to dose changes and which can be easily measured repeatedly provides the end-point. Adjustment of dose must be accurate. Adrenocortical replacement

therapy falls into this group whereas adrenocortical pharmacotherapy falls into (2) above.

4. *Maximum tolerated dose* is used where the ideal therapeutic effect

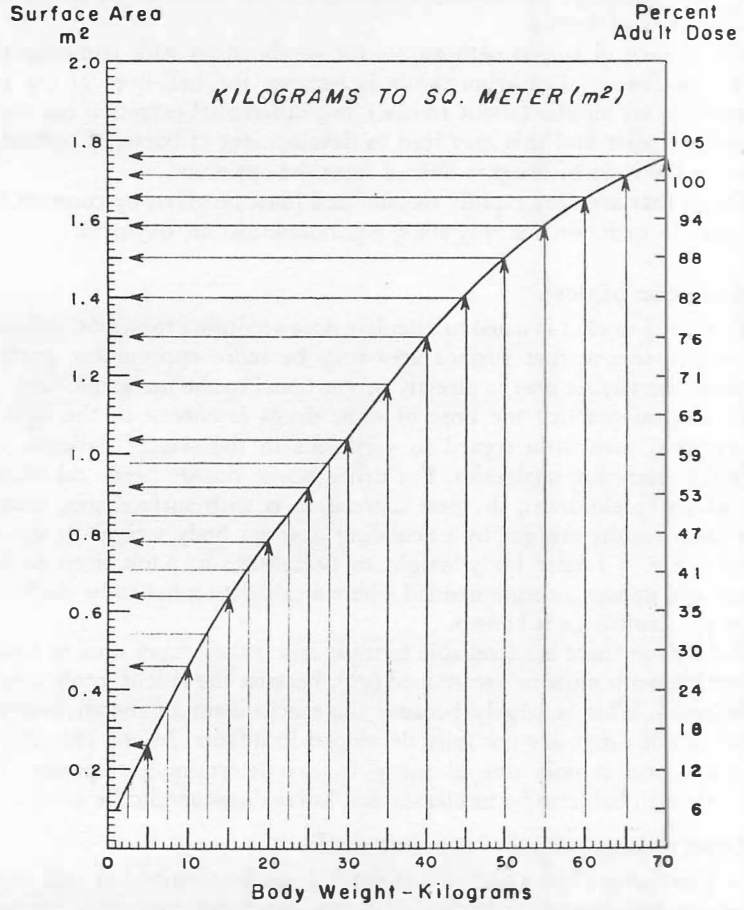

FIG. 3. **Chart for estimation of dose from body weight and surface area.** The figures on the right show what per cent of the adult dose should be given. (By courtesy of the authors and publishers; Talbot, N. B., Richie, R. H., and Crawford, J. D. *Metabolic Homeostasis: a syllabus for those concerned with the care of patients.* Cambridge: Harvard Univ. Press, 1959.)

cannot be achieved because of the occurrence of unwanted effects (anti-cancer drugs: some antimicrobials).

A usual way of finding this is to increase the dose until unwanted effects begin to appear and then to reduce it slightly.

5. *Minimum tolerated dose.* This concept is not so usual as the above, but it applies to long-term adrenocortical steroid therapy against inflammatory or immunological conditions, e.g. in asthma or rheumatoid

arthritis the dose that provides symptomatic relief may be so high that serious adverse effects are inevitable if it is continued indefinitely. The patient must be persuaded to accept incomplete relief on grounds of safety. This can be difficult to achieve.

ROUTES OF ADMINISTRATION

Commonsense considerations of anatomy, physiology, pathology, pharmacology, therapeutics and convenience determine the route by which a drug is administered. In general, drugs are given orally on an empty stomach for maximum absorption, or after food if irritant, or if it is desired to avoid high peak plasma concentration, e.g. antihypertensives, unless there is a good reason to use another route; they are usually absorbed from the small intestine. Parenteral administration is generally chosen when speed or reliability are especially desired; or when the drug is irritant or is not absorbed from the gut. Some notes follow.

Oral administration by swallowing

(a) **For systemic effect:** *Advantage*—convenience, but whether given before or after food is of importance with some drugs (e.g. cloxacillin gives markedly higher plasma concentrations if taken before food).

Disadvantages—absorption may be slow or irregular, especially after food, and drugs are exposed to hepatic metabolism before reaching the general circulation: some drugs are not absorbed (streptomycin), some drugs are destroyed in the gut (insulin, oxytocin, some penicillins).

(b) **For effect in gut:** *Advantage*—drug is introduced at site of action (streptomycin, some sulphonamides, carbenoxolone) and with non-absorbed drugs the local concentration can be higher than would be safe if the drug were also in the blood.

Disadvantage—drug distribution may be uneven and, even in diseases of the gut, it may be desirable to obtain effective blood levels if the disease affects the whole thickness of the gut wall (severe bacillary dysentery, typhoid).

Oral administration sublingually for systemic effect

Advantages—lipid soluble drugs pass readily across the mucous membrane and enter the general circulation without passing through the liver: useful where a quick effect is wanted (glyceryl trinitrate, isoprenaline, ergotamine): tablets are chewed and the fragments held in the mouth.

Disadvantage—inconvenient for frequent regular use: irritation of mucous membrane.

Intravascular administration

Advantages—immediate effective blood level: rapid modification of dose: immediate cessation of administration if unwanted effects occur: administration of drugs that are not absorbed from the gut or that are too

irritant (anticancer agents) to be given by other routes: drugs that are rapidly destroyed can be infused continuously (oxytocin).

Disadvantages—hazard is great if drug is given too quickly as blood level may rise at such a rate that normal mechanisms of distribution and elimination are outpaced. The heart and brain are particularly liable to give a dramatic response, e.g. it is dangerous to give Adrenaline Inj. B.P. (1 mg/ml) i.v. at all, and aminophylline and iron can cause cardiovascular disturbances unless given slowly. Indeed *all* i.v. injections should be given slowly so that they are diluted by the blood. The arm to tongue circulation time is 13 ± 3 sec, and 4 or 5 circulation times is a reasonable allowance. The technique requires enough skill to limit its use to people who have had some special training. Thrombosis is liable to occur, particularly with prolonged infusions. An overdose is both less recoverable as well as more effective than if it has been given orally.

The i.v. route is usual, but intra-arterial administration is sometimes used to perfuse an organ (liver, limb) with a drug that is rapidly tissue bound or metabolised, thus avoiding a systemic high blood concentration (nitrogen mustard). Thrombosis is more serious in an artery than in a vein and patients have sometimes lost an arm when thiopentone solution (pH 11·0) has been accidentally injected into the brachial artery which lies so close to the veins in the antecubital fossa.

Subcutaneous injection

Advantages—reliable and rapid action: acceptable for self-administration where essential: depot preparations (hormone implants) can be used.

Disadvantages—less convenient than oral administration: irritant drugs cause pain, poor absorption in peripheral circulatory failure (shock).

Intramuscular injection

Advantages—reliable, and perhaps more rapid than subcutaneous injection (soluble preparations absorbed within 10 to 30 min): irritant drugs can be given: depot preparations (penicillins) can be used: less affected by peripheral circulatory failure than subcutaneous (but i.v. preferred in this state): plasma concentrations higher in ambulant than in resting patients.

Disadvantages—not acceptable for self-administration: liable to be painful.

Inhalation

Drugs are given as *gases*, or as *aerosols*, i.e. clouds of liquid or solid particles of less than 10 microns diameter, so that settling velocity is low.

Advantages—enormous area for rapid absorption (general anæsthetics): high local concentration for effect on bronchi (isoprenaline, cromoglycate): self-administration practicable.

Disadvantages—special apparatus needed: drug must be non-irritant if patient is conscious: for local effect bronchi should not be obstructed (mucus plugs in asthma): particle size is critical, if too big (more than

7 microns) they will not reach small bronchi, if too small (less than 1 micron) they will be exhaled.

Rectal (for systemic effect: suppositories or solutions)

Advantages—drugs irritant to the stomach can be given by suppository (aminophylline, indomethacin): in vomiting (motion sickness, migraine): where cooperation is lacking (sedation in children).

Disadvantages—psychological, the patient may be embarrassed or may like the route too much: rectal inflammation can occur with repeated use: absorption can be unreliable, especially if the rectum is full of faeces.

Topical application (to skin, eye, anal canal and rectum, vagina etc.)

Advantage—provides high local concentration without systemic effect (usually).

Disadvantage—absorption can occur, especially where there is tissue destruction so that systemic effects result (adrenal steroids and resorcinol to the skin: atropine to the eye).

Other routes. Intrathecal, intradermal, intranasal, intrapleural, etc. are used when appropriate.

ASPECTS OF DRUG ACTION

Circadian Rhythms and Drug Action (*98*)

Circadian (Latin: *circa* = about; *diem* = day) rhythms occur in many physiological functions relevant to drug action, e.g. hepatic microsomal activity, C.N.S. sensitivity to depressants, urinary excretion, adrenocortical function, blood volume. Knowledge is still limited and there has been little application to prescribing except with adrenal steroids (larger doses in morning) and hypotensives with long $t_{\frac{1}{2}}$ (low morning blood volume with morning hypotension).

Pharmaceutical Formulation and Biological Availability (*4*, *42*, *89*, *90*)

If the same total dose of two drug preparations is given to a patient, it cannot be assumed that the amount absorbed will be identical, for the biological availability* of the drug may not be the same in each case.

When a patient is treated with a drug he does not generally receive the drug alone. He receives a complex mixture of the drug with other substances which are added to allow the drug to be offered in a convenient, stable and easily manufactured form.

Physicians tend to ignore pharmaceutical formulation as a factor in variable or unexpected responses, probably because they do not understand it and feel entitled to rely on others to provide reliable potent preparations. Good drugs firms reasonably point out that, having a reputation to lose, much trouble is taken to make their preparations

* The percentage of drug released from a formulation that becomes available for biological effect.

consistently reliable. This is a matter of great importance where dosage requires to be precise (anticoagulants, antidiabetics, adrenal steroids) though considerably less so where precision is unimportant (iron, aspirin).

With tablets, particle size (surface area exposed to solution), diluting substances, tablet size and the pressure used in the tabletting machine can affect the biological availability of the drug. A particularly florid example (phenytoin) is described under *interactions*.

Thus, when a preparation is changed, as when a patient goes home from hospital and obtains his drug from a different source, this can be tantamount to changing the dose of the drug. "A very unfortunate case occurred sometime ago in a doctor who had prescribed aconitine to a patient and gradually increased the dose. ***He thought he was quite certain that he knew what he was doing.*** The druggist's supply of aconitine ran out, and he procured some new aconitine from a different maker. This turned out to be many times stronger than the other, and the patient unfortunately became very ill. ***The doctor said, 'It cannot be the medicine'***, and to show that this was true, he drank off a dose himself, with the result that he died. So you must be careful to remember the difference in the different preparations of aconitine" (Lauder Brunton, 1897).

But it is important not to exaggerate the risk of changing formulations; in one study of six formulations of isoniazid it was found that biological availability was similar and they were therapeutically equivalent (*91*). But digoxin formulations vary, which is serious.

Prolongation of Drug Effect

The most obvious way to prolong a drug effect is to give a larger dose, for, although the half-life may not be changed, the plasma concentration will be at or above that which is effective for longer. This is, of course, only practicable with relatively non-toxic drugs, e.g. benzylpenicillin, for initial peak plasma concentrations will be very much higher. But doubling the dose does not double the duration, for example, 12 mg benzylpenicillin given each hour will maintain the plasma concentration above a particular minimum. Hourly injections are not acceptable, however, and if the same minimum is required with 6-hrly intervals, each dose would have to be 360 mg! But an even as well as a prolonged effect is usually needed and this has led to the development of *delayed-absorption* preparations (e.g. procaine penicillin) in which the physical properties of the drug are altered.

To prolong drug action by delaying metabolism involves either altering its chemical formula to make a new drug, e.g. the barbiturate series, or interfering with the metabolic path, e.g. blocking the enzyme responsible for its destruction (anticholinesterases). *Delaying excretion* is seldom practicable, the only important example being the use of probenecid to block renal tubular excretion of penicillin.

Oral preparations designed to give slow continuous release of drugs in the intestine are becoming popular. The possible advantages are

obvious; frequency of medication is reduced, which is convenient for the patient and may be more efficient for that reason, i.e. a single morning dose is less likely to be forgotten than are 3 or 4 doses in the day. In addition, slow release preparations may avoid local bowel toxicity (e.g. ulceration of the small intestine with KCl tablets) due to high local concentrations and may also avoid the toxic peak plasma concentrations that can occur where dissolution and absorption of the formulation is rapid. Greater success has been had with preparations aimed to reduce local bowel toxicity (KCl, Fe) than with those aimed at producing prolonged even absorption and effect. Where reliable absorption and accurate dosage are essential slow release preparations cannot yet be relied on.

The great variability of the functions of the stomach and intestine show why this must be so and why demonstration of even release in *in vitro* tests is irrelevant. One drug manufacturer is said to have "taunted his competitors by preparing a long-acting placebo".*

Techniques for prolonging release include various coatings which may dissolve at different rates, chelates, resins and plastic matrices. Before using one of these preparations it is as well to consider whether it is really required and what may be the consequences of failure to provide evenly sustained action. In epilepsy, for example, they could be serious. The risks are not only of failure of the preparation to give up its drug, but also failure to refrain from giving it up all at once.

It may be mentioned here, though it is not a matter of prolonging action or release, that drugs that irritate the stomach are sometimes given special "*enteric*" *coatings* (varnish, hardened gelatin) to delay disintegration of the tablet until it has reached the small intestine. Many of these "enteric"-coated tablets probably pass intact into the W.C.

Long-acting, or depot, injectable preparations are more reliable because the environment in which they are deposited is more constant than can ever be the case in the alimentary tract. The aim with these preparations is generally to render the drug relatively insoluble and so only slowly dissolved at the site of injection. In general such preparations are chemical variants, or the original drug in oil, wax, gelatin or synthetic media. They include phenothiazine tranquillisers, the various insulins and penicillins and oily preparations of vasopressin, also solid tablets of hormones are sometimes implanted s.c. Perhaps the best-known example of prolongation of action by delaying absorption is that of the combination of adrenaline with local anæsthetics.

Reduction of Absorption Time

This can be achieved by making a soluble salt, e.g. barbiturates, or in the case of s.c. injections, by using hyaluronidase. **Hyaluronidase** is an enzyme which depolymerises hyaluronic acid, a background substance in connec-

* Dragstedt, C. (1958). *J. Amer. med. Ass.* **168**, 1652.

tive tissue which prevents the spread of foreign substances, e.g. bacteria, drugs. By combining an injection with hyaluronidase a drug spreads rapidly over a wide area and so is absorbed more quickly, e.g. ergometrine in the hands of nurses who are not trained to give i.v. injections.

Where an i.v. injection of an irritant drug has accidentally leaked into perivenous tissue and there is pain, or risk of damage to another structure (e.g. thiopentone in antecubital fossa may damage the median nerve), hyaluronidase and saline may be injected locally to dilute the irritant and to hasten its absorption.

Acquired and Natural Tolerance (*35*)

Tolerance is said to have developed when it becomes necessary to increase the dose of a drug to obtain an effect previously obtained with a smaller dose. **Acquired tolerance** is familiar, especially with opiates with which it is due to reduced sensitivity of receptor sites. It can also be due to increased metabolism as a result of enzyme induction. There is commonly cross-tolerance between drugs of similar chemical constitution and sometimes between dissimilar substances (alcohol and barbiturates). There is also **natural tolerance** which is not a result of using a drug but an example of individual genetic variation, often due to more rapid metabolism.

Acquired bacterial resistance is a form of tolerance of great practical importance.

Tachyphylaxis is a quickly-developing tolerance, e.g. to indirectly-acting sympathomimetics.

Antagonism

Antagonism occurs when drugs with opposing actions are administered simultaneously. It may be that two drugs simply have opposite pharmacological effects (histamine and adrenaline on the bronchi), *physiological or non-competitive antagonism.* Or, it may be that they compete reversibly for the same drug receptor (morphine, nalorphine) or irreversibly for the same molecule (chelating agents in metal poisoning), *competitive antagonism.*

Synergism

The probability that pharmacologists will, in the forseeable future, agree on the terminology to describe drug synergism (acting together) is exceedingly remote. Therefore the following will suffice: synergism is of two sorts:

1. **Summation or addition** occurs when the effects of two drugs having the same action are additive (alcohol/ether).
2. **Potentiation** (to make more powerful) occurs when one drug increases the action of another. Sometimes the two drugs both have the action concerned (trimethoprim/sulphonamide) and sometimes one drug lacks the action concerned (MAOI/amphetamine).

Potency and Efficacy

These terms are sometimes confused. It is useful to make a clear distinction between them, particularly in relation to claims made for usefulness in therapeutics.

Potency (*absolute* potency): weight for weight drug A has a greater effect than drug B; but the maximum effect obtainable may be similar; differences in potency are often without clinical importance.

Efficacy (*therapeutic* potency): drug A can produce a therapeutic effect that cannot be obtained with drug B however much of drug B is given; differences in efficaciousness are of great clinical importance.

Biological Assay and Standardisation

Biological assay, of which the therapeutic trials can be considered a special form, is a process by which the activity of a substance (identified or unidentified) is measured on living material. It is only used where chemical or physical methods are not practicable. It involves comparing the effect of the unknown preparation with that of a known standard which should be substantially identical, e.g. the amount of noradrenaline or histamine in blood can be measured by comparing its effect with that of solutions made from the pure substance at known active strength.

If the standard is a different substance, as it generally is in therapeutic trials, and as it may be in animal laboratory experiments, then some would hold that the term bio-assay cannot be used, for the dose-response curves are not only unlikely to be parallel but may even cross. i.e. potency comparisons are then only relevant for particular doses; it is not then possible to state that one drug is x times the potency of the other.

Sometimes enthusiastic academic pharmacologists, obsessed by the elegance of their techniques, and proud of their skill in extracting accurately reproducible responses from variable biological material, give the impression that bio-assay is an end in itself as indeed it has so become for them; but it is not an end, it is only a means or a tool. In skilled hands it is a tool of remarkable sensitivity.

Where it is practicable to use them, chemical and physical methods of assay are generally preferable, but sometimes they cannot be used, as in the case of mixtures of active substances, incompletely purified preparations, or where no chemical method has been developed.

Chemical methods can only be used where the scientist knows *exactly* what he is measuring and that his technique will measure that alone. For the foreseeable future, if it is desired to compare the effect of two chemicals, on say vascular, bronchial or uterine muscle, only a bio-assay on these tissues can give an answer.

Bio-assay is an everyday procedure in academic and industrial laboratories and, in the hospital ward and clinic, the comparison of the effects of drugs on diseases is, or should be, equally familiar.

Biological standardisation is a specialised form of bio-assay. It

involves matching of material of unknown potency with an International or National Standard with the intention of providing a preparation for use in therapeutics and research.

It does not properly come within the scope of this book, but as it is of the first importance in providing the clinician with drugs of known potency, it deserves a mention for, if the potency of a potentially toxic agent is not accurately known, then the physician dare not use it and the results of research can be made meaningless: see also under *pharmaceutical formulation and biological availability* for sad story.

Biological methods are always a second best or necessary evil, to be abandoned as soon as chemical and physical methods can be used instead, e.g. tubocurarine had an International Standard made in 1951 and it was discontinued in 1955; chloramphenicol was biologically standardised from 1953 to 1956.

Substances at present biologically standardised include immunological preparations (antigens, antibodies), blood clotting factors, many antibiotics, many hormones, some vitamins, crude digitalis preparations, protamine and pyrogen.

The World Health Organisation organises the system of International Biological Standards (an International Unit exists) and International Biological Reference Preparations (there is no I.U.), and these are kept at the National Institute of Medical Research, London, England and at the Statens Seruminstitut, Copenhagen, Denmark.

They are made by sending out samples of the prospective Standard preparation to 10 to 20 laboratories throughout the world for an "international collaborative assay", the results of which are used in the final preparation of what will be for many years the new International Standard.

The institutes distribute samples, free, to national laboratories in all countries so that National Standards can be made. There is not enough of the International Standards for them to be used in routine commercial production, for they are very expensive, having been made with obsessive attention to detail.

From time to time the International Standard preparations become nearly used up. When this happens a further sample is made and submitted to international collaborative assay.

For example, the first digitalis standard was made in 1926 and further specimens were needed in 1936 and in 1949; the first insulin standard was made in 1925 and further standards in 1935, 1952 and 1958.

Influence of Age, Sex, Disease and Personality

(*9, 18, 19, 24, 27, 29–34, 36, 41, 50*)

Age. The very old and the very young are liable to be intolerant of many drugs, largely because the equipment for disposing of them in the body is less efficient. The young, it has been aptly said, are not simply "small adults".

The **newborn** have relatively lower glomerular filtration and renal plasma flow than adults and are seriously deficient in drug metabolising enzymes for at least a month. It is also probable that a wide variety of enzyme reactions are less well developed. These deficiencies are enhanced in premature babies. Neonates may fail to eliminate in the usual time, vitamin K analogues, sulphonamides, barbiturates, morphine, curare, and possibly many other drugs. Excretion of many antibiotics is delayed. Failure to conjugate chloramphenicol as well as reduced renal excretion can result in fatal vascular collapse.

Total plasma protein and albumin concentrations are lower in the newborn than in older children. This means that binding capacity for drugs is lower so that more of the drug is free and available for diffusion into the tissues as well as for elimination. The total plasma concentrations may therefore be lower, although risk of toxicity remains high.

It is thus clear that differences in drug response in neonates may be due to a variety of factors including all aspects of pharmacokinetics (absorption, distribution, metabolism, excretion) as well as to differences in responsiveness of the end organs. This last factor may be responsible for the increased tolerance of neonates to depolarizing neuromuscular blockers and their decreased tolerance to morphine and inhalation anæsthetics, especially halothane.

Older children are more tolerant than adults of digitalis, but tolerance to atropine and morphine is probably normal although the contrary is sometimes stated. Amphetamine sedates hyperkinetic children.

For drug dosage in children, see above.

In the aged, renal glomerular filtration rate declines and increased half-life of drugs has been shown despite normal serum creatinine concentration (creatinine production is less in the old). In one study of geriatric inpatients (*24*) the mean plasma half-life of antipyrine (phenazone) was increased by 45% and that of phenylbutazone by 29% above that in young controls. No doubt this extension of half-life is a factor contributing to the known increased liability of the old to adverse reactions.

All central nervous system depressants are especially liable to have greater effect than normal and acute confusional states may occur, which is why atropine is often substituted for hyoscine in anæsthetic premedication, and a benzodiazepine or chloral hydrate or a derivative is preferred to a barbiturate. Phenothiazines with extrapyramidal effects, and barbiturates, are liable to lead to immobility which causes pressure sores, but phenothiazines are probably drugs of choice for senile restlessness, confusion and agitation. Nitrazepam is a hypnotic of choice.

The old are relatively intolerant of digitalis and of anticoagulants.

The time of onset of an initial dose of i.v. anæsthetic in the old can be twice as long as in younger subjects due to prolonged circulation time; this has led to overdose by anæsthetists who are unaware of this and who give a second dose before the first has had time to act.

Sex. There are no clinically important qualitative sex differences in

drug action, except, of course, to drugs affecting sex characteristics and fertility, but the subject is poorly documented. Women are said to be more liable to become excited by morphine than are men; in this respect they resemble cats. In a study on depression women responded more than men to electroconvulsion therapy and less to antidepressant drugs.

Disease. Examples of the modification of drug action by disease are legion. ***Hepatic and renal insufficiency*** often result in defective metabolism or excretion and it is necessary to be wary whenever using drugs in such cases: see special sections.

Patients with a malfunctioning respiratory centre (raised intracranial pressure, severe pulmonary insufficiency) are intolerant of drugs which are well known to depress respiration (opiates, barbiturates) but ***any*** sedative, e.g. benzodiazepines, may precipitate respiratory failure in such patients. The respiratory depressant effect of morphine is first manifested by slowing of the rate and normal people compensate for this by breathing more deeply, but patients with *severe emphysema* cannot do this and should therefore be treated circumspectly. Patients with raised intracranial pressure may be restless and it is important to avoid respiratory depression when using drugs to quieten them.

Other examples include:—

Asthmatic attacks may be precipitated by cholinergic drugs, by histamine or by β-adrenoceptor block.

Patients with ***myocardial infarction*** are especially liable to develop cardiac arrhythmias with digitalis or sympathomimetic amines.

In *infectious mononucleosis* rashes with ampicillin are usual; this is important as the patients commonly present with a sore throat and are liable to receive the drug; the mechanism is unknown; the rash may not recur with subsequent administration.

Hepatic porphyrias (acute intermittent p., variegate p., hereditary coproporphyria, p. cutanea tarda). The first step in hæm synthesis is the formation of aminolævulinic acid (ALA) and this is catalysed by the enzyme ALA-synthetase. In the porphyrias later stages of hæm synthesis are partially blocked and there results an increase in ALA-synthetase in an "attempt" to overcome these blocks. But the blocks are not to be so easily overcome and the result is over-production of ALA, prophobilinogen and porphyrins.

It is of interest that those who inherited acute intermittent porphyria and variegate porphyria suffered no biological disadvantage from the natural environment and bred as well as the normal population until the introduction of barbiturates and sulphonamides. They are now at serious disadvantage, for these drugs can precipitate fatal acute attacks.

Many drugs that precipitate attacks of porphyria are inducers of hepatic ALA-synthetase as well as of the hæm-containing drug oxidising enzyme, cytochrome P-450. Much remains unexplained, but *the following*

drugs should be avoided: all barbiturates, all sulphonamides, griseofulvin, glutethimide, dichloralphenazone*, chloroquine, pentazocine, methyldopa, hydantoin and succinimide anticonvulsants, meprobomate, chlordiazepoxide, phenylbutazone and derivatives, œstrogens including oral contraceptives, ergot. In variegate porphyria and porphyria cutanea tarda any potentially hepatotoxic drug may precipitate an attack, and skin reaction may be provoked by alcohol and sunlight as well as by drugs.

The following drugs may be used safely: morphine, pethidine, methadone, aspirin, promazine, chlorpromazine (brief use to avoid hepatic damage), adrenergic neurone blockers, propanidid (for i.v. anæsthesia), chloral,* triclofos,* paraldehyde. Diazepam may also be safe.

Myasthenia gravis is made worse by quinine and myasthenics are very sensitive to competitive neuromuscular blocking agents and resistant to depolarising agents. Patients with either this disease or *dystrophia myotonica* are liable to develop respiratory failure under general anæsthesia.

Patients with *hypopituitarism* and *hypothyroidism* are intolerant of cerebral depressants and probably other drugs, due to low metabolic rate.

In *shock*, drugs injected subcutaneously may not be absorbed owing to existing intense vasoconstriction and then, as this passes off, all doses previously given may be absorbed simultaneously with dire results, e.g. repeated doses of morphine to travelling battle casualties. In both severe *œdema* and in shock, drugs should be injected i.m. or i.v., not s.c.

Schizophrenics are often tolerant of drugs affecting the central nervous system and high doses may be needed.

Hysterics sometimes show exaggerated responses, especially to sedatives, and stagger and fall about on the smallest doses.

Men with *prostatic enlargement* are liable to develop urinary retention if a vigorous diuresis occurs, and with sympathomimetic, anticholinergic and ganglion-blocking drugs. *Pyloric stenosis* may be converted to obstruction if gastric peristalsis is abolished by anticholinergic drugs.

In a variety of *malignant diseases*, particularly Hodgkin's disease, alcohol induces pain. This can be useful in diagnosis.†

A patient in *pain* may become confused if given a hypnotic without an accompanying analgesic, for the pain keeps him awake.

Some drugs may be given in a chemical form unsuited to a particular occasion, e.g. sodium salicylate should not be used in cases of *heart failure* (aspirin would be better) nor should sodium-containing antacids, and potassium citrate to alkalinise the urine is dangerous in renal failure. Drug absorption, metabolism and excretion can be impaired by the circulatory changes of heart failure.

It is impossible to list completely the possible important alterations of drug effects caused by disease. The examples given above suffice to show that safety lies in knowledge of both drug and disease.

* Note that chloral and triclofos are in one group and dichloralphenazone is in the other; this is because of the phenazone component.

† LEWIS, D. and VALENTINE, J. C. (1962). *Lancet*, **1**, 461.

Personality. Not enough is known to enable any generalisation of practical utility to be made, but there is no doubt that the response to drugs acting on the central nervous system is influenced by personality.

It is a commonplace that the response to alcohol is different and characteristic for some individuals and this is probably a personality difference. Pavlov noted that dogs of "excitatory" temperament might need eight times as much sedative as dogs of "inhibitory" temperament. Another prominent example is the response to placebo or dummy administration. It is also known that placebo-reactors are liable to respond atypically to other drugs and that the response to a drug may vary with alterations in mental state.

UNWANTED EFFECTS OF DRUGS (*53, 57–72*)

Cur'd yesterday of my disease,
I died last night of my physician.
From *The Remedy Worse than the Disease*. Matthew Prior (1664-1721)

Unwanted effects may be classified as **adverse reactions** and **side-effects.** The distinction is one of convenience, it has no precise scientific basis.

A sensible operational definition of adverse reaction is "any noxious change . . . which a physician suspects may be due to a drug, which occurs at dosages normally used in man, and which (1) requires treatment, or (2) indicates decrease or cessation of therapy . . . or (3) suggests that future therapy with the drug carries an unusual risk in this patient". It does not include trivial and expected side-effects, nor absolute overdose (*58*).

It is obviously useful to know the incidence of adverse reactions so that attention can be given to ways of reducing drug-induced disease by better use of drugs as well as by withdrawing unduly hazardous drugs from clinical use. Many countries operate voluntary spontaneous reporting systems, but these inevitably all suffer from incompleteness due to gross underreporting, and the number of patients given a drug in general use is usually unknown. Despite the fact that true incidence of adverse reactions cannot be calculated these systems allow delineation of adverse reaction profiles which help the physician to choose a drug for the individual, e.g. the principal adverse reactions to phenylbutazone fall on fluid balance, the skin and the gastrointestinal tract, whereas an alternative antirheumatic, indomethacin, though troublesome in the gut and the central nervous system is less troublesome on fluid balance. Spontaneous reporting has uncovered serious effects, e.g. liver damage, and had led to withdrawal of drugs; it has also discriminated between the incidence of thromboembolism with high and low œstrogen dosage oral contraceptives.

But, if the true incidence of adverse reactions is wanted, organised programmes in which the reactions are positively sought are required.

Adverse reactions are very common; they have been found to account

for about 4% of hospital admissions, and 10 to 20% of inpatients suffer an adverse reaction during their stay. Predisposing factors include being female, over 60 years, taking several drugs, and a previous history of drug reaction. Drugs are thus an important cause of disease and must be considered routinely when seeking a diagnosis. Adverse reactions are not always recognised for what they are. Symptoms or signs, such as fever, rash or collapse due to a drug may be attributed to disease, especially if the doctor does not habitually take a drug history. Patients frequently take drugs for minor ailments and only come to a doctor when some unwanted effect occurs; such symptoms are rarely connected with the drug by the patients. In addition patients may take drugs without realising they are doing so. The quinine in tonic water was responsible in the following example of intolerance*†:

"I saw a 43-year-old man in consultation who had a 7-week history of tinnitus and hearing loss. He had consulted an otologist, who found bilateral diminution in hearing, and a neurologist, who suggested the diagnosis of bilateral angle meningioma. Because of the history of ingestion of seven to eight drinks per day he was sent for a medical evaluation prior to further workup for neurosurgery. The history of alcohol ingestion was correct, but his diet was in general adequate. After a physical examination, which was not remarkable except for the facts already noted, casual discussion brought out the fact that the drinks were always gin and tonic. Since I had seen cinchonism in the southwest Pacific, I thought it worth while to change the beverage to Tom Collins. Within 48 hours the symptoms had disappeared. A test dose of 300 mg. of quinine brought a return of the tinnitus. Later, a test dose of 150 mg. produced the same effect. Three weeks after the discontinuance of the quinine, audiogram showed restoration of hearing.

"While I have not obtained the exact formula of quinine water, I am informed that the Schweppes brand contains about 30 mg. per pint. The man was ingesting about 100 mg. daily. It is clear that it would take an enormous consumption to produce the symptoms in the normal adult."

Unwanted effects may be classified (*70*):

Overdose: *a.* absolute; *b.* relative
Intolerance
Side-effects
Secondary effects
Idiosyncrasy
Allergy (hypersensitivity)
- *a.* anaphylactic shock
- *b.* pulmonary reactions, including asthma
- *c.* urticaria and angioneurotic œdema, immediate or delayed
- *d.* serum-sickness syndrome (arthralgia, lymphadenopathy, fever, plus *c* above)

* YOHALEM, S. B. (1953). *J. Amer. med. Ass.*, **153**, 1304.
† See also, CUNDALL, R. D. (1964). Hypersensitivity to quinine in Bitter Lemon. *Brit. med. J.*, **1**. 1638.

e. thrombocytopenia
f. granulocytopenia and agranulocytosis
g. aplastic anæmia
h. hæmolysis

} *blood disorders*,* often called "dyscrasias" to help conceal the almost total ignorance of how they arise. *They are also caused by non-immunological mechanisms*, see below.

i. rashes, non-urticarial
j. fever
k. syndromes resembling the collagen diseases, e.g. polyarteritis nodosa, disseminated lupus erythematosus.
l. hepatitis and cholestatic jaundice.
m. severe hæmatemesis provoked by aspirin, peripheral neuritis, "nephritis" and some other rare drug-induced phenomena are sometimes due to allergy.

Overdose

With overdose of a drug ill effects occur in direct relation to the total amount of drug in the body. They may be:—

a. **Absolute**, due to an acute excess or to accumulation of the drug in the body.

b. **Relative**, due to an underlying abnormality in the patient. In renal failure a usual dose of any drug normally excreted by the kidney will cause abnormally high blood levels, e.g. streptomycin. Patients who have an abnormally low serum potassium are abnormally sensitive to digitalis, and ordinary doses may produce toxic effects, which are reversed if potassium is given.

Intolerance

Intolerance means a low threshold to the normal pharmacological action of a drug. Individuals vary greatly in their susceptibility to drugs, those at one extreme of the normal distribution curve being intolerant of the drugs, those at the other, tolerant.

Side-effects

The term side-effects may be usefully restricted to therapeutically *undesired but unavoidable* effects, because they are normal pharmacological actions of the drugs. They may be extensions to an undesirable extent of a therapeutic effect (e.g. drowsiness with phenobarbitone when used as an anticonvulsant), or an effect which is never wanted (e.g. vomiting with digoxin). A side-effect on one occasion may be the desired effect on another; e.g. atropine is used in anæsthetic premedication to reduce salivary and bronchial secretion, but this can be a troublesome side-effect

* Where cells are being destroyed in the periphery and production is normal, transfusion is useless or nearly so, as the transfused cells will be destroyed, though in an emergency even a short cell life (platelets, erythrocytes) may tip the balance usefully. Where the bone marrow is depressed, transfusion is useful as the transfused cells will survive normally.

when it is given to Parkinsonian patients to reduce tremor. The hypotensive effect of adrenergic neurone blocking drugs may be accompanied by failure of ejaculation. Some object to the use of the term side-effect because they think it encourages doctors to shrug off as unavoidable, and so not their responsibility, ill-effects that are serious and/or ought to have been avoided.

Secondary effects

Secondary effects are the indirect consequences of a primary drug action. Examples are vitamin deficiency or superinfection which may occur in patients whose normal bowel flora has been altered by antibiotics. The Herxheimer reaction (probably due to products released by killed organisms, usually spirochætes) is another type of secondary effect.

Idiosyncrasy (see also *pharmacogenetics*)

Idiosyncrasy implies an inherent qualitatively abnormal reaction to a drug usually due to genetic abnormality. Porphyria is an example and so is the hæmolytic anæmia caused by antimalarials of the 8-aminoquinoline group (primaquine, pentaquin, pamaquine), which has been shown to be due to a deficiency of glucose-6-phosphate-dehydrogenase in red cells.

Analgesic-induced asthma syndrome (*55*) may be provisionally classified as an idiosyncrasy. It characteristically begins in middle life with rhinitis followed by nasal polyps and asthma; urticaria may occur. The drugs that precipitate it include aspirin (chiefly), and paracetamol, indomethacin, flufenamic acid, mefenamic acid and dextropropoxyphene, and there is great individual variation. The cause is unknown; it is unlikely to be immunological. An ingenious suggestion is that these drugs, which ordinarily show some antagonism to the broncho-constrictor substances released in response to tissue injury, (e.g. bradykinin, prostaglandins, slow reacting substance or SRS-A) become agonists due to an alteration in the tissue receptors. When exacerbations of asthma occur in patients with any painful condition, analgesics should be considered a possible cause; challenge with aspirin is more dangerous than with other drugs.

Allergy to drugs (*54–56*)

Allergic reactions are mediated either by classic antigen-antibody combination or by cell-mediated immune reaction (delayed-type allergy) involving sensitised lymphocytes. The reactions require previous exposure either to the drug itself or to a closely related drug or other chemical. Lack of previous exposure is not the same as lack of *history* of previous exposure. Exposure is not necessarily medical, e.g. penicillins occur in dairy products following treatment of cattle, and penicillin antibodies are commonly present in those who deny having received the drug.

Whilst macromolecules (proteins, peptides, dextran polysaccharides) can act as complete antigens, most drugs are simple chemicals (mol.wt. less than 1,000) and act as incomplete antigens or haptens which become

complete antigens in combination with a body protein. The fact that antibodies are produced does not mean a patient will necessarily respond to re-exposure with clinical manifestations; most of our population have antibodies to penicillins, but, fortunately, comparatively few are allergic to penicillins.

Allergy may be due to the drug itself, to a metabolite, to contaminants in the preparation or to non-drug substances in the pharmaceutical formulation.

Why allergy is commoner with some drugs, e.g. penicillins, than with others and why the same drug produces different effects in different people is unknown; a genetic basis in the host is suggested; in addition, patients with allergic diseases, e.g. eczema, are more likely to develop allergy to drugs.

Allergic reactions are not closely dose related and may be extremely severe with minute doses, or only with high doses. No doubt this is due to the complexity of the immunological factors involved.

Cross-allergy within a chemical group of drugs is usual. Some notes on **mechanisms** follow:

Antibodies to a drug or metabolite may be of two main kinds:

1. **Antibodies fixed to tissues,** e.g. skin or mucous membranes (tissue sensitising or reaginic antibodies) (mainly of IgE class); these mediate the immediate*-type immune reactions (**anaphylactic shock, asthma, rhinitis, angioneurotic oedema**) which occur within a few minutes of re-exposure and which are due to release of pharmacologically active substances from the tissues, e.g. histamine; 5-hydroxytryptamine (5HT), slow-reacting substance (SRS-A), bradykinin, prostaglandins etc. In addition, the delayed*-type reactions, e.g. **fever and rashes**, including photoallergy and contact dermatitis, are cell-mediated.

2. **Antibodies in the circulation** (usually IgG, IgM class) seldom cause symptoms, and indeed may mop up antigen before it reaches the tissues ("blocking" antibodies) and so protect from anaphylaxis. This latter mechanism can account for the disappearance of some allergic reactions (e.g. rash) if therapy is continued, a somewhat risky form of hyposensitisation. But accelerated*-type reactions (some rashes), occurring within hours of re-exposure, and retarded* type reactions occurring within days to weeks of re-exposure are also due to circulating antibodies. The retarded type includes **serum sickness syndrome** (lymphadenopathy, fever, arthralgia) and **polyarteritis** and **disseminated lupus erythematosus.** These occur when circulating antibodies are also complement-fixing (some are not) and result from the antigen/antibody/complement aggregation lodging in small blood vessels where, as a result of activating the complement system, proteolytic enzymes are released to cause tissue damage.

* These terms do not refer to the time of onset of the reaction, they are immunological jargon implying different mechanisms.

Auto-allergy is another type of reaction; here the drug combines with a tissue cell to form an antigen, and the antibodies that result damage the cell by activating the complement system. Examples are (1) combination of apronal (Sedormid) with blood platelets leading to **thrombocytopenic purpura** and (2) combination of methyldopa or levodopa with erythrocytes leading to **hæmolytic anæmia**; a majority of patients develop the antibody, but only a minority suffer hæmolysis.

Some notes on **clinical manifestations and treatment** follow:

a. **Anaphylactic shock** may occur when penicillin, horse serum and a huge variety of other drugs, is given to a patient sensitised to that drug. The combination of antigen with antibody in the cells is followed by release of histamine and other substances from tissue stores, with a severe fall in blood pressure, bronchoconstriction and sometimes death due to loss of fluid from the intravascular compartment. Bronchospasm and sometimes laryngeal œdema and anaphylactic shock usually occurs suddenly, in less than an hour after the drug, but within minutes if it has been given i.v. Treatment is urgent, 1 ml of Adrenaline Inj. B.P. should be given i.m.* to raise the blood pressure, to dilate the bronchi and to reduce the release of active substances. Noradrenaline would ordinarily be preferred to constrict the dilated arterioles (α effect), but it lacks any useful bronchodilator action (β effect) and adrenaline is the best compromise in this emergency. The adrenaline should be accompanied by an antihistamine (say, chlorpheniramine 10 mg i.v.) and hydrocortisone (100 mg i.v.). The adrenal steroid may benefit by reducing vascular permeability and by suppressing further response to the antigen-antibody reaction. Benefit from an adrenal steroid is not immediate; it takes hours to reach its maximum. Aminophylline is useful if the bronchospasm is severe. Any place where anaphylaxis may be expected should have the drugs and tools necessary to deal with it, for when they are needed there is little time to think and none to run about from place to place.

A reaction is said to be "anaphylactoid" if it clinically resembles anaphylactic shock but is not thought to have an immunological mechanism.

b. **Pulmonary reactions: asthma.** The antigen-antibody reaction causes local liberation of substances, including histamine, which cause contraction of smooth muscle. Stimulation of the bronchial muscle may result in an asthmatic attack which can be fatal. 0·25 to 1·0 ml. of Adrenaline Inj. B.P., s.c., will usually cut short an attack; the other treatments for asthma are also effective.

Nitrofurantoin causes a reversible pulmonary infiltration that can cause considerable diagnostic difficulty; other drugs have been incriminated in a similar syndrome, though more rarely.

Organic dusts (e.g. posterior pituitary powder taken as snuff for

* Not s.c., for the intense local vasoconstriction added to the low blood pressure will result in delayed absorption. In extreme urgency 0·5 ml. diluted × 10 may be given slowly i.v. It can cause ventricular fibrillation, but this may be thought to be the lesser risk.

diabetes insipidus, as well as dusts met occupationally) cause not only asthma, but also syndromes resembling acute and chronic lung infections.

c. **Urticarial rashes and angioneurotic œdema.** These are probably the commonest type of drug allergy. They are usually accompanied by itching. The eyelids, lips and face are usually most affected; œdema of the larynx is rare but may be fatal if tracheostomy is not done. The itching œdematous lesions are due to the liberation of histamine, etc. in the skin. Such reactions may be generalised, but frequently are worst in and around the area of administration of the drug. They respond to adrenaline (i.m. if urgent), ephedrine, antihistamines and adrenal steroids.

Anaphylactic shock, asthma and urticarial skin lesions may occur separately or in combinations of varying severity; they are usually accompanied by fever, general malaise and nausea and vomiting.

d. **The serum-sickness syndrome** occurs about 1 to 3 weeks after administration. Treatment is by an adrenal steroid, and as above if there is urticaria.

e. **Thrombocytopenic purpura** due to drugs is not common except with apronal (Sedormid) which is deservedly obsolete, but it has been reported occasionally after a large number of drugs, including phenylbutazone, gold, sulphonamides, quinine, quinidine, antimitotic agents, phenazone, streptomycin, tetracycline, PAS, troxidone, phenobarbitone, thiourea derivatives, mercurials, thiazides, œstrogens, digitoxin. In addition to allergy, it may also be due to bone marrow depression when too few platelets are made. Adrenal steroids can help.

f. **Granulocytopenia,** sometimes leading to **agranulocytosis,** is a very serious, though rare, allergy which may occur with many drugs, e.g. chloramphenicol, sulphonamides and diuretic and antidiabetic derivatives, colchicine, gold, anticonvulsants, methyldopa, etc. Amidopyrine is notorious in this respect and need never be used, as there are adequate substitutes. Treatment of agranulocytosis involves both stopping the drug responsible and giving a *bactericidal* drug (e.g. penicillin) to treat or prevent infection. If the blood picture does not improve following withdrawal of the drug an adrenal steroid should be given in severe granulocytopenia and in all cases of agranulocytosis, but proof of its beneficial effect is naturally hard to get.

g. **Aplastic anæmia.** About 50% of cases of aplastic anæmia may be drug-induced (*61*). Chloramphenicol is the most important but other causes include sulphonamides and derivatives (diuretics, antidiabetics), phenylbutazone, hydantoin anticonvulsants, troxidone, gold, perchlorate and some insecticides, e.g. dicophane (DDT). In the case of chloramphenicol, bone marrow depression is a normal pharmacological effect of the drug (*63*), although aplastic anæmia may also be due to idiosyncrasy or allergy.

Death occurs in about 50% of cases, and treatment is as for agranulocytosis, with, obviously, blood transfusion.

h. **Hæmolysis** of all kinds is included here for convenience. There are three principal categories.

1. *Dose-related pharmacological action on normal cells*, e.g. lead, benzene, phenylhydrazine, chlorates, methyl chloride (refrigerant), some snake venoms.

2. *Idiosyncrasy*—cells are defective in the enzyme glucose 6-phosphate dehydrogenase and hæmolyse readily in the presence of oxidant drugs such as 8-aminoquinoline antimalarials (primaquine, pentaquin, pamaquine), quinine, sulphonamide, sulphones, nitrofurans (nitrofurantoin, furazolidone), phenacetin, aspirin and other antipyretic analgesics, PAS, ascorbic acid, probenecid, fava beans. The genetically determined defect is commonest in Negroes, Asiatic Jews and Filipinos. Characteristically there is an acute hæmolytic episode 2 to 3 days after starting the drug. The hæmolysis is self-limiting, only older cells with least enzyme being affected.

3. *Allergy*—a drug (hapten) combines with protein in the erythrocyte membrane to form an antigen. On re-exposure this antigen reacts with antibody and the erythrocyte is destroyed. This mechanism has been demonstrated in the case of the rare penicillin hæmolysis. It has not been proved for other drugs that also induce allergic hæmolysis such as, methyldopa, levodopa, phenacetin, PAS, quinine, quinidine, sulphasalazine and organic antimony. It may be that in some of these cases a drug-protein-antigen/antibody interaction involves erythrocytes casually, i.e. a true "innocent bystander" phenomenon.

Precipitation of a hæmolytic crisis may also occur with the above drugs in the rare chronic hæmolytic states due to unstable hæmoglobins.

Treatment is to withdraw the drug, and an adrenal steroid is useful in severe cases if the mechanism is immunological. Blood transfusion may be needed.

i. **Non-urtical rashes** occur in great variety; frequently they are weeping exudative lesions. It is often difficult to be sure when a rash is due to drugs. Apart from stopping the responsible drug, treatment is non-specific; in severe cases an adrenal steroid should be tried. Skin sensitisation to antibiotics may be very troublesome, especially amongst those who handle them. See *drugs and the skin.*

j. **Fever.** Treatment is to stop the drug.

k. **Syndromes resembling the collagen diseases** are sometimes caused by drugs, e.g. hydrallazine, procainamide, isoniazid, anticonvulsants, sulphonamides. Adrenal steroids are useful.

l. **Hepatitis and cholestatic jaundice** are sometimes allergic (see *drugs and the liver*).

Diagnosis of drug allergy is still largely on clinical criteria, history, type of reaction, response to withdrawal and systemic rechallenge (if thought safe to do so).

Simple skin testing is naturally most useful in diagnosing contact

dermatitis, but it is unreliable for other allergies; also it is not necessarily safe and can cause anaphylactic shock.

Detection of drug-specific circulating antibodies only proves that an immunological response has occurred; it does not prove allergy. Development of reliable *in vitro* predictive tests is a matter of considerable importance not merely to avoid hazarding patients, but to avoid depriving them of a drug that may be useful, for drug allergy, once it has occurred, is not necessarily permanent, e.g. less than 50% of patients giving a history of allergy to penicillin have a reaction if it is given again.

Hyposensitisation. Once a patient becomes allergic to a drug, it is better that he should never again come into contact with it. However, this can be inconvenient, for instance in allergy to antituberculosis drugs both in patients, and in nurses. Such people can be hyposensitised by giving very small amounts of allergen, which are then gradually increased (usually every few hours) until a normal dose is tolerated. This may have to be done under cover of either an antihistamine or of an adrenal steroid, or both, to prevent reactions during the procedure. A full kit for treating anaphylactic shock should be handy.

The ease and safety of hyposensitisation varies with different drugs; penicillin is troublesome, and antituberculous drugs generally less so.

The mechanism underlying hyposensitisation is not understood but may involve the production by the patient of blocking antibodies (see above) which compete successfully for the allergen but whose combination with it is innocuous. Sometimes allergy is to a part of the preparation other than the essential drug and merely changing the preparation is sufficient, e.g. some cases of fever from mercurial diuretics or skin reactions to ointments. Impurities are sometimes responsible and purified forms of penicillins (e.g. Purapen-G) have been shown to induce fewer reactions than standard forms.

Prevention of allergic reactions is important since they may be fatal. Patients should always be told when they are thought to be allergic to a drug, and it is essential that if a patient says he is allergic to some drug then that drug should *not* be given without careful testing.

Assumption that patients are all either ignorant or stupid has caused deaths: a young man was admitted to hospital for an interval appendicectomy, but had a sore throat and slight fever. The house surgeon said this would soon clear up with penicillin, but the patient at once protested, saying that he was seriously allergic to penicillin. The doctor said that in that case he would use another drug, but in fact he gave penicillin and the patient died from anaphylactic shock (*70*).

A doctor has also been known, when choosing an alternative drug to avoid a reaction, to prescribe inadvertently another drug from the same group, because the proprietary name gave no indication of the nature of the drug; another good reason for adopting the commonsense system of one drug, one sensible name.

Repeated blood counts in patients taking drugs known to cause blood disorders, especially agranulocytosis, appear at first sight to be desirable, but as the onset is ordinarily sudden they commonly fail to give protection and may give a false sense of security.* In addition, spontaneous fluctuations in the number of granulocytes make the interpretation of such counts difficult, especially in children. Such routine blood counts are probably not worth doing†. The best protection is to tell the patient to report at once any fever, enlarged glands or sore throat (evidence of infection) and to stop taking the drug until he has had advice. Unfortunately, this can lead to frequent interruption of therapy in nervous patients. Although innumerable drugs are capable of causing blood disorders, troxidone, antithyroid drugs, phenylbutazone, methoin, phenacemide, gold and prolonged courses of sulphonamides are particularly notorious. A few drugs such as amidopyrine and phenazone have been abandoned because of the risk of blood disorders, and courses of others, such as chloramphenicol, are kept short for this reason.

The only way to completely prevent allergic reactions to drugs is to cease to use drugs; but at least the unnecessary use of drugs for trivial complaints should be avoided.

Miscellaneous Adverse Reactions

Reactions to Intravenous Injections are fairly common, hypotension, renal pain, rigors and fever may occur, especially if the injection is very rapid. Some are due to foreign substances in the solutions and probably not to allergy, and some just due to excessive speed causing a transient very high blood level in, say, the brain.

Toxic cataract can be due to chloroquine and related drugs, adrenal steroids (perhaps), phenothiazines, naphthalene, carbromal, ergot, dinitrophenol, galactose, lactose and paradichlorobenzene.

DRUGS AND THE FETUS (*73–86*)

Passage of drugs into the fetus. The placenta is not simply a passive "barrier" between mother and fetus. The majority of substances essential for fetal growth (e.g. amino acids) are transferred actively *against* a concentration gradient. However, drugs administered to the mother pass across principally by passive diffusion *down* a concentration gradient. For practical purposes the placental "barrier" may be considered equivalent to the blood-brain "barrier". The principal property affecting transfer is solubility in lipids (see *pharmacokinetics*), and lipid soluble drugs pass rapidly into the fetus. Drugs that are relatively insoluble in lipids will, if present in high concentration, eventually enter the fetus. But the rate (i.e. amount of drug in unit time) is slow and single moderate doses to the

* *Not* a sense of false security.

† Though where a drug causes bone marrow depression as a pharmacological dose-related effect (rather than because of idiosyncrasy or allergy) they are a sensible precaution, e.g. anticancer drugs.

mother may leave the fetus unaffected, e.g. tubocurarine given as a muscle relaxant during Cæsarian section does not affect the infant, whereas, used in high doses over a prolonged period to control convulsions it has resulted in a paralysed infant. Thus accurate prediction of entry into the fetus depends on knowledge of the rate of transfer and the dose and duration of administration. Since maternal erythrocytes and immune globulins have been shown to enter the fetus it is plain that any drug may do so.

Once a drug is in the fetus its pharmacokinetics may differ from that of the mother (see *age and drug action*), and the drug and its metabolites may persist due to undeveloped metabolic and excretory processes.

Enzyme inducers (e.g. phenobarbitone, alcohol) are also effective in the fetus and can be given to the mother before labour to enhance the ability of the newborn to conjugate free bilirubin (by inducing the hepatic enzyme glucuronyl transferase) and so to prevent kernicterus (see *enzyme induction*).

If drugs can enter the fetus it is not surprising that they are capable of modifying development in the early stages before a placenta has developed.

Teratogenesis (*teratos* = a monster)

The activity of a teratogen is most devastating soon after implantation for modest interference with a developmental process at its outset during the phase of organ differentiation has greater potentiality than a similar interference later on after an organ has been formed. The CNS develops throughout pregnancy.

Selective interference can produce characteristic abnormalities, and this was one factor that caused thalidomide to be so readily recognised; the others were the previous rarity of phocomelia and the widespread use of the drug.

Teratogenic effects can occur at doses that do not harm the mother, and they are associated with increased intra-uterine mortality, i.e. if the abnormality is gross enough, abortion occurs.

Teratogens may act:

1. **directly** on the fetus (thalidomide, anticancer drugs).
2. **indirectly:**
   (a) on the placenta (vitamin A, 5-HT);
   (b) on the uterus (vasoconstrictors reduce blood supply and cause fetal anoxia);
   (c) on the mother's hormone balance (uncertain);
   (d) on the father's sperm (uncertain).

It is plain that major fetal damage by drugs taken in early pregnancy (the first 12 weeks, but especially perhaps weeks 3 to 8, measured from the first day of the last menstruation) is a reality of great practical importance, and also that prediction of this effect from animal tests is still imperfect.

Whilst everyone will wish to avoid giving to women drugs that have

been shown to cause fetal abnormalities in animals, they will also properly be reluctant at present to accept the corollary that failure to induce such abnormalities in animals means that a drug can be safely used.

Human toxic effects not predicted from animal experiments are often reversible, but even the most optimistic enthusiast for drugs must shrink from the thought that his hand wrote a prescription resulting in a deformed, surviving baby.

Clinical data are, at present, inevitably open to doubt, and any list of suspected drugs must, so slight is our knowledge, become obsolete and misleading very quickly. This topic must, therefore, be followed in the periodical press.

It is possible that some drugs in common use may be low-grade teratogens. In one retrospective study (74) of the drug consumption of mothers of infants with congenital abnormalities it was found that more of these took aspirin, antacids, amphetamine, barbiturates, iron, cough medicines and sulphonamides in early pregnancy than did those in the control group (mothers of infants without congenital abnormalities). The authors acknowledge that such studies do not give proof of cause, e.g. a drug may be taken to control symptoms of a disease that causes the abnormality. But they conclude that it would be wise to avoid these drugs (prescribed or self medication) on which suspicion falls unless there is a specific indication for them, not only during known pregnancy but also in any women of childbearing age in whom conception is likely; a counsel of perfection, perhaps.

The medical profession clearly has a grave duty to refrain from all inessential prescribing of drugs with, say, less than 10–15 years' widespread use behind them, for all women of childbearing age. It is not sufficient safeguard merely to ask a woman if she is or may be pregnant (the natural reluctance to broach this subject to unmarried women may act as a salutary check to casual prescribing), but it will also be necessary to consider the possibility of a woman who evidently is not pregnant at the time of prescribing, becoming so whilst taking the drug, and this can be difficult to predict.

Since morning sickness of pregnancy occurs during the time when the fetus is vulnerable, it is especially important to restrict drug therapy of this symptom to a minimum.

Before a drug is condemned as a cause of fetal damage it is necessary to consider whether the disease for which it was given, or other intercurrent disease, might perhaps be responsible.

Since the only way to discover whether a drug causes fetal damage in man is to test it in man, it is necessary that doctors should (a) suspect a drug-induced abnormality when it occurs and (b) report it to a central organisation (Committee on Safety of Medicines). Unfortunately, neither of these requirements is easily satisfied. Minor congenital abnormalities are common in the absence of drug therapy and some may be virtually undetectable, e.g. reduced intelligence or learning ability (*85*). Human

frailty also causes any reporting system based on voluntary co-operation to be less than perfect. For example, the Committee on Safety of Medicines has found that when a letter exhorting doctors to report drug reactions is sent out, there is a large, but very short-lived increase in reports.

In addition, the more cautiously a new drug is introduced, the more difficult it is going to be to detect, by epidemiological methods, a capacity to cause fetal abnormality. This is especially so if the abnormality produced is already fairly common.

Careful study of the drug history of thousands of women who have given birth to normal and abnormal babies offers perhaps the best hope of early detection at present.

The possibility of fetal abnormalities resulting from drugs taken by the father exists, but has only begun to be explored in animals.

The above refers to early pregnancy, but drugs can also affect the fetus when given in **late pregnancy.**

Because the important organs are already formed, drugs will not cause the gross anatomical defects that can occur when they are given in early pregnancy. Administration of hormones, androgens or progestagens, can cause fetal masculinisation; iodide and antithyroid drugs in high dose can cause fetal goitre; tetracyclines can interfere with tooth and bone development.

It is probable that drug allergy in the mother can also occur in the fetus and it is possible that the fetus may be sensitised where the mother shows no effect, e.g. neonatal thrombocytopenia from thiazide diuretics used in toxæmia of pregnancy.

Other drugs suspected of harming the fetus at some stage include sulphonamides and oral antidiabetics; streptomycin damage to the fetal eighth nerve is rare, if it occurs.

The suggestion that congenital cataract (due to denaturation of lens protein) might be due to drugs has some support in man, and aromatic compounds can cause cataract in animals.

Chloroquine and chlorpromazine are concentrated in the fetal eye. Since both can cause retinopathy it would seem wise to avoid them in pregnancy if possible.

Drugs given just **prior to labour** can cause diseases after birth: reserpine (nasal discharge, costal retraction, lethargy, feeding difficulty): chloramphenicol (collapse due to failure to conjugate): vasoconstrictors (fetal distress by reducing uterine blood supply): sulphonamides (displacement of bilirubin from plasma protein): anticoagulants (hæmorrhage).

Babies born to mothers dependent on opiates may show a physical withdrawal syndrome.

Drugs given **during labour.** Any drug that depresses respiration in the mother can cause respiratory depression in the newborn; opiate analgesics are notorious in this respect, but there can also be difficulty with barbiturates and basal and general anæsthetics; they may also cause fetal distress by reducing uterine blood flow, and prolong labour by depressing uterine muscle.

Thalidomide Disaster

Until 1961 the public took a largely romantic interest in the development and introduction of new drugs and its attention was only turned to the subject when it learned from the press, generally incorrectly, and several times a year, that a major advance or "breakthrough" had taken place. In 1961 a major breakthrough did occur—man discovered that drug introduction was more hazardous than he had previously believed. The thalidomide disaster aroused public opinion, forced governments to intervene in the process of drug introduction and all concerned with this process got a salutary shock. Our attitude to casual use of drugs can never be, and should never be the same since thalidomide, and therefore the story is given in some detail here.

In 1960–61 in W. Germany an outbreak of phocomelia occurred. Phocomelia means "seal extremities"; it is a congenital deformity in which the long bones of the limbs are defective and substantially normal or rudimentary hands and feet arise on, or nearly on, the trunk, like the flippers of a seal; other abnormalities may occur simultaneously. Phocomelia is ordinarily exceedingly rare.

Most W. German clinics had no cases during the 10 years up to 1959. In 1959, in 10 clinics, 17 were seen; in 1960, 126; in 1961, 477. The outbreak seemed confined to W. Germany, and this, with the steady increase, made a virus infection, such as rubella, seem unlikely as a cause. Radioactive fall-out was considered and so were X-ray exposure of the mother, hormones, foods, food preservatives and contraceptives. One doctor, investigating his patients retrospectively with a questionnaire, found that 20% reported taking Contergan in early pregnancy. He questioned the patients again and 50% then admitted taking it; *many said they had thought the drug too obviously innocent to be worth mentioning initially.*

In November, 1961 the suggestion that a drug, unnamed, was the cause of the outbreak was publicly made by the same doctor at a pædiatric meeting, following a report on 34 cases of phocomelia. "That night a physician came up to him and said, 'Will you tell me confidentially, is the drug Contergan? I ask because we have such a child and my wife took Contergan.' " (77). Several letters followed, asking the same question, and it soon became widely known that thalidomide (Contergan, Distaval, Kevadon, Talimol, Softenon) was probably the cause. It was withdrawn from the W. German market in November, and from the British market in December, 1961.

In a series of 46 cases of phocomelia it was found that 41 mothers had certainly taken thalidomide and of 300 mothers with normal babies none had taken thalidomide, between the fourth and ninth week of pregnancy.

Soon more reports were forthcoming and despite the fact that such retrospective studies do not provide conclusive evidence of cause and effect, judgement could no longer be suspended on such an important matter, for the drug was not a vital one. Prospective enquiries were

quickly made in ante-natal clinics where women had yet to give birth—though few, they provided evidence incriminating thalidomide. The worst had happened, a trivial new drug was the cause of the most grisly disaster in the short history of modern scientific drug therapy. Many thalidomide babies died, but many live on with grotesquely deformed limbs,* eyes, ears, heart and alimentary and urinary tracts.

The W. German Health Ministry estimated that thalidomide caused about 10,000 birth deformities in babies, 5,000 of whom survived and 1,600 of whom would eventually need artificial limbs. In Britain there were probably at least 600 live births of malformed children of whom about 400 survived.

Thalidomide had been marketed in W Germany in 1956 as Contergan, and in Britain in 1958, as Distaval, as a sedative and hypnotic. Its chief merit seemed to be that overdose did not cause coma, probably because, with suitable particle size, elimination balanced absorption; given orally to animals a lethal dose could not be reached. Suicides were disappointed by thalidomide.

Thalidomide seemed a safe and pleasant hypnotic, and no doubt some patients found it preferable to others, but in the context of all drug therapy its advantages were trivial, however worthwhile they may have seemed to victims of insomnia.

Despite the absence of any other notable properties, thalidomide, skilfully promoted and credulously prescribed and taken by the public—it was also sold without prescription—achieved huge popularity, it "became W. Germany's baby-sitter" (77). It was a routine hypnotic in hospitals and was even recommended to help children adapt themselves to a convalescent home atmosphere and was sold mixed with other drugs for symptomatic relief of pain, cough and fever (Grippex, Polygripan, Peracon Expectorans, Valgis, Tensival, Valgraine, Asmaval, etc.). This may help explain the difficulties of patients and of doctors in determining who had had thalidomide and who had not, and the statement, probably true, that some women, knowing the danger of thalidomide from press publicity, but not the confusion that reigns amongst drug names, continued to use their supplies of the drug alone or in a mixture, for none of these prominently featured the non-proprietary name on the label. When a drug is in disfavour the advantages of its non-proprietary name become suddenly obvious to those who promote the use of proprietary names, and so more publicity of its teratogenic effect was under the name, thalidomide, than under the numerous proprietary names.

In 1960–61 it had become evident that prolonged use of thalidomide could cause hypothyroidism and peripheral neuritis. The latter effect was the reason why approval for marketing in the U.S.A., as Kevadon, had been delayed by the U.S. government Food and Drug Administration. Approval had still not been given when the fetal effects were discovered

* For pictures of thalidomide deformities, see *Brit. med. J.*, 1962, **2**, 646, 647, and *J. Amer. med. Ass.*, 1962, **180**, 1106.

and so general distribution was avoided. None the less some "thalidomide babies" were born in the U.S.A. following indiscriminate pre-marketing clinical trials by 1,270 doctors who gave the drug to 20,771 patients of whom at least 207 were pregnant.* Other countries in which cases of thalidomide phocomelia occurred include Australia, Belgium, Brazil, Canada, E. Germany, Egypt, Israel, Lebanon, Peru, Spain, Sweden and Switzerland, although the drug was not marketed in all these.

When a drug becomes popular it crosses frontiers. It is interesting to speculate why modest apparent improvements can give a drug a therapeutic reputation such that people will go to great trouble to get it Responsibility may perhaps be divided amongst manufacturers who over-promote, doctors who write testimonials on inadequate evidence, thus encouraging over-promotion, the press which so ably both satisfies and stimulates the public appetite for "wonder-drugs" and the self-deluding vanity of patients that makes them feel it a desired distinction to be able to boast of being under treatment with the latest drug, particularly if it is one which is not available to their associates.

Perhaps the fact that the incidence of phocomelia was greatest amongst children of professional classes reflects the urge of doctors to ensure that their own families, as well as those of their perhaps most demanding or critical patients, should get the very newest and therefore, it is optimistically assumed, the best, drugs. Or, as the drug was freely sold in W. Germany, it may reflect a greater neurotic desire for self-medication in this group, or merely the ability to pay for it.

So rapidly did the news of the thalidomide disaster spread that some mothers who had taken it knew of the risk weeks before their babies were born. Of course, not all who took thalidomide during the crucial period (37th to 54th days from the first day of the last menstruation) had abnormal babies, perhaps no more than 20%, but there is no reliable figure.

Thalidomide has been a terrible lesson to the world and it deserves to be remembered. Its implications in both human and scientific terms merit the attention of all concerned in medical practice. A few are suggested below:

1. It is impossible to believe that all women in early pregnancy who took or were given thalidomide were in serious need of a sedative or hypnotic and that well-tried drugs had failed to give relief. There was certainly a lot of casual use of "the latest" drug without good reason. This must never be allowed to happen again. Commercial pressures for widespread use in uncontrolled situations, before a drug is thoroughly tried in controlled situations, though understandable, must be resisted. This may make drugs more expensive but it is undoubtedly the lesser evil.

2. Thalidomide was incriminated a mere 5 years after first marketing, because it was extensively used and because the abnormalities it caused were both dramatic and unusual. It is not known whether any other drugs in general use are causing either fetal loss in early pregnancy or fetal

* *New York Times* quoted by *Pharm. J.* 1963, Jan. 12.

abnormalities of a less obvious kind, e.g. reduction in intelligence; meprobamate can cause a reduced "intelligent quotient" in the young when given to pregnant rats, but the significance, if any, of this for man is obscure. However clinical caution is indicated for "intelligence is not so freely available that it can lightly be interfered with".†

3. Thalidomide, like most drugs, was not tested on pregnant animals before marketing. All new drugs are now tested thus, but the meaningfulness of the results for man is still uncertain. It is also possible that abnormal babies may result from drugs taken by their fathers (*80*).

4. Because prediction of clinical effects from animals is imperfect, machinery for reporting all possible drug toxicity to a central bureau to enable real effects to be detected at the earliest moment is essential and such monitoring schemes have been set up in many countries.

5. Except for demonstrably life-saving introductions, newness of a drug should be regarded as a reason for *not* prescribing it except as part of a scientific evaluation or where older, well-tried drugs have failed, until its place in relation to existing drugs is established.

6. In general, doctors are too ready to prescribe drugs and patients are too ready to take them for conditions which are self-limiting or cause only trivial discomfort.

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Chapter 7

CHEMOTHERAPY AND CHEMOTHERAPEUTIC AGENTS

The term chemotherapy is used for the drug treatment of parasitic infections in which the parasites (bacteria, viruses, protozoa, fungi, worms) are destroyed or removed without injuring the host. The use of the term to cover all drug, or synthetic drug, therapy needlessly removes a distinction which is convenient to the clinician and has the sanction of long usage. By convention the term is used to include therapy of cancer.

Chemotherapy has been practised empirically since ancient times. The Ancient Greeks used male fern, and the Aztecs chenopodium, as intestinal anthelmintics. The Ancient Hindus treated leprosy with chaulmoogra; there are numerous other examples. For hundreds of years moulds have been applied to wounds, but, despite the introduction of mercury as a treatment for syphilis (16th cent), and the use of cinchona bark against malaria (17th cent), the history of modern chemotherapy does not begin until the late 19th cent.

With the knowledge of bacterial and protozoal causation of diseases and the development of techniques for infecting laboratory animals, scientific therapeutic experiments could be performed. These animal experiments were not subject to the restrictions of clinical therapeutics, toxicity could be risked, and large numbers of infections treated under controlled conditions. In addition, acceptance of archaic authority and belief in magic were on the wane and a scientific approach to medical problems was becoming less rare.

It is not surprising that the differential staining of tissues and bacteria should have been the basis of early chemotherapeutic research for it was an obvious instance of chemicals affecting parasite and host differently and gave hope of usefully selective toxicity. Aniline dyes were used for staining and, when it was shown that these dyes could also kill bacteria, Ehrlich, already interested in the differential staining of leucocytes, tried the effect of dyes on infected experimental animals. In 1891 he cured experimental malaria in guinea-pigs with methylene blue, but it was less effective than quinine. In 1904 he controlled trypanosome infections in mice with another dye, trypan red, but it was ineffective in other species.

Ehrlich thus developed the idea of chemotherapy and he invented its name. In 1906 he wrote: "In order to use chemotherapy successfully we must search for substances which have an affinity for the cells of the parasites and a power of killing them greater than the damage such substances cause to the organism itself, so that the destruction of the parasite will be possible without seriously hurting the organism. This means we must strike the parasites and the parasites only, if possible, and to do this

we must learn to aim, learn to aim with chemical substances!" (*18*). Or, as a modern microbiologist has put it in reverse, formaldehyde "admittedly will fix the patient's bacteria, but will also fix the patient" (*48*).

Knowledge of the relationship between chemical structure and pharmacological action (i.e. learning to aim with chemicals) has steadily increased until at last it is being effectively applied to the development of new drugs.

By 1906 it was clear that chemotherapy was a practical proposition and not the fantasy that eminent contemporaries declared it. Inorganic arsenic had been shown to clear trypanosomes from the blood of infected horses and an organic arsenical had been used successfully on man. This inspired Ehrlich to make and test further compounds. His efforts resulted in the introduction of arsphenamine (Salvarsan) for the treatment of syphilis and it was soon followed by neoarsphenamine (Neosalvarsan) which was widely used until 1945 when penicillin superseded it.

Ehrlich also introduced the concept of a "chemotherapeutic index" (which see). The concept is valuable and now plays a part in everyday thought about drugs.

After neoarsphenamine there was a lull. Then the antimalarials pamaquin and mepacrine were developed from dyes and in 1935 the first sulphonamide, linked with a dye (Prontosil), was introduced as a result of empirical experiments by Domagk.

The results obtained with sulphonamides in puerperal sepsis, pneumonia and meningitis were dramatic and caused a reorientation of medical thought. Up to then chemotherapy had been virtually confined to protozoa and metazoa, spirochætes being considered as a special case. To kill pyogenic bacteria in the body had seemed impossible.

In 1928, seven years before the discovery of the sulphonamides, Fleming, whilst studying staphylococcal variants, found one of his culture plates contaminated with a fungus which destroyed surrounding bacterial colonies. This accidental rediscovery of the long-known ability of penicillium fungi to suppress the growth of bacterial cultures was now followed up. Fleming investigated the properties of "mould broth filtrates" which, for brevity, he named "penicillin". He described penicillin as an antiseptic more powerful than phenol which yet could safely be applied to the tissues. The name "penicillin" has since been applied to the pure antibiotic substances.

Attempts to isolate penicillin were made, but lack of appreciation of its potentialities and the difficulty of preparing enough for experiments caused it to be put aside as a curiosity, although Fleming used it in his laboratory as a method of differentiating bacterial cultures throughout the 1930's.

In 1939, principally as an academic exercise, Chain and Florey undertook an investigation of antibiotics (i.e. substances produced by microorganisms that, in high dilution,* are antagonistic to the growth or life

* This proviso is necessary to exclude various metabolic products such as alcohol and hydrogen peroxide.

of other micro-organisms). They prepared penicillin, discovered its *systemic* in addition to its local chemotherapeutic power against experimental infections in mice and confirmed its remarkable lack of toxicity.

The importance of this discovery for a nation at war was obvious to these workers but the time, July 1940, was unpropitious, for Britain was being bombarded from the sky with increasing vigour. It was necessary to manufacture penicillin in the Oxford University Pathology Laboratory where enough was made to start a small clinical trial in 1941. The results appeared good and it was clear that penicillin might have military importance, but because of the war large-scale production in Britain was not possible. The U.S.A. was still at peace, so arrangements were made for the production of penicillin there. Ample supplies were available to treat casualties in the latter part of the war.

Since 1939 large programmes of screening fungi, actinomycetes and bacteria for antibiotic production have been conducted. The first success was the isolation of streptomycin from a soil organism and this was followed by the tetracyclines, erythromycin and others. Simultaneously there have been developments in synthetic agents, especially against tuberculosis and tropical diseases, including malaria, leprosy and amœbiasis. That nothing is beneath the notice of some investigators is illustrated by the discovery of antibacterial substances in the anal gland secretion of the Argentine ant and in the fæces of blow-fly larvæ.

Most important infective diseases are now, to some extent at least, treatable. Prominent exceptions include small viruses and S. American trypanosomiasis. The small viruses present a special problem in that they enter host cells and use host mechanisms to multiply there, so that selective chemical attack may be specially difficult, though progress is being made. Substances capable of preventing the virus entering the host cell also exist but are more likely to be of use in prophylaxis than in therapy because the peak of virus multiplication precedes symptoms.

Effect of Chemotherapy on the Pattern of Disease

Since the introduction of effective antimicrobials for the commoner acute infections their prevalance has declined and their natural history is seldom seen because chemotherapy is generally given. Perhaps as a consequence of this the danger of some infections, if untreated, has become exaggerated. Suspicion is growing that chemotherapy does not alter the course of all diseases as dramatically as is sometimes assumed. The routine use of chemotherapy in mild cases of boils, endemic sore throat, chronic bronchitis, and whooping-cough is of particularly doubtful merit.

Despite the decline in some infections the total prevalence of infections has not lessened correspondingly. This is because of a simultaneous increase in infections due to organisms indigenous to the host and not previously considered highly pathogenic (enterococci, staphylococci, coliforms, pseudomonas, proteus). These organisms are adaptable and liable to become drug resistant. It is likely that the general use of chemo-

therapy is responsible for this change in, for example, urinary infections and endocarditis.

Though it would not be possible to make out a convincing case that modern chemotherapy has done more harm than good, it is salutary to remember that advances in therapy can have undesired repercussions in medicine. In addition the social effects of preserving life, with or without restoration of useful health, pose problems that cannot be discussed here.

Classification of Antibacterial Agents

The term *antimicrobial* is used in this book to mean all chemotherapeutic agents used against micro-organisms. The term antibiotic has a more limited definition, see above. Sulphonamides, isoniazid and quinine are *not* antibiotics: they are antimicrobials. It may be thought that this distinction is no longer useful.

Antibacterial chemotherapeutic agents may, for practical purposes, be divided into two groups, those which act primarily by stopping bacterial growth and those which act primarily by killing the bacteria:

PRIMARILY BACTERISTATIC	PRIMARILY BACTERICIDAL
sulphonamides	penicillins, cephalosporins
tetracyclines	streptomycin, neomycin, kanamycin, gentamicin
chloramphenicol	
erythromycin, novobiocin } low concentration	co-trimoxazole
PAS (sodium aminosalicylate)	polymyxin, colistin
lincomycin, clindamycin	erythromycin, novobiocin } high concentration
nitrofurantoin (in alk. medium at lower concs.)	isoniazid
	vancomycin, bacitracin, nitrofurantoin (in acid medium at higher concs.)

Most bacteristatic drugs become bactericidal at very high concentration or after a very long time, and so they may really all be bactericidal. The classification is given here because it has clinical relevance in that combinations of chemotherapeutic agents may be synergistic or antagonistic depending on various factors about some of which little is known; see below.

Also, when a bacteristatic drug is used the phagocytic defence mechanism of the body is relied on to destroy the organisms whose multiplication has been stopped by the drug, and this local reaction is inadequate for the purpose in carriers, bacterial endocarditis, osteomyelitis and in some debilitated patients, as well as in agranulocytosis and aplastic anæmia. In these cases bactericidal drugs should be used whenever possible even if laboratory *in vitro* tests show sensitivity to bacteristatic drugs, for the

patient is an *in vivo* experiment under conditions that differ from those in a bacteriology laboratory.

How Antimicrobials Act

There are four principal sites of action, on:

1. *The cell wall*, interfering with the osmotic defences so that the cell absorbs water and bursts, e.g. penicillins, cephalosporins.
2. *The lipoprotein cell membrane* (inside the cell wall), disorienting the molecules (like a detergent at an oil-water interface), so that the membrane becomes more permeable and vital metabolites escape, e.g. colistin.
3. *Ribosomes and nucleic acid metabolism*, interfering with cell protein synthesis, e.g. tetracyclines, chloramphenicol.
4. *Intermediary metabolism*, e.g. sulphonamides, PAS, isoniazid.

Choice of Antimicrobial Drugs

From the point of view of treatment, infections fall into two main classes (*19*) in which—

1. Choice of antimicrobial follows automatically from the clinical diagnosis because the causative organism is always the same and is virtually always sensitive to the same drug: some hæmolytic streptococcal infections (scarlatina, classical erysipelas), syphilis, typhus, plague, malaria, amœbiasis, leprosy.

2. Choice of antimicrobial should be based, whenever possible, on bacteriological identification and sensitivity tests because:

a. The infecting organism is not identified by the clinical diagnosis, for instance, bronchopneumonia, empyema, meningitis, urinary tract infection, although a useful guess can often be made.

b. The infecting organism is identified by the clinical diagnosis, but no assumption can be made as to its sensitivity to any one antimicrobial, for instance, carbuncle, tuberculosis.

The results of *in vitro* sensitivity tests are only one factor in the choice of drug. The tests are often unnecessary and can even be misleading and the physician must decide their relevance to the particular clinical problem before him. For example routine tests do not distinguish between bacteristatic and bactericidal effects and sometimes bactericidal drugs are essential. Occasionally these tests do not even parallel *in vivo* sensitivity.

On the other hand sensitivity tests can sometimes be essential to successful therapy especially in chronic or recurrent diseases, e.g. urinary tract infections, abscesses, osteomyelitis.

With these provisos, in general, where tests indicate that the organism is very sensitive to a drug, that drug should be used provided the patient is not allergic to it. Where tests show general resistance to drugs or where the apparent drug of choice fails after adequate trial it is worth trying a drug to which the bacteriologist has found the organism less sensitive or even quite resistant. It is always possible that the organism isolated

by the bacteriologist is not the prime cause of the disease, especially in cultures from sputum or throat.

In infections in either sub-division of the second group above there are a number of possible courses of action:

When bacteriological services are not available at all it may be necessary to choose antimicrobial drugs which cover the maximum range of organisms, e.g. gentamicin plus a cephalosporin or a penicillin. Alternatively the infection might be treated by a single broad-range antibiotic, such as tetracycline, a cephalosporin or ampicillin (if respiratory) which are effective against many Gram-positive and Gram-negative organisms. Treatment should be changed only after adequate trial, usually three days, for over-hasty alterations cause confusion and tend to produce resistant organisms. Lack of bacteriological assistance is not an excuse for indiscriminate polypharmacy.

When bacteriological services are available but treatment cannot be delayed it is obviously necessary to act as if they are absent, except that any appropriate specimens (blood, pus, urine, sputum, cerebrospinal fluid) *must* be taken for bacteriological examination before administering any antimicrobial, so that appropriate modification of treatment can be made later if necessary after identification and sensitivity tests.

When bacteriological services are available but treatment can only be delayed until simple staining tests have been done, the antimicrobial will be selected on the knowledge that the organism is a Gram-positive or a Gram-negative coccus or bacillus. It is therefore necessary to know the approximate range of antimicrobial drugs over organisms so classified (see tables below).

Activity of some important antimicrobials:

BENZYL-PENICILLIN	Gram-positive (except many staphs) and Gram-negative cocci. Some Gram-positive bacilli (C. diphtheria, clostridia, B. anthracis). Spirochætes
AMPICILLIN	Gram-positive cocci (except many staphs) and bacilli Gram-negative bacilli
CEPHALOSPORINS	Gram-positive cocci Gram-negative bacilli
STREPTOMYCIN	Gram-negative bacilli Gram-positive cocci Myco. tuberculosis
TETRACYCLINES	Gram-positive and Gram-negative cocci and bacilli Rickettsiæ Spirochætes E. histolytica
SULPHONAMIDES AND CO-TRIMOXAZOLE	Gram-positive and Gram-negative cocci Gram-negative bacilli

CHLORAMPHENICOL Restricted use because of rare hazard

Some organisms are invariably sensitive to certain antimicrobials when they occur in previously untreated patients. Temporary resistance, which may revert to sensitivity, may occasionally occur in some organisms (streptococcus) in some patients taking antimicrobials over long periods. The following list gives **organisms virtually always sensitive to certain antimicrobials:**

Streptococcus pyogenes (Group A)	penicillin
Streptococcus pneumoniæ (pneumococcus)	penicillin
Hæmophilus influenzæ and *parainfluenzæ*	ampicillin, chloramphenicol
Pseudomonas æruginosa	polymyxin, colistin
Neisseria meningitidis	penicillin
Treponema pallidum	penicillin

When bacteriological services are available and treatment may reasonably be delayed for up to 48 hours, then treatment may be chosen with knowledge both of the organism and of its sensitivity to drugs. This course should be followed whenever possible because it gives the best results.

Initial treatment of serious infections—In such serious infections as meningitis, gram-negative bacillary sepsis, and endocarditis, prompt treatment is essential and antimicrobial drugs should not be withheld until laboratory studies are completed. Parenteral administration, preferably intravenous, is usually mandatory if an infection is severe. After the infection appears to be under control, an oral formulation can be used for maintenance therapy.

Dr. Ernest Jawetz writes* "Before administering (an antimicrobial) the physician must . . . convince himself that the patient suffers from a microbial infection.

"As a second step it is necessary to acknowledge that each antimicrobial drug has a specific effect on a limited number of micro-organisms. Before selecting a drug the physician must therefore formulate a specific ætiological diagnosis on clinical grounds. The skilled physician's 'best guess' can be correct with surprising frequency. Having arrived at a specific clinical diagnosis, the physician can then select a suitable drug aimed at the ætiological micro-organism.

"But is it really rationally possible, from the hundreds of antimicrobial drug names, to choose a specific drug for a specific bug? . . . A physician needs to know only *one* representative of each (important antimicrobial) class and should forget about the conflicting advertising which claims superiority for one member of a class over another . . . Each physician can devise for himself a short list of specific primary and secondary indications for each representative of a class of drugs. . . . if the physician follows his own rules, given in *his* list, and rejects the frequent

* *Brit. Med. J.* (1963). **2**, 951.

personal and community pressures to alter them, he can greatly simplify the decision on which drug to use and when to use it.

"The physician's initial ætiological diagnosis on clinical grounds permits prompt selection of a drug to institute therapy. Before administering antimicrobial drugs suitable specimens are often obtained to permit the isolation of specific micro-organisms in the bacteriological laboratory. The isolation of a significant organism may confirm the physician's original impression and support his choice of drug. Conversely, it may force a change in antimicrobial therapy. The identification of the ætiological micro-organism is often far more meaningful than 'sensitivity tests' to antimicrobial drugs."

The following notes and table provide a summary of the choice of antimicrobial drugs. They are published here by permission of the Editor of *The Medical Letter on Drugs and Therapeutics* (*U.S.A*). I am very grateful to the Editor for permission to use this material.

The table should be used in conjunction with the text. There is some repetition between text and table, but I think that presenting the data in different ways may be helpful.

Note: the table does not include co-trimoxazole which, at the time of writing is only marketed in the U.S.A. for urinary infection. There are also some minor differences between table and text due to differences in practice between U.S.A. and Britain.

The Choice of Systemic Antimicrobial Drugs

"For each pathogenic organism there is generally one drug, or occasionally a combination of drugs, that is likely to be a better choice than other drugs or drug combinations. When the patient does not respond to a first-choice drug or cannot tolerate it, there is usually a preferred order of choice among alternative drugs. For each organism, therefore, the accompanying table lists first-choice drugs, and alternative drugs in order of preference.

"**Identification of the organism**—In choosing an antimicrobial drug, the physician must identify, at least tentatively, the organism responsible for the infection. The experienced clinician can often correctly identify or classify the organism on the basis of clinical evidence. A Gram stain of sputum, urine, wound exudate, or spinal fluid often yields a clue to the identity of the infecting organism and aids in the choice of a drug, at least for initial therapy before identification of the organism by culture. In most infections requiring antimicrobial therapy, smears and cultures are necessary.

"The physician can do Gram stains and simple cultures in his own office; whether he does tests himself or entrusts them to a laboratory, however, he should interpret the results with caution if they appear to conflict with the clinical evidence. Caution is especially necessary in interpreting the results of cultures from the upper respiratory tract. Such cultures may contain Hæmophilus influenzæ or pneumococci even when

Antimicrobial Drugs of Choice

"The table which follows is based on the results of susceptibility studies, published clinical studies, and the experience of Medical Letter consultants specialising in infectious diseases in the United States and abroad. While there was full agreement among the consultants on many recommendations, the table generally represents a consensus, not unanimity. New studies and the introduction of new antimicrobial drugs will doubtless require future revision of some recommendations. All of the drugs listed, without exception, have adverse effects.

(*P*) For drugs used both parenterally and orally, the symbol (P) means that for the indicated infection, parenteral administration is preferred."

Infecting Organism	*Drug of First Choice*	*Alternative Drugs*
GRAM-POSITIVE COCCI		
Streptococcus pyogenes groups A, B, C, and G	penicillin G[1]	an erythromycin[2]; lincomycin
*Viridans group of Streptococcus[3]	penicillin G (P)[1] with or without streptomycin[5]	cephalothin[4]; vancomycin [5,6]; an erythromycin with streptomycin[5]
*Enterococcus[3]	penicillin G (P)[1,7] (or ampicillin [P][7]) with streptomycin[5] or kanamycin (P)[5,6]	vancomycin[5,6]
*Streptococcus, anærobic	penicillin G (P)[1]	a tetracycline[8]; an erythromycin
Diplococcus pneumoniæ[9]	penicillin G[1]	an erythromycin[2]; lincomycin; clindamycin; chloramphenicol[5]
*Staphylococcus aureus non-penicillinase-producing	penicillin G[1]	lincomycin; clindamycin; vancomycin[5,6]; kanamycin (P)[5,6]; gentamicin[5]; cephalothin[4]
penicillinase-producing	a penicillinase-resistant penicillin[1]	same alternative drugs as for non-penicillinase-producing strains
GRAM-NEGATIVE COCCI		
Neisseria meningitidis	penicillin G (P)[1]	chloramphenicol (P)[5]; a tetracycline (P)[8]; an erythromycin (P); a sulfonamide (P)[10]
*Neisseria gonorrhoeæ[11]	penicillin G (P)[1]	a tetracycline[8]; ampicillin (P); spectinomycin; kanamycin (P)[5,6]

See following pages for footnotes.

Infecting Organism	*Drug of First Choice*	*Alternative Drugs*
GRAM-POSITIVE BACILLI		
Bacillus anthracis (anthrax)	penicillin G[1]	an erythromycin; a tetracycline[8]
*Listeria monocytogenes	penicillin G[1] or ampicillin	a tetracycline[8]; an erythromycin
*Bacillus perfringens (Clostridium welchii) (gas gangrene)[12]	penicillin G (P)[1]	an erythromycin (P); a tetracycline)P)[8]
*Clostridium tetani[13]	penicillin G (P)[1]	a tetracycline (P)[8]
Corynebacterium diphtheriæ[14]	penicillin G (P)[1]	an erythromycin (P)
GRAM-NEGATIVE BACILLI		
*Salmonella[15]	chloramphenicol[5]	ampicillin
*Shigella	ampicillin	oral kanamycin[6] or an oral polymyxin[6]; a tetracycline[8]
*Escherichia coli[16] enteropathogenic	an oral polymyxin[6]	oral kanamycin[6]
sepsis community-acquired	ampicillin (P)	a tetracycline (P)[8]; cephalothin[4]; kanamycin (P)[5,6]
hospital-acquired	kanamycin (P)[5,6]	gentamicin[5]; a polymyxin (P)[5,6,17]; a tetracycline (P)[8]; cephalothin[4]; carbenicillin
*Klebsiella pneumoniæ[16] community-acquired	kanamycin (P)[5,6] with or without cephalothin[4]	gentamicin[5]; a tetracycline[8]; cephalothin[1]
hospital-acquired	gentamicin[5]	kanamycin (P)[5,6]; a polymyxin (P)[5,6,17]; cephalothin[1]; chloramphenicol[5]
*Enterobacter (Aerobacter)	gentamicin[5]	kanamycin (P)[5,6]; a polymyxin (P)[5,6,17]; chloramphenicol[5]; a tetracycline[8]; carbenicillin
*Serratia	gentamicin[5]	kanamycin (P)[5,6]; chloramphenicol[5]; carbenicillin
*Proteus mirabilis[16,18]	ampicillin	kanamycin (P)[5,6]; cephalothin[4]; gentamicin[5]

Infecting Organism	*Drug of First Choice*	*Alternative Drugs*
GRAM-NEGATIVE BACILLI (*Continued*)		
other Proteus[16]	kanamycin (P)[5,6]	gentamicin[5]; carbenicillin; a tetracycline[8]; chloramphenicol[5]
Providencia	carbenicillin	gentamicin[5]
*Mima, Herellea	kanamycin (P)[5,6]	gentamicin[5]; a polymyxin (P)[5,6,17]
*Pseudomonas æruginosa[19]		
urinary tract infection	carbenicillin	a polymyxin (P)[5,6,17]; gentamicin[5]
other infections	gentamicin[5] with carbenicillin	a polymyxin (P)[5,6,17]
*Bacteroides		
respiratory strains	penicillin G[1]	chloramphenicol[5]; ampicillin; a tetracycline[8]; clindamycin; lincomycin; an erythromycin
gastrointestinal strains	a tetracycline[8] or chloramphenicol[5]	ampicillin; clindamycin; lincomycin
Actinobacillus mallei (glanders)	streptomycin[5] with a tetracycline[8]	streptomycin[5] with chloramphenicol[5]
*Pseudomonas pseudomallei (melioidosis)	a tetracycline[8] with or without a sulfonamide	chloramphenicol[5] with or without a sulfonamide; kanamycin (P)[5,6]
*Brucella (brucellosis)	a tetracycline[8] with or without streptomycin[5]	chloramphenicol[5] with or without streptomycin[5]
*Francisella (Pasteurella) tularensis (tularemia)	streptomycin[5]	a tetracycline[8]
Pasteurella pestis (bubonic plague)	streptomycin[5]	a tetracycline (P)[8]
Pasteurella multocida	penicillin G[1]	a tetracycline[8]
Hæmophilus influenzæ		
respiratory infections	ampicillin	a tetracycline[8]; streptomycin[5]; a sulfonamide
*meningitis[20]	ampicillin (P)	chloramphenicol (P)[5]; a tetracycline (P)[8]
Hæmophilus ducreyi (chancroid)	a tetracycline[8]	a sulfonamide; streptomycin[5]
Bordetella (Hæmophilus) pertussis (whooping cough)[21]	ampicillin	a tetracycline[8]; an erythromycin
Fusobacterium fusiforme (Vincent's infection)	penicillin G[1]	a tetracycline[8]; an erythromycin
Calymmatobacterium granulomatis (granuloma inguinale)	a tetracycline[8]	streptomycin[5]; ampicillin
Vibrio choleræ (cholera)[22]	a tetracycline[8]	chloramphenicol[5]; an erythromycin

Infecting Organism	*Drug of First Choice*	*Alternative Drugs*
ACID-FAST BACILLI		
*Mycobacterium tuberculosis	isoniazid combined with ethambutol, with or without streptomycin[5]	rifampin[23]; aminosalicylic acid (PAS); pyrazinamide[5]; cycloserine[5]; ethionamide[5]; viomycin[5]; kanamycin (P)[5,6]; capreomycin[5]; an erythromycin
*Atypical mycobacteria[24]	isoniazid combined with ethambutol, with or without streptomycin[5]	ethionamide[5]; cycloserine[5]; pyrazinamide[5]; viomycin[5]; kanamycin (P)[5,6]; capreomycin[5]; an erythromycin; aminosalicylic acid (PAS)
Mycobacterium balnei	cycloserine[5]	isoniazid
Mycobacterium lepræ (leprosy)	a sulfone[5,25]	amithiozone[5]
SPIROCHETES		
Spirillum minor (rat bite fever)	penicillin G[1]	an erythromycin; streptomycin[5]
Borrelia recurrentis (relapsing fever)	a tetracycline[8]	penicillin G[1]
Treponema pallidum (syphilis)	penicillin G[1]	a tetracycline[8]; an erythromycin
Treponema pertenue (yaws)	penicillin G[1]	a tetracycline[8]; an erythromycin
Leptospira[26]	penicillin G[1]	a tetracycline[8]
ACTINOMYCETES		
*Actinomyces israelii (actinomycosis)	penicillin G[1]	a tetracycline[8]; an erythromycin
Actinomyces muris ratti (rat bite fever, Haverhill fever)	ampicillin	an erythromycin; streptomycin[5]
*Nocardia	a sulfonamide with streptomycin[5]	a tetracycline[8] with cycloserine[5]
RICKETTSIA		
(Rocky Mountain spotted fever; endemic typhus; Q fever)	a tetracycline[8]	chloramphenicol[5]

Infecting Organism	*Drug of First Choice*	*Alternative Drugs*
MISCELLANEOUS FILTERABLE AGENTS, CHLAMYDIAE, AND VIRUSES		
Mycoplasma pneumoniæ (atypical pneumonia)	an erythromycin or a tetracycline[8]	no alternative
Agent of psittacosis (ornithosis)	a tetracycline[8]	chloramphenicol[5]
Lymphogranuloma venereum	a tetracycline[8]	chloramphenicol[5]; a sulfonamide
Chlamydia trachomatis (trachoma)	a tetracycline (topical)	an erythromycin (oral); chloramphenicol (topical); a sulfonamide (oral)
Virus of inclusion conjunctivitis	a tetracycline[8] (oral or topical)	chloramphenicol (topical)
Vaccinia	methisazone[27] with or without vaccinia immune globulin	no alternative
Herpes simplex (keratitis)	idoxuridine (topical)	no alternative
Influenza A2 strain[28]	amantadine[29]	no alternative
FUNGI		
Histoplasma capsulatum	amphotericin B[5]	no dependable alternative
Candida albicans	amphotericin B[5,30]	5-fluorocytosine; nystatin[30] (oral or topical)
Aspergillus	amphotericin B[5]	no dependable alternative
Cryptococcus neoformans	amphotericin B[5]	5-fluorocytosine
Mucor	amphotericin B[5]	no dependable alternative
Coccidioides immitis	amphotericin B[5]	no dependable alternative
Blastomyces dermatitidis (N. Amer.)	amphotericin B[5]	2-hydroxystilbamidine[5]
Blastomyces brasiliensis (S. Amer.)	amphotericin B[5]	a sulfonamide
Sporotrichum schenckii	an iodide	amphotericin B[5]; griseofulvin
Fonsecaea (chromoblastomycosis)	amphotericin B[5,31]	no dependable alternative
Dermatophytes (tinea, etc.)	griseofulvin [32]	no alternative systemic drug

* Because resistance may be a problem, susceptibility tests should be performed.

1. Penicillins should always be used with awareness of the possibility of hypersensitivity reactions. Penicillin V can be used as an alternative to penicillin G for oral treatment of infections by non-penicillinase-producing staphylococci and other gram-positive cocci. Although penicillin G is more susceptible to gastric acid degradation than penicillin V, adequate amounts are usually absorbed if it is taken on an empty stomach or in doses several times larger than V. For initial therapy of severe infections, crystalline penicillin G, administered parenterally, is first choice. For somewhat longer action in less severe infections due to Group A streptococci, pneumococci, gonococci, or Treponema pallidum, procaine penicillin G aqueous, an intramuscular formulation, is administered once or twice daily. Benzathine penicillin G, a slowly absorbed intramuscular preparation, is used in a single injection of 1,200,000 units for adults and 300,000 to 900,000 units for children for the treatment of Group A streptococcal pharyngitis. The same dose is repeated once monthly for prophylaxis against rheumatic fever. For oral use against penicillinase-producing staphylococci, cloxacillin or dicloxacillin is preferred; for severe infections, a parenteral formulation of nafcillin, methicillin, or oxacillin should be used. Penicillinase-resistant penicillins should be used only against known or suspected penicillinase-producing staphylococci. Occasional strains (fewer than 3 per cent) of coagulase-positive staphylococci may be resistant to penicillinase-resistant penicillins, and these strains are usually also resistant to cephalosporins; vancomycin is the most consistently active antibiotic against such strains. Any laboratory, however, that finds frequent methicillin-resistance in staphylococci should suspect the potency of the discs used in testing susceptibility. Ampicillin is not effective against penicillinase-producing staphylococci.
2. Occasional strains of Group A streptococci and pneumococci are resistant to erythromycin.
3. With endocarditis, disc sensitivity testing may not be sufficiently reliable; quantitative dilution tests for sensitivity should be used to assess bactericidal as well as inhibitory end points; bactericidal activity of the patient's serum against his own organism should be assayed during therapy and peak activity should be adequate at a serum dilution of at least 1:8.
4. The parenteral cephalosporins—cephalothin and cephaloridine—are effective against many coccal and some gram-negative bacillary infections. Both are administered only parenterally. Cephalothin is more effective than cephaloridine against penicillinase-producing staphylococci. Renal toxicity contraindicates the use of cephaloridine in patients with impaired renal function. These drugs have been used as alternatives to penicillins in patients with severe infections who are allergic to penicillins, but the cephalosporins can also induce hypersensitivity reactions, and there is some cross-sensitivity with penicillins. Cephaloglycin is an oral cephalosporin that has antibacterial activity only in the urine. Cephalexin is a well-absorbed oral cephalosporin that gives satisfactory antibacterial activity in the blood and tissues as well as in the urine.
5. Because of the frequency of serious adverse effects, the drug should be used only in severe infections and when less hazardous drugs are ineffective.
6. The oral preparation is usually not absorbed in significant amounts.
7. Large doses are needed in endocarditis. Lower doses, without streptomycin or kanamycin, are often effective in urinary tract infections.

8. Many different systemic tetracycline drugs are available. Tetracycline hydrochloride and phosphate complex, chlortetracycline, and oxytetracycline are available in both oral and parenteral formulations; tetracycline base, demeclocycline, methacycline, and doxycycline only for oral use; rolitetracycline only for parenteral use. There is no acceptable evidence of important therapeutic differences among the different tetracyclines. Doxycycline is preferred for uremic patients with infections outside the urinary tract for which a tetracycline is indicated; its low renal clearance prevents accumulation in uremia but makes questionable its effectiveness in urinary tract infection.

9. Erythromycin is preferred for respiratory infections in penicillin-allergic patients, and a combination of erythromycin and chloramphenicol is preferred for meningitis in penicillin-allergic patients.

10. Sulfonamide-resistant strains are frequent at present in the United States and sulfonamides should be used only when susceptibility is established by susceptibility tests. A soluble sulfonamide such as sulfisoxazole diolamine or sodium sulfadiazine should be administered intravenously. An oral sulfonamide can be used for prophylaxis in contacts of patients infected by sulfonamide-sensitive organisms.

11. Some strains of gonococci are relatively resistant to penicillin G and large doses may be required. Penicillin V and phenethicillin should not be used for gonococcal infections.

12. Debridement is primary; the value of antitoxin is not certain; large doses (at least 30 million units daily) of penicillin G are required, and hyperbaric oxygen therapy should also be used in the spreading, necrotic type.

13. For prophylaxis, proper debridement and a fluid toxoid booster dose are primary. If the patient has not received previous toxoid immunisation, tetanus immune globulin (human) in doses of at least 300 units should be administered. Clinicians disagree over the usefulness of including penicillin G for prophylaxis or therapy.

14. Antitoxin is primary; antibiotics are used only to halt further toxin production and to prevent the carrier state.

15. Chloramphenicol, oral or parenteral, is the first choice for Salmonella typhi although parenteral ampicillin may be effective in milder cases. Parenteral ampicillin should generally be used for other severe systemic Salmonella infections; in those not responding to ampicillin, chloramphenicol should be substituted. Most cases of Salmonella gastroenteritis subside spontaneously without antimicrobial therapy. The drug of choice for S. typhi carriers is ampicillin.

16. If the organism is responsible for an acute, uncomplicated lower urinary tract infection, the drug of first choice is one of the oral soluble sulfonamides, such as sulfisoxazole, sulfisomidine, sulfamethizole, or trisulfapyrimidines, with oral ampicillin or an oral tetracycline as an alternative. If there is no improvement after 48 hours, or if the urinary tract infection is chronic, recurrent or severe, cultures and susceptibility tests should aid in selecting an effective drug. Among other drugs useful for urinary tract infections are nitrofurantoin, nalidixic acid, methenamine mandelate, methenamine hippurate, cephaloglycin, and cephalexin.

17. The polymyxins are effective when used systemically in the treatment of urinary tract infections; systemic therapy of tissue infections with the polymyxins is of limited efficacy and probably totally ineffective in pulmonary infections.

18. Ampicillin is often the most active drug (as determined by susceptibility tests) against Proteus mirabilis, but large doses (6 Gm or more daily) are usually necessary. Large doses (about 20 million units) of penicillin G have also been effective.

19. In the absence of septicæmia, urinary tract infections due to Pseudomonas are usually effectively treated with low doses of carbenicillin (50 mg/kg/day). For severe infections due to Pseudomonas, especially those outside the urinary tract, many Medical Letter consultants recommend large doses of gentamicin (5 mg/kg/day) and carbenicillin (400 to 500 mg/kg/day). These two drugs act synergistically against many strains of Pseudomonas. There have been reports of inactivation of gentamicin when these two agents are mixed in the same bottle for intravenous administration and when both are given by any route to patients with severe renal insufficiency.

20. Medical Letter consultants are divided as to the first-choice drug; most prefer ampicillin administered intravenously until the results of susceptibility tests are known.

21. There is doubt whether antimicrobial therapy is of value once paroxysmal coughing has begun.

22. Antibiotic therapy is an adjunct to and not a substitute for prompt fluid and electrolyte replacement.

23. Rifampin should be used only in combination with other drugs to prevent emergence of resistance. It is the drug of choice in the treatment of isoniazid-resistant organisms. For initial treatment of advanced cavitary tuberculosis some Medical Letter consultants favour a combination of rifampin and isoniazid.

24. In spite of frequently encountered resistance of atypical mycobacteria to most antituberculosis drugs, vigorous chemotherapy with combinations of drugs (guided by drug susceptibility tests) can be effective.

25. Acetosulfone, dapsone, sulfoxone sodium, or glucosulfone sodium.

26. A clear-cut choice is difficult because of the paucity of data.

27. Methisazone is an investigational drug not yet approved for marketing by the Food and Drug Administration in the United States, but it can be obtained by application to the manufacturer, Burroughs Wellcome.

28. Uncomplicated influenza usually needs no specific treatment.

29. Approved for prophylaxis but not for therapeutic use in the United States by the Food and Drug Administration. Some consultants suggest that it may have some value therapeutically in severe cases of A2 influenza.

30. Amphotericin B administered intravenously is first choice, for systemic Candida infections; where oral or topical therapy is indicated, nystatin is preferable to amphotericin B.

31. Amphotericin B administered subcutaneously beneath lesions.

32. Oral griseofulvin should be used when topical drugs are ineffective.

other organisms are responsible for the infection; the relative numbers of different organisms may be helpful. When an organism is the only one isolated, or is predominant, or is present in large numbers, it is likely to be the cause of the illness; but even then, the exercise of clinical judgment is essential in interpreting the laboratory findings.

"**Susceptibility tests**—*In vitro* tests of the susceptibility of an organism to various antimicrobial agents are especially useful with organisms notorious for their inherent or developing resistance, such as Staphylococcus, Enterobacter, Klebsiella, Proteus, Pseudomonas, and Escherichia coli. An agent found active in susceptibility tests may prove ineffective if dosage is inadequate, if an organism other than the one responsible for the infection was isolated, if host resistance to infection is poor, or if abscesses or empyemas are present. Occasionally, an antimicrobial agent that is relatively inactive *in vitro* will be effective clinically. Even when an agent is very active *in vitro*, if the infection does not respond with reasonable rapidity, another drug should be substituted for it."

Bacterial Resistance to Drugs

Bacterial resistance to antimicrobials is a matter of great importance; if sensitive strains are supplanted by resistant ones, then a valuable drug may become useless. So far new discoveries have kept pace with development of resistance, but already it is sometimes necessary to use the more toxic antimicrobials, and there are no grounds for assuming that new drug development will always outrun resistance. For several years penicillinase-producing staphylococci were a grave clinical problem and killed many people.

Types of drug resistance

1. *Drug tolerant* (primary or acquired): the organism is capable of growing in the presence of the antimicrobial: this is the most usual form.

2. *Drug destroying:* the organisms inactivate the drug: this is the less common form: the chief example is penicillinase-producing staphylococci, a primary or natural resistance.

Origin of resistance in clinical practice

1. *Selection* of primary or natural resistant strains. In the course of therapy the naturally sensitive strains are eliminated and those naturally resistant (whether drug tolerant or drug destroying) proliferate and become dominant. This has happened in the case of gonococci and of penicillinase-producing staphylococci. Such natural selection by the environment is why resistant strains are more common in hospitals where, for example, there may even be important amounts of penicillin in the air.

2. *Spontaneous mutation*, with selective multiplication of the resistant strain so that it eventually dominates as in (1) above. A high degree of resistance may occur in a single step mutation (e.g. streptomycin) or it may

develop gradually in a series of small steps over a period of days (e.g. erythromycin), or even more slowly.

3. *By transmission of genes from other organisms* by:
   (a) *conjugation*: sexual intercourse which may be between cells of the same or of different species.
   (b) *transduction*: passage from one organism to another by bacteriophage.
   (c) *transformation*: direct incorporation from the environment.

Conditions suitable for gene transfer occur in clinical practice, especially in the large bowel; conjugation and transduction are the usual mechanisms.

Resistance may be both gained and lost to single or multiple drugs.

Wherever any one antimicrobial is widely used in a hospital, resistant organisms are favoured and drug-resistant infections can become a problem. Restrictive control of drug use by agreement between clinicians and bacteriologist can prevent this happening and can partially reverse existing trends (*21*, *22*, *40*).

An example of what can happen when drug-resistant organisms dominate is provided by experience in a 350-bed hospital in the U.S.A. during the period when penicillinase-producing staphylococci were common in hospitals and the penicillinase resistant penicillins had not yet been produced. It is obvious from the table (below) that staphylococcal infections acquired casually were trivial but that those acquired in hospital were dangerous. This was attributed to the fact that in hospitals staphylococci were commonly resistant to a wide range of antimicrobials in addition to the fact that the patients were already ill.

INCIDENCE OF STAPHYLOCOCCAL INFECTION IN A 350-BED HOSPITAL IN THE U.S.A. DURING 3½ MONTHS.*

Time infection occurred	*No. of infections*	*% of infections sensitive to all antibiotics tested*†	*Deaths*
Before admission	57	40	2
During stay in hospital	100	3	21
Within 60 days of leaving hospital	32	3	1

* Data from Wysham, D. N., and Kirby, W. M. M. (1957). *J. Amer. med. Ass.*, **164**, 1733.

† Tetracycline, chloramphenicol, streptomycin, penicillin, erythromycin, bacitracin.

Clinically the greatest problems of drug resistance occur with coliforms and M. tuberculosis. Staphylococci are still troublesome, but less so since the penicillinase-resistant penicillins were introduced in 1960. The problem is complex, for some organisms never become resistant to certain anti-

microbials whereas others readily do so. For example, pneumococci and Strept. pyogenes never develop penicillin resistance, whereas enterobacteria readily acquire resistance to any drug.

Some bacteriologists treat the fact that a microbe does not become resistant to a drug as a challenge to be met rather than as a blessing for which to give thanks. Their laboratory efforts in this field have not, so far, led to clinical disaster.

Gonococci rapidly became sulphonamide resistant. By 1945, ten years after the introduction of sulphonamides, the incidence of resistant strains had risen from less than 30% to over 70%, but fortunately by this time the efficacy of penicillin had been established. By 1959 strains of gonococcus relatively penicillin-resistant were reported and penicillin dosage was being increased in some clinics. Since sulphonamides have been abandoned in gonorrhoea the organism has gradually regained sensitivity to sulphonamides.

It is certain that inadequate dosage, in amount or duration, of antimicrobial drugs can promote resistant strains, and that extensive spread of resistant organisms can be delayed or prevented by proper use of drugs, including the use of combinations.

Cross-resistance with chemically related drugs is usual, and it occasionally occurs with chemically unrelated drugs.

That new problems of drug-resistance can be expected continuously is illustrated by the first appearance of tetracycline-resistant pneumococci in a general hospital more than ten years after their introduction. These organisms spread in the ward by cross-infection and killed five old men. Patients harbouring resistant organisms in an open ward are dangerous to others and not only to themselves.

The Masking of Infections

The masking of infections by chemotherapy is an important possibility. The risk cannot be entirely avoided but it can be minimised by intelligent use of antimicrobials. For example, a course of penicillin adequate to cure gonorrhœa may prevent simultaneously contracted syphilis from showing primary and secondary stages. Casual use of streptomycin in undiagnosed pyrexia may cause delay in diagnosing tuberculosis as well as development of drug resistance.

Nutritional Deficiencies and Malabsorption

The question of the development of nutritional deficiencies due to prolonged antimicrobial therapy preventing bacterial synthesis of vitamins in the intestine is a vexed one. In animal experiments deficiency of vitamin B complex and of vitamin K have been induced but conclusive evidence of their occurrence in normal man is lacking, though oral anticoagulants may be potentiated. It would obviously be wise to administer vitamin B complex to patients in whom any symptoms similar to deficiency

of this group of vitamins occur. Vitamin K deficiency may occur with severe intestinal hurry from any cause.

Oral neomycin induces a malabsorption syndrome with steatorrhœa and characteristic changes in the mucous membrane of the small intestine. Absorption of drugs is also impaired.

Superinfection or Secondary Infection

When any antimicrobial drug is used there is suppression of part of the normal bacterial flora of the patient, which varies according to the drug used. Often this causes no ill-effects, but sometimes a drug-resistant organism, freed from competition, proliferates and causes disease which can even be fatal. This superinfection, which may be due to bacteria or fungi, has been found to be commoner than was supposed. In a study of over 3,000 patients treated with antimicrobials 2% developed superinfection. The organs involved most frequently were those affected by the primary disease and superinfection occurred most commonly on the fourth day of chemotherapy. It was concluded that those most liable to superinfection were patients less than three years old, those with middle ear and lower respiratory tract infections and those treated with broad-spectrum drugs or combinations. The principal responsible organisms are Candida albicans, Proteus, Pseudomonas and staphylococci. Routine incorporation of nystatin oral preparations is probably needless, but it may be used if there is any particular reason to fear candidiasis. The mere presence of yeast in the sputum does not mean they are causing disease.

Superinfection also occurs with drugs that interfere with the response of the body to infections, adrenal steroids and other immunosuppressives.

A famous example of superinfection is that induced in guinea-pigs by penicillin. The drug, that is so remarkably non-toxic (except for allergy) in man and other species, is highly fatal to guinea-pigs. Deaths do not occur in germ-free guinea-pigs, and can be prevented by a mixture of non-absorbed antibiotics that are active against coliform bacteria. The penicillin, by interfering with normal gut flora, allows an enormous proliferation (10 million-fold) of coliform bacteria in the cæcum, with enterocolitis and fatal bacteræmia. This condition may be analogous to the enterocolitis that occurs in man during broad spectrum antibiotic treatment.*

Treatment Failure

Treatment failure may be due to drug resistance, natural or acquired. Where the organism is sensitive to the drug used, failure is usually due either to the way the drug is used or to some factor peculiar to the patient. Sabath (*2*) lists six causes:

1. Treatment begun too late to save the patient.
2. Suboptimal use of drug,

* FARRAR, W. E., *et al.* (1965). *Amer. J. Path.*, **47**, 629.

(a) dose too small,
(b) intervals between doses too long,
(c) duration of course too short,
(d) unsuitable route,
(e) adjuvant medications not used.

3. Organisms present in altered state (dormancy, variant forms).
4. Substances antagonising effect of drug present in the patient, e.g. pus, or unsuitable pH.
5. "Barriers" to adequate access of drug to organism,
   (a) natural, e.g. poor entry into eye, cerebrospinal fluid.
   (b) pathological, e.g. abscess, fibrosis.
6. Reduced host defences,
   (a) disease, e.g. congenital agammaglobulinæmia, reticuloses, leukæmia, old age, diabetes, cystic fibrosis.
   (b) immunosuppression, e.g. anticancer drugs and adrenal steroids: bacteri*cidal* drugs to be used here.

Combinations of Antimicrobials (*10*, *11*)

A critical attitude is essential towards the use of two or more antimicrobials, whether prescribed separately to suit the patient and his infection (concomitant therapy) or as a fixed-dose combined formulation.

The indications for use of two or more antimicrobials are four:

1. *To obtain synergism*, i.e. an effect unobtainable with either drug alone, e.g. co-trimoxazole; penicillin plus streptomycin (in enterococcal bacterial endocarditis).
2. *To delay development of drug resistance*, especially in chronic infections, e.g. tuberculosis.
3. *To broaden the spectrum of antibacterial activity* in a known mixed infection or where treatment is essential before a diagnosis has been reached; full doses of each drug are needed.
4. *To reduce severity or incidence of adverse reactions* where the organism is fully sensitive to each drug, but only if doses liable to cause adverse reactions are used; here lower therapeutic doses of each drug are used. This use is uncommon.

The attitude "if one drug is good, two should be better, and three should cure almost anybody of almost anything" is naive and irrational (*11*).

When combined therapy is used to treat an infection due to a single organism the result may be:

1. *Indifference:* this is common.
2. *Synergism:* uncommon except in certain specific situations, e.g. enterococcal endocarditis, tuberculosis and gram-negative bacillus infections.
3. *Antagonism:* also uncommon but most likely when minimally active doses of a bacteristatic and of a bactericidal drug are used together; the timing as well as the dose is important in this complex situation.

Clinical demonstration of antagonism has been made for penicillin + chlortetracycline in pneumococcal meningitis and in Group A streptococcal infection; for penicillin + erythromycin in Group A streptococcal infection; and in some urinary infections.

Bactericidal drugs act most effectively on rapidly dividing organisms. Thus a bacteristatic drug, by reducing multiplication, may protect the organism from the bactericidal drug. When a combination must be used blind, it is best to use two bacteristatic or two bactericidal drugs. But this is not a firm rule, since it is known that penicillin plus sulphonamide is a synergistic combination.

Jawetz (*11*) makes the following important points:

1. A particular combination cannot be specified as generally synergistic, but only as synergistic in relation to a particular micro-organism.
2. The need for combinations of antimicrobials arises only infrequently.
3. Drug combinations must never take the place of proper diagnosis or specifically directed antimicrobial therapy.
4. Fixed-dose combinations are unsuitable for general clinical use.

Disadvantages of combined therapy include:

1. False sense of security, discouraging efforts towards accurate diagnosis.
2. Increased incidence of adverse reactions.
3. Increased variety of adverse reactions.

Drugs between which there is cross-resistance should obviously not be used together.

There are difficulties with even the few rational fixed-dose combinations, e.g. co-trimoxazole. Sulphonamide resistant organisms are common and so use of this combination could be equivalent to exposure to trimethoprim alone thus encouraging development and spread of trimethoprim resistant organisms.

pH and Antimicrobial Activity (*15*, *16*)

The efficacy of some antimicrobials is greatly affected by pH and this has three aspects of practical importance:

1. Most laboratory sensitivity tests are conducted at pH 7·2–7·4.
2. Whilst the pH of the body cannot be altered to suit the drug, the pH of the urine often can be, over a range of 5 to 8·5.
3. Since the pH effect increases antimicrobial activity without increasing toxicity to the host, it is possible to use some of the more toxic antimicrobials (streptomycin, gentamicin, kanamycin) at lower doses, obtaining therapeutic efficacy with less risk of toxicity.

It is also possible that by pH adjustment useful activity may be obtainable against organisms ordinarily considered unsusceptible to a drug.

Examples: streptomycin and gentamicin are many times more active at pH 8·5 than at pH 5·5.

See also under *urinary infections.*

Duration of Antimicrobial Therapy

Too brief therapy fails to cure.

Unnecessarily prolonged therapy leads to adverse reactions, and promotes emergence of resistant strains and superinfection.

Evidence of cure may be hard to get, and empirical experience must sometimes be the sole guide. The variations in conduct of therapy, e.g. between sore throat, typhoid and urinary infections is due to the different characteristics of the infecting organisms and to the differences in pathology of the host. Notes will be found under *general principles* and under the individual diseases.

Administration of Antimicrobials

Oral administration is convenient, less unpleasant than parenteral administration and is commonly adequate. Published studies on plasma concentrations in relation to dose give results of administration on an empty stomach. Food retards absorption and maximum plasma concentrations are therefore less. In general antimicrobials should be taken between meals or at least one hour before a meal. In the case of cloxacillin the timing in relation to food can make the difference between success and failure.

Intravenous (or i.m.) administration is used for its increased certainty in urgent situations or where vomiting or malabsorption are feared. For therapeutic efficacy it is probably immaterial whether the drug is given intermittently (about 4 hrly) or in a continuous infusion.* But continuous infusion introduces risks of incompatibility and drug instability; though this may be more convenient to doctors, especially at night, where nurses are not permitted to give i.v. injections even into the tubing of an infusion.

Some drugs are given by routes decided by their chemical or biological (e.g. irritant) properties.

Chemoprophylaxis and Suppressive Therapy

(*29, 36, 37, 49*)

It is sometimes assumed that what a drug can cure it will also prevent, but this is not so.

The basis of effective true chemoprophylaxis is the use of a drug against one organism of virtually uniform susceptibility, e.g. penicillin against group A streptococci.

But the term chemoprophylaxis is commonly extended to include

* But a dose that gives peak concentrations well above the minimum inhibitory concentration (MIC) for the organism when given intermittently, may be too low to reach this concentration in the blood if infused continuously over 4 to 6 hrs.

prevention of *disease* as well as prevention of *infection* and the main categories of chemoprophylaxis may be summarised as follows— (1) true prevention of infection (rheumatic fever),* (2) suppression of existing infection before it causes overt disease (tuberculosis, malaria), (3) prevention of exacerbations of a chronic infection (bronchitis) and, (4) prevention of disease due to commensals getting into the wrong place (bacterial endocarditis after dentistry and peritonitis after bowel surgery); note that these are both high risk situations of short duration. Prolonged use of drugs would result in the areas concerned (mouth, bowel) being colonised by drug resistant organisms with potentially disastrous results. The urinary tract is a special case, see later.

Other situations in which chemoprophylaxis may be effective include epidemics of meningococcal meningitis, dysentery, rickettsial infection and plague as well as trypanosomiasis and syphilis and gonorrhœa. The indications for its use vary and may be non-existent in some cases, e.g. venereal diseases. Recurrent and post-surgical urinary and lung infections can be at least partially prevented. In "dirty" surgery there is no virtue in waiting for the infection to produce clinical manifestations before treating it. In "clean" surgery chemoprophylaxis is controversial, but a bactericidal drug probably reduces postoperative wound infection; the decision to use it routinely rather than only in special risk cases is influenced by non-pharmacological factors.

In hepatic failure the suppression of bowel flora to prevent coma due to absorption of toxic protein metabolites can also be considered a form of chemoprophylaxis.

Smallpox in contacts can be prevented by methisazone and influenza partially prevented by amantadine.

Prophylaxis of bacterial infection can often be achieved by doses that are inadequate for therapy. Details of the practice of chemoprophylaxis are given in the appropriate sections.

Attempts to use drugs routinely in groups specially at risk to prevent infection by a range of organisms, e.g. in pneumonia in the unconscious or in patients with heart failure, and in the newborn after prolonged labour have not only failed but have sometimes induced more infections with less susceptible organisms. Attempts to routinely prevent bacterial infection secondary to virus infections, e.g. in respiratory tract infections, measles, have not been sufficiently successful to outweigh the disadvantages (drug allergy and infection with drug resistant bacteria). It is probably generally better to await complications and then to treat them vigorously, than to try to prevent them.

* Rheumatic fever is caused by a large number of types of group A streptococci. But immunity is type specific so that recurrent attacks are commonly due to infection with different strains. All strains are sensitive to penicillin and so chemoprophylaxis is used.

Acute glomerulonephritis is also due to group A streptococci. But only a few types cause it, so that natural immunity is more likely to protect and, in fact, second attacks are rare. Therefore chemoprophylaxis is not used.

General Principles of Chemotherapy

The following notes apply to most patients for whom chemotherapy is being considered:

1. To decide whether chemotherapy is really necessary.

As a general rule, to which there are obvious exceptions, acute infections require chemotherapy whilst chronic infections do not. Chronic abscess, empyema or osteomyelitis for example, respond poorly, although chemotherapeutic cover is essential if surgery is undertaken, in order to avoid a flare-up of infection or its dissemination due to the breaking down of tissue barriers.

The best time to treat an infection is at the beginning when organisms are multiplying fast and are maximally susceptible to drugs.

2. To choose the drug on clinical or bacteriological grounds as described earlier.

3. To administer the drug in full dose having regard to the nature of the organism, its accessibility to the drug and the severity of the infection. An initial loading dose is often desirable.

4. To ensure not only that the total dose is adequate but that it is given at the proper intervals and by the best route or routes. Inadequate dosage may lead to the development of bacterial resistance.

5. To remove barriers to cure, e.g. lack of free drainage of abscesses, obstructions in urinary or respiratory tracts.

6. To ensure that therapy, once embarked on, is not changed without the best of reasons until an adequate time for a therapeutic response has elapsed, usually three days in acute infections.

7. If apparent cure is achieved the drug should be continued for about three days further to avoid relapse. There are many exceptions to this, such as typhoid fever, tuberculosis and bacterial endocarditis, in which it is known that relapse is possible long after apparent clinical cure and so the drugs are continued for a time determined by experience.

8. It is abuse of antimicrobials to use them merely as antipyretics. This causes diagnostic confusion, may fail to cure the patient and can even kill him. Unless a pyrexia is found to be undiagnosable after every reasonable effort, or is immediately life-endangering, antimicrobials should be withheld until the illness is diagnosed or the patient recovers spontaneously.

9. Two or more antimicrobials should not be used simultaneously without good reason.

10. Test of cure, In some infections bacteriological proof of cure is desirable because disappearance of symptoms and signs occurs before the organisms are eradicated, e.g. in urinary infections. Bacteriological examination must be done, of course, after the withdrawal of chemotherapy.

11. Measurement of blood levels of antimicrobials is seldom needed, but is essential if there is renal damage and toxic drugs which are excreted

by the kidney are used. This is especially likely to happen in the treatment of renal tuberculosis when the first dose or two of streptomycin may give adequate blood levels lasting for days.

12. Carriers need to be treated with bactericidal drugs, for bacteristatic drugs are ineffective in the absence of local inflammatory response.

INDIVIDUAL ANTIMICROBIALS

Sulphonamides and Sulphonamide Combinations (*13*, *17*)

The first preparations (1935) were linked to dyes (Prontosil Rubrum and Album) but it was soon discovered that it was the sulphonamide that had the antibacterial effect and that the dye was unnecessary. One of the first definitive clinical trials was done in 1936 on hæmolytic streptococcal puerperal infections (*20*). In the five preceding years the mortality rate from this infection in hospital had averaged 23%. From January 1936, when the sulphonamide treatment was begun, to August, the mortality was 4·7%. This fall was so dramatic that it was unnecessary to delay publication of the results until treatment had continued for a full year as had been intended. The authors admitted that the design of their clinical trial did not exclude as possible explanations of the result a spontaneous alteration in bacterial virulence or, more remotely, the chance admission to hospital of only mild cases in 1936. They discussed these possibilities but found it "difficult to resist the conclusion that the treatment has profoundly modified the course of the infection". This conclusion was soon amply confirmed.

Nowadays it would be considered essential to avoid the undoubted hazard of relying on previous mortality figures for infections by having two groups of patients treated concurrently and allotted randomly to old and new treatments.

In 1938 sulphapyridine, widely known as M. & B. (May & Baker) 693, was introduced and now there is a surfeit of sulphonamides from which to choose.

Mode of action. A fairly detailed account is given because sulphonamides illustrate well the important pharmacological principle of competitive inhibition.

Folic (pteroylglutamic) acid is essential for the growth of many bacteria. It is a precursor of purines which are precursors of DNA and RNA. Para-aminobenzoic acid (PABA) is a precursor of folic acid and sulphonamides are closely related chemically to PABA, see Fig. 4.

Some bacteria (e.g. streptococci) are obliged to synthesise their own folic acid from PABA. The hypothesis is that in these bacteria sulphonamides compete with PABA in this metabolic process but that their slightly different chemical structure prevents the bacteria from completing the synthesis to folic acid. As a result the bacteria are deprived of folic acid and cease to multiply. Sulphonamides are therefore primarily bacteristatic.

This hypothesis is supported by the following facts:

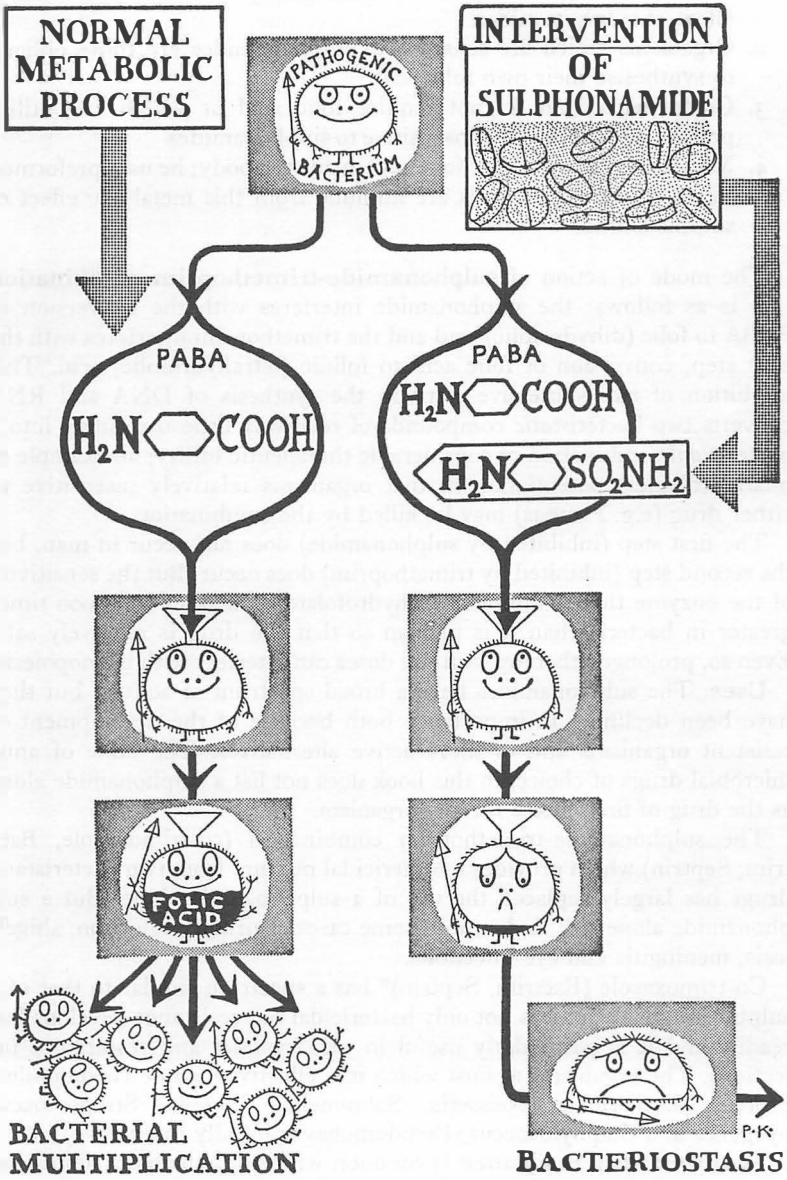

FIG. 4. The mode of action of sulphonamides, illustrating the principle of "competition".

1. PABA added to a culture medium antagonises the bacteristatic effect of sulphonamides.
2. Organisms which are sensitive to sulphonamides are those obliged to synthesise their own folic acid.
3. Organisms which do not require folic acid or which can utilise preformed folic acid are insensitive to sulphonamides.
4. Man does not synthesise folic acid inside the body; he uses preformed folate; therefore his cells are immune from this metabolic effect of sulphonamides.

The mode of action of **sulphonamide-trimethoprim combination** (*17*) is as follows: the sulphonamide interferes with the conversion of PABA to folic (dihydrofolic) acid and the trimethoprim interferes with the next step, conversion of folic acid to folinic (tetrahydrofolic) acid. This inhibition of two successive steps in the synthesis of DNA and RNA converts two bacteri*static* compounds of relatively little use singly into a bacteri*cidal* combination of considerable therapeutic utility; an example of pharmacological potentiation in that organisms relatively insensitive to either drug (e.g. Proteus) may be killed by the combination.

The first step (inhibited by sulphonamide) does not occur in man, but the second step (inhibited by trimethoprim) does occur. But the sensitivity of the enzyme that is inhibited (dihydrofolate reductase) is 50,000 times greater in bacteria than it is in man so that the drug is relatively safe. Even so, prolonged therapy with full doses can interfere with hæmopoiesis.

Uses. The sulphonamides have a broad spectrum of activity but they have been declining in importance both because of the development of resistant organisms and of more active alternatives. The table of antimicrobial drugs of choice, in this book does not list a sulphonamide alone as the drug of first choice for any organism.

The sulphonamide-trimethoprim combination (co-trimoxazole, Bactrim, Septrin) which provides a bactericidal mixture from two bacteristatic drugs has largely replaced the use of a sulphonamide alone. But a sulphonamide alone still finds use in some cases of urinary infection, shigellosis, meningitis and eye infections.

Co-trimoxazole (Bactrim, Septrin)* has a spectrum similar to that of a sulphonamide alone; it is not only bactericidal but resistance develops less readily and it is particularly useful in urinary tract and respiratory infections. The organisms against which it is effective include Hæmophilus, Proteus, Escherichia, Neisseria, Salmonella, Shigella, Streptococcus pyogenes and Staphylococcus (Pseudomonas is usually insensitive).

Acquired drug resistance is common with sulphonamides alone, but is still uncommon with co-trimoxazole.

Primary drug resistance. In laboratory tests for bacterial sensitivity the two ingredients of co-trimoxazole should be tested separately for it is important to know that the organism is sensitive to both drugs, for if it is

* Co-trimoxazole is not included in the table of antimicrobials of choice.

resistant to one and sensitive to the other the administration of the mixture is tantamount to treatment with one drug only.

Sulphonamide inhibitors occur in pus and may be a cause of failure of therapy when laboratory tests show sensitivity.

Pharmacokinetics. Sulphonamides for systemic use are rapidly *absorbed* from the gut. In the blood protein binding varies between 20% and 90% according to the compound, so that total plasma concentrations give no precise information on antibacterial activity unless the proportion of free and pharmacologically active drug is known. Sulphonamides displace bilirubin from plasma protein resulting in higher free bilirubin concentrations. Given in late pregnancy or to the newborn this can result in kernicterus.

Free unbound sulphonamide diffuses moderately readily throughout the body and enters serous cavities particularly easily if there is inflammation.

Cerebrospinal fluid (CSF) has a lower protein content than blood so that the proportion of free and bound drug will differ. Concentrations are 40% to 80% of those in blood. Sulphadiazine enters CSF more readily than others.

Rapid attainment of adequate plasma concentration is achieved by giving a *priming dose* which is twice the maintenance dose.

Metabolism. The principal path is conjugation with acetate (acetylation) (but with glucuronic acid in the case of sulphadimethoxine). Acetylated sulphonamide has no antibacterial effect and is less soluble (in some cases) so that it may cause crystalluria. Sulphasomidine is highly soluble in urine and but little acetylated so that it is excreted chiefly in the active form and so is specially suited to treatment of urinary infections.

The capacity to acetylate is genetically determined in a bimodal form, i.e. there are slow and fast acetylators (see *pharmacogenetics*) but the differences are insufficient to be of practical importance in therapy.

Excretion. Both the free drug and its acetylated form enter the glomerular filtrate and this is the principal mode of excretion; there is variable tubular secretion. Renal tubular reabsorption is also variable, it is substantial for the long acting sulphonamides, contributing to this property. Thus the half-life varies between drugs according to proportion of drug free and available for glomerular filtration, tubular secretion and tubular reabsorption, which latter is also influenced by urinary pH.

In an alkaline urine sulphonamides are more soluble (except sulphadimidine), more active and at a higher concentration (due to less tubular reabsorption).

The concentration of sulphonamides in the urine is greater than that in the blood, since the daily intake, distributed throughout the body, is concentrated into about two litres of urine per day. Thus urinary infections may be treated with lower doses than systemic infections, with correspondingly less risk of toxicity. However, some acetyl conjugates are relatively insoluble and so are prone to precipitate in the renal tubules.

In an attempt to avoid this risk, sulphonamide mixtures were tried, taking advantage of the fact that the solubility of each sulphonamide is independent of the others, although the antibacterial effect is additive. However the highly soluble modern sulphonamides have rendered the use of mixtures unnecessary.

The risk of *crystalluria* is present, even with the most soluble sulphonamides wherever they are being used in full doses for a systemic infection.

Crystalluria can cause renal colic, hæmaturia, oliguria and even anuria and death. The risks can be reduced by:

a. Ensuring a urinary volume of at least two litres a day, which may be difficult in a sick person.
b. Making the urine alkaline.

Renal insufficiency leads to higher plasma concentrations and enhances toxicity, so that sulphonamides are more dangerous in patients with a raised blood urea.

Sulphonamides may be classified according to pharmacokinetic properties:

1. **Well absorbed and rapidly eliminated:**

   (a) *general purpose*: e.g. sulphadiazine, sulphadimidine (sulphamezathine), sulphamethoxazole, and sulphonamide mixtures, e.g. Sulphatriad (sulpha-thiazole,-diazine,-merazine): Novotriad (sulpha-diazine, dimidine, furazole). This group has half-lives of 7 to 20 hrs; they are given 4 to 6 hrly.
   (b) *for urinary infections principally*: e.g. sulphafurazole, sulphasomidine, sulphamethizole. The half-lives are somewhat shorter than the above due to rapid renal clearance, and acetylation is less so that high urinary concentrations of active drug result. But this rapid excretion means that plasma concentrations adequate to treat tissue infection (e.g. renal substance) may not be attained. Solubility in urine is relatively high even if it is acid. They are given 4 to 6 hrly.

2. **Well absorbed and slowly eliminated:** long-acting sulphonamides: e.g. sulphadimethoxine, sulphasomizole, sulphamethoxypyridazine, sulphamethoxydiazine, sulphaphenazole, sulfadoxine, sulfametopyrazine.

These are particularly heavily protein bound and there is substantial renal tubular reabsorption so that half-lives are as high as 30 to 40 hrs and the drugs can be given once or twice a day, or, in the case of sulfadoxine (also used for malaria and leprosy), once a week. The long acting sulphonamides do not adequately substitute for the general purpose sulphonamides, for they provide low plasma concentrations of free drug at safe doses. The incidence of adverse reactions is relatively high, especially of the serious Stevens-Johnson syndrome (a severe form of

erythema multiforme), probably because accumulation is difficult to avoid if plasma concentrations are not monitored.

3. **Poorly absorbed:** e.g. succinylsulphathiazole, phthalylsulphathiazole. These provide high concentration of antimicrobial effect in the colon lumen where bacterial hydrolysis releases sulphathiazole. Systemic toxicity can occur since 5% to 10% is absorbed. Since about 80% of the solid matter of the fæces is bacterial (70% of total fæces is water) it is not surprising that these drugs reduce fæcal volume and render it soft or semi-fluid. Sulphaguanidine is about 50% absorbed and is obsolescent.

4. **Topical application:** sulphacetamide, though of relatively low antibacterial potency gives a neutral solution and so can safely be used on eye: mafenide (Sulfamylon) and silver sulphadiazine for prophylaxis of infection of burns (wide spectrum including Pseudomonas) (maphenide is preferable as there is not cross-allergy with other sulphonamides).

5. **Miscellaneous:** sulphasalazine (salicylazosulphapyridine) is useful in ulcerative colitis; its mechanism of therapeutic action is unknown; it is not due to antibacterial effect: sulphapyridine is useful in dermatitis herpetiformis, curiously.

Choice of sulphonamide is made on the basis of the above classification.

Obsolescent or obsolete drugs, for a variety of reasons, e.g. toxicity, insolubility in urine, partial absorption, include, sulphanilamide, sulphathiazole, sulphamerazine, sulphaguanidine, (though some are used in low dose in mixtures).

Administration. *Oral.* Tablets (usually 0·5 g) may be crushed, which is most easily done in water. Flavoured suspensions are available for children.

In systemic infections a "loading dose" (twice the maintenance dose) is given to raise the blood level to therapeutic height as rapidly as possible and then regular maintenance doses to keep it there until the temperature has been normal for two or three days. The dose of the sulphonamide may then be halved for a further two or three days, except in the most severe infections. If a good response is not achieved in three days an antibiotic should generally be substituted for the sulphonamide. Treatment should seldom exceed a week or a total of 30 g, because after this the likelihood of allergic toxic effects increases rapidly.

Unless an infection is a threat to life it is sometimes permissible to omit one dose of sulphonamide in the night if the patient is asleep, since it is now known that the importance of maintaining blood levels continuously at bacteristatic levels is not as great as was once thought; sleep may sometimes be more valuable to the patient than drugs.

Parenteral. The route of choice is intravenous, *very* slowly from a syringe, or better in a saline (*not* blood or plasma) infusion. The dose schedule can be as for oral sulphadiazine, but infusion need not be repeated more often than 8 hrly and should be replaced by oral therapy as soon as possible. The concentration of sulphonamide in the solution to be given should not exceed 2·5 g/100 ml. Parenteral administration is very rarely required except in severe meningitis. They must *not* be given intrathecally and if given i.m.

sites must be widely spaced and well away from nerves. They are strongly alkaline except for sodium sulphasomizole which is neutral.

Adverse effects. The less serious effects include malaise, headache, nausea or vomiting, mental depression and rarely cyanosis, which latter is due to methæmoglobinæmia. These may all be transient and are not necessarily indications for stopping the drug.

Serious toxic effects include:

CRYSTALLURIA, which may progress to anuria: renal tubular necrosis.
ALLERGIC REACTIONS of many kinds.
DIARRHŒA. HÆMOLYSIS.

When any of these occur the drug should be stopped at once, although a mild crystalluria can be reversed by prompt treatment.

Crystalluria (see also above) may be symptomless if very mild. If detected before anuria develops, much fluid should be given and the urine made alkaline with potassium or sodium citrate orally or sodium bicarbonate, orally or i.v. according to the state of the patient. The reaction of the urine should be tested to ensure that enough alkali is being given and the sulphonamide should be changed for another antimicrobial.

Anuria due to crystals must be distinguished from that due to renal tubular necrosis. A surgeon should be consulted in the former case because ureteric catheterisation or nephrostomy may be necessary; otherwise the anuria is treated in the usual way.

Allergic reactions due to sulphonamides are not very common but may include rash, fever, hepatitis, agranulocytosis, purpura, aplastic anæmia, peripheral neuritis, a serum-sickness-like syndrome and polyarteritis nodosa. If any of these toxic effects occur the patient should never again take any sulphonamide, and should be warned accordingly.

Diarrhœa sometimes results from alteration of the intestinal flora, especially with the poorly absorbed sulphonamides. Superinfection is uncommon. The B group of vitamins may be given but may do no good.

Doses of some sulphonamides: sulphadiazine, sulphadimidine (0·5 g*) systemic infections, priming oral dose 3 g, then 1 g, 4 to 6 hrly: urinary infections, 1 g, 6 hrly: sulphasomidine, sulphafurazole (0·5 g) in urinary infection 1 g, 6 hrly: sulphamethoxazole, sulphaphenazole, (0·5 g) priming dose 2 g, then 1 g, 12 hrly: sulphadimethoxine, sulphamethoxydiazine (0·5 g) priming dose 1 to 2 g, then 0·5 g, daily: phthalylsulphathiazole (0·5 g), 1 to 1·5 g, 4 to 6 hrly: succinylsulphathiazole (0·5 g), 2 to 3·5 g, 4 to 6 hrly: sulphasalazine (0·5 g), 1 g, 4 to 6 hrly.

Co-trimoxazole tabs. consist of trimethoprim 80 mg and sulphamethoxazole 400 mg (the pædiatric tabs. contain 20 mg and 100 mg respectively). The mode of action, advantages and uses of this combination have already been described. Sulphamethoxazole is preferred in the combination because its half-life (about 10 hrs) is similar to that of tri-

* Throughout this book tablet sizes are indicated thus.

methoprim so that, unless there is selective renal excretion in cases of renal disease, the infecting organism is always exposed to approximately the optimum ratio of drugs.

Trimethoprim is also antimalarial, it is related to pyrimethamine, and the mechanism of action is the same.

Adverse reactions are similar to the sulphonamides. The risk of macrocytic anæmia due to interference with conversion of folic to folinic acid is only important with prolonged full-dose therapy: if it occurs it can be reversed by giving folinic acid and this will not reverse the antibacterial effect of the trimethoprim since bacteria cannot utilise either preformed folic or folinic acid because they do not absorb it. Generally the drug will be withdrawn in preference to continuing it under folinic acid treatment.

The **dose** is 2 tabs 12 hrly; an i.v. formulation is available.

The Penicillins

Penicillin is produced by growing one of the penicillium moulds in deep tanks. According to the variety of the fungus and the composition of the medium either benzylpenicillin (penicillin G) or phenoxymethylpenicillin (penicillin V) results. Various other natural penicillins occur but are not important.

The first clinical trials of penicillin were done in 1941 on a few patients with severe staphylococcal and streptococcal infections which had not responded to surgery or sulphonamides. Even though the patients were given, by present standards, only tiny doses, the beneficial effects were clear. Large-scale statistical clinical trials were out of the question; indeed the drug was so scarce that the patients' urine was collected, the penicillin extracted and used again.

In 1957 the penicillin nucleus (6-aminopenicillanic acid) was made by fermentation and it became possible to add various side-chains and so to make semi-synthetic penicillins with different properties.

It must now be recognised that all penicillins have not the same antibacterial activity and that it is necessary to choose between a number of penicillins just as between antimicrobials of different chemical groups.

Clinically important penicillins fall into three main groups:

1. **Benzylpenicillin,** and alternatives to it that are resistant to gastric acid, e.g. phenoxymethylpenicillin, phenethicillin.

2. **Penicillinase-resistant penicillins** used solely against resistant (drug-*destroying*) staphylococci, for they are less active against other penicillin-sensitive organisms, e.g. cloxacillin, methicillin, etc. Unfortunately drug-*tolerant* staphylococci are being increasingly encountered.

3. **Broader spectrum penicillins,** e.g. ampicillin, carbenicillin, etc. which have lower efficacy so that they are not adequate substitutes for organisms sensitive to benzylpenicillin.

The **mode of action** is by interference with cell wall mucopeptide synthesis so that organisms explode from internal pressure. Penicillin is thus bactericidal, and only effective against multiplying organisms

since resting organisms are not making new cell wall. This also explains how bacteristatic drugs, e.g. tetracyclines, may antagonise the effect of penicillin.

An account of *benzylpenicillin* (soluble penicillin) follows, and then of other penicillins in so far as they differ.

Uses. Benzylpenicillin is used in a wide range of infections, having largely displaced the relatively toxic sulphonamides, but there can now be few occasions where the indications for it are absolute as there are so many other antibiotics.

The principal organisms against which benzylpenicillin is used are streptococcus, pneumococcus, gonococcus, treponema, penicillinase-negative staphylococcus, clostridia. Some newer penicillins, of course, are virtually different drugs (cloxacillin, ampicillin).

Drug resistance. Amongst sensitive species there are some natural or primary resistant strains, e.g. Staph. aureus and Strep. viridans and, under treatment, these proliferate owing to lack of competition from sensitive strains that are suppressed by penicillin. Acquired resistance is uncommon but has appeared amongst gonococci. Fortunately the resistance is still incomplete and can be overcome by increasing the dose.

Pharmacokinetics. Benzylpenicillin is an acid that is provided as its more stable sodium or potassium salts. Its half-life is about 30 min. and concentrations in acutely inflamed tissues follow approximately the same time course. This is why reasonably spaced doses of penicillin have to be so large.* About 60% of an injected dose quickly appears unchanged in the urine. About 80% of this amount is excreted by the renal tubule (this can be blocked usefully by probenecid) and the rest comes out through the glomerulus. Where high plasma concentrations are required it is simpler, except in small children, or in bacterial endocarditis where very large doses may be needed, to increase the dose rather than to use probenecid. In the first few months of life penicillin excretion is slower than in older children and adults. Although much penicillin is excreted in the urine it is not often used in renal tract infections because few of the responsible organisms are sensitive to it.

Oral administration is less reliable, partly because benzylpenicillin is destroyed by acid in the stomach and partly because absorption from the intestine is incomplete.

Distribution is throughout the body, except bone and nervous tissue, but concentrations vary and it is necessary to inject penicillin locally if high concentrations are desired in the cerebrospinal fluid, pericardium, pleura, joints and eye (subconjunctival injection). However, inflamed membranes pass it quite well so that this is seldom necessary.

* The high renal clearance is illustrated by the fact that 50,000 units i.m. will keep the plasma concentration above 0·16 units/ml for 2 hrs; but to double the duration, the dose must be multiplied 12 times. Of course, very high peak plasma concentrations will be reached in about 30 min. Only the extraordinary lack of dose-related toxicity of penicillin allows such fluctuations, sometimes above 10 times the therapeutic concentration, to be acceptable.

Adverse reactions hardly occur following s.c. or i.m. injection except in patients allergic to penicillin, although a dull pain at the injection site is common. The successful i.m. administration of 100 million units (60 g.) a day has been recorded, but nowadays any patient thought to need such doses would be better treated with another drug. But if there is renal insufficiency, doses exceeding 15 g/day may be toxic to the CNS (coma, convulsions); also, at such doses, the amount of cation (Na, K) in the salt of penicillin may be enough to produce characteristic adverse effects. Mental disturbance, pulmonary and cardiovascular symptoms occur after procaine penicillin, due to accidental i.v. injection and blockage of capillaries by crystals.

Mild diarrhœa may occur with oral penicillin, due to interference with the normal intestinal flora. Superinfection in the bowel is uncommon.

Excessive doses into the subarachnoid space may cause meningeal reaction, or even convulsions.

Penicillin lozenges are of no value in throat infections and are liable to cause soreness of the mouth and tongue. The cause of this symptom is uncertain, but it is important to recognise it, for it has led doctors to intensify the offending treatment.

Antibodies to penicillin occur in virtually everyone who has had penicillin and in many who think they have not had it (e.g. it is liable to be present in milk from treatment of bovine mastitis; it is even present in the air in hospitals). The mere presence of antibodies does not, of course, mean that there is clinical allergy.

Allergies of all kinds occur in up to 10% of patients, principally itching rashes, eczematous or urticarial (especially with ampicillin). Anaphylactic shock, though rare, can be fatal. It is said to be most likely to occur with intravenous injection, which may be accidental, but it also occurs with oral administration. Anaphylactic shock is also more likely if a previous reaction has been serum-sickness-like than if it has been urticarial. It occurs almost at once after administration.

After a tonsillectomy penicillin was administered to a young man and he developed a rash. It was decided to change the treatment, but due to an oversight the patient's name was not removed from the "penicillin list". The patient told the nurse of his sensitivity to penicillin as she was about to give the next injection, but the nurse relied on the list, proceeded with the injection and the patient died of an anaphylactic reaction. All patients should be asked about previous allergy as a routine, and a positive answer taken seriously.

Doctors and nurses who prepare injections carelessly sometimes sensitise themselves to penicillin.

Allergy generally occurs to all forms of penicillin at once, but rarely it may occur to a particular side-chain or to another ingredient of a preparation, but this is difficult to identify.

The reason for cross-allergy amongst penicillins is probably that allergy is not to the penicillin itself but to degradation products common

to all the clinically used penicillins. These may form *in vitro* or *in vivo*. Attempts are being made to use these degradation products in developing tests for allergy that will neither induce serious reactions in the allergic nor sensitise the non-allergic. Such tests include, detection of circulating antibodies, and detection of reaginic antibodies using sensitised tissues (lung, leucocytes), etc. But no reliable test that is practicable for routine use has yet been found.

If a patient is believed to be allergic to penicillin the drug is best avoided for tests for allergy and hyposensitisation can be dangerous and unreliable. Nowadays it is generally possible to use another drug. However, if penicillin must be used intradermal tests may be done first. The reactivity of the skin to penicillin itself does not accurately reflect the presence or absence of general allergy, for the sensitising substance is likely to be a metabolite/protein conjugate. Thus false negatives to skin tests are common but false positives are rare. Intradermal tests are more reliable than scratch or patch tests, although a patch test is proper to test for allergy caused by dermal use. 0·1 mg of the penicillin preparation to be used, dissolved in normal saline (say 0·05 ml) may be injected intradermally on the flexor side of the forearm with a control injection of an equal volume of normal saline on the other side. Even this amount of penicillin can induce a serious reaction and some advise a smaller dose. If the result is negative when read in 20 minutes a 5 or 10 times stronger solution may be tried. It may then be safe to try a small dose s.c., and so on. The test outlined above will not predict a delayed serum-sickness-type reaction, but such cases may show a positive local reaction after 48 hrs.

This brief account of a most complicated subject should suffice to show that when there is even a suspicion of penicillin allergy the drug is best totally avoided *and the patient warned.*

Penicillin allergy may disappear spontaneously but cannot be relied on to do so. The kind of allergy that manifests itself as urticaria is especially likely to disappear over a period of months.

Attempts to treat penicillin allergy by injecting penicillinase have not been as successful as was hoped. Now that it is known that the allergy is due to metabolites rather than to the penicillin itself, this is not surprising. In addition, the penicillinase preparation is allergenic.

Elimination of protein impurities from penicillins has been found to reduce the incidence of allergy, e.g. Purapen G (*23*).

If a patient reacts to a skin test and the physician feels obliged to persist with penicillin then hyposensitisation may be carried out under cover of an adrenal steroid and an antihistamine. A small subcutaneous injection, less than 1 mcg, may be given and at first increased tenfold and then, at higher doses, doubled, hourly as commonsense counsels, for there are no fixed rules. If a reaction occurs it will be necessary to reduce the dose again and increase it more slowly. Numerous alternative schemes have been proposed and they are probably no less satisfactory. It may be possible to withdraw the steroid gradually after reaching therapeutic doses of peni-

cillin, but if symptoms recur it must be continued. It is also necessary to consider the perhaps unpredictable effect of the steroid on the disease process itself. Every effort should be made to find alternative chemotherapy.

No attempt should be made to hyposensitise healthy people who are known to be allergic to penicillin if they can be protected from exposure for hyposensitisation often fails, is dangerous, and, if achieved, may not last, so that the subject must still continue to avoid penicillin.

If a minor reaction occurs during a course of therapy it is sometimes possible to continue with antihistamine and/or adrenal steroid cover as above but this should only be done in grave conditions where no adequate alternative is available.

For general discussion, see *drug allergy*.

Patients with infectious mononucleosis or lymphatic leukæmia almost always develop a characteristic rash with ampicillin. It is thought to be related to the abnormal lymphocytes and to be a dose-related toxicity rather than an allergy so that penicillins may often safely be used again.

Preparations and dosage. It is salutary to reflect that the first clinically useful antibiotic is also the least toxic. Because toxicity is confined (except for intrathecal injection) to allergy, the dose can be adjusted to the known or assumed sensitivity of the organism. There has been a tendency to use huge doses routinely on the basis that what a little will do well, more will do better. But this is not necessarily so, and the best bactericidal concentration is 5 to 10 times the minimum inhibitory amounts in culture (*32*). It has even been shown experimentally that greater amounts can have *less* effect in some bacterial strains. In addition the rate of clinically important superinfection of the respiratory tract increases substantially with increasing dose.*

The penicillin level in inflamed tissue is the same as that in the blood, but where there is tissue destruction, exudate, or the tissue is relatively avascular (heart valves) then the tissue level lags behind that in the blood so that a transient drop in blood level below the effective level will not matter.

It is probably best to aim at continuous bactericidal effect even though damaged bacteria need four hours to recover their ability to multiply when penicillin is withdrawn.

For a sensitive infection, *Benzylpenicillin Injection, B.P.* 300 to 600 mg† (0·5 to 1·0 mega-units) i.m., 6 hourly is enough. This is obviously inconvenient in domiciliary practice and 600 mg (1,000,000 units, 1 mega-unit) 12 hourly can be used, but because renal excretion is rapid and increases with increased dose the minimum blood level will fall below that of the same total dose given at shorter intervals. Thus the maximum blood level rises hugely with a big dose, but the duration of effect increases only a little. If infrequent dosage is unavoidable, a mixture of benzylpenicillin and one of its long-acting variants is used (see below).

* Louria, D. B. *et al.* (1963). *J. Amer. med. Ass.*, **186**, 987.

† 1 mg benzylpenicillin = 1,670 units.

For relatively insensitive infections and where sensitive organisms are in avascular tissue (subacute bacterial endocarditis: tissue necrosis) 6 to 18 g (10 to 30 mega-units) are used. For such cases it is useful, especially in children, to block renal tubular excretion with probenecid (which see), to get higher blood levels for a longer time with smaller volumes of injection.

When an infection is subdued a change may be made from injected to oral penicillin (phenoxymethylpenicillin) to avoid the discomfort and labour of injections, but it is unwise to depend on the vagaries of intestinal absorption in the very ill.

Dosage with the different penicillins varies because, not only do their activities differ in relation to each other, but also in relation to different range of organisms susceptible to them and the degree of plasma protein binding. Claims of superiority based solely on plasma concentrations are therefore meaningless. Only actual measures of antibacterial effect at different blood levels against particular organisms are relevant.

For injection

Benzylpenicillin Inj., B.P., see above and, for routes other than i.m., below.

Procaine Penicillin Inj., B.P. is given i.m. only. It is a comparatively stable salt and liberates benzylpenicillin over 12 to 24 hours according to the dose administered. An average dose would be 900 mg once a day or 600 mg 12 hourly. There is no general agreement on its place in therapy. It is probably best to use soluble benzylpenicillin in the most severe infections, especially at the outset, as procaine penicillin will not give therapeutic blood levels for some hours after injection.

Procaine Penicillin Inj., Fortified B.P. is an attempt to combine the advantages of soluble benzylpenicillin, rapid absorption and high peak blood level, with that of procaine penicillin, slow absorption with lower but steady blood level. It contains 300 mg of the procaine salt to 60 mg of benzylpenicillin in 1 ml.

Benzathine Penicillin is a depôt preparation which gives low blood levels lasting from a few days to four weeks following i.m. injection and according to dose. It is little used in acute infections because the blood levels are low, but has a place in chemoprophylaxis. The dose against Strept. pyogenes is 900 mg (1·2 mega-units) i.m., 2 to 4 weekly.

Various other "depôt" or "repository" penicillin preparations, e.g. benethamine penicillin, penicillin in oils and mixtures of the above, e.g. Triplopen, Penidural All Purpose, are available.

For oral use

Phenoxymethylpenicillin Tabs., B.P. (250 mg) (penicillin V), is resistant to gastric acid and so reaches the small intestine intact and is reliably absorbed. It is less active than benzylpenicillin against H. influenzæ, Proteus and the gonococcus and so is unsuitable for use in bronchitis and gonorrhœa. It is a satisfactory substitute for benzylpenicillin against pneumococci and staphylococci. The dose is 250 to 500 mg 4 hourly.

Benzylpenicillin Tabs., B.P. (250 mg). Since it is destroyed by gastric acid it is essential that it be taken on an empty stomach. The dose is 250 to 500 mg 4 hourly, or more.

Alternative oral, semi-synthetic, acid-resistant penicillins, each with its slightly varying relative potency against particular organisms include *phenethicillin, propicillin.*

All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food.

Other routes of administration

Topical applications. *For oral infections.* Penicillin Lozenges B.P.C. (0·6 mg, 1,000 units) allowed to dissolve in the mouth, which takes one or two hours may be used. They are useless for sore throats.

Preparations for other sites, eye, wounds, etc. are available. Penicillin should not be used on skin because rashes commonly result.

Intrathecal administration is probably never essential, but if a diagnostic puncture gives purulent cerebrospinal fluid, it would seem sensible, in a seriously ill patient, not to lose the opportunity of injecting 6 mg (10,000 units) benzylpenicillin, in at least 10 ml fluid to avoid direct damage to the central nervous system. Ampicillin (10 to 40 mg) and cloxacillin (10 mg or more) can also be used intrathecally.

Intrapleural injection of 0·6 g (1 mega-unit) of benzylpenicillin is useful in empyema.

Penicillinase-resistant Semi-synthetic Penicillins

Penicillinases (beta-lactamases chiefly) destroy penicillins by interfering with the beta-lactam ring which is common to all. But accessibility of this ring to the enzyme varies according to the kind of side-chain so that penicillins differ in the rate at which they are destroyed. In 1960 there was introduced the first penicillin so highly resistant to penicillinase that it could kill resistant (drug-destroying) staphylococci despite actually inducing the production of this enzyme. These penicillins are invaluable in treating staphylococcal infections in hospitals, where resistant organisms are particularly common.

Bacteria can also develop a drug-tolerant type of resistance to this group of penicillins. Where this occurs it is obviously important to prevent it spreading; patients should be isolated.

Methicillin is destroyed by gastric acid and so must be injected i.m. or i.v.; the dose is 1·0 g 4 hrly. for 24 hours, then 6 hrly.

Cloxacillin is absorbed when swallowed, but more variably than **flucloxacillin** which is well absorbed. Cloxacillin, B.P. (250, 500 mg) is given orally, 500 mg 6 hrly, or i.m. 250 to 500 mg 4 to 6 hrly; flucloxacillin (250 mg) orally or i.m. 250 mg 6 hrly. Alternatives include oxacillin, dicloxacillin, nafcillin.

Other Semi-synthetic Penicillins

Ampicillin (250, 500 mg) has a broader spectrum. It is acid-stable and so is orally active. It is bactericidal to Gram-negative bacilli including salmonellæ, shigellæ, E. coli, H. influenzæ and some Proteus strains. It is destroyed by penicillinase. The dose is 0·5 to 1·5 g 6 to 8 hrly orally, and 250 to 500 mg 4 to 6 hrly i.m. It is combined with cloxacillin (as Ampiclox) for early treatment of neonatal infection which may include resistant

staphylococci. **Amoxycillin** is bacteriologically the same as ampicillin but pharmacokinetically superior, i.e. smaller doses give effective plasma concentrations.

Carbenicillin differs from other penicillins in that it is useful against Pseudomonas æruginosa; but high doses are needed. It is also used against some (indole-positive) Proteus and E. coli. It is destroyed by penicillinase. It must be injected i.m. or i.v., 4 to 6 hrly; the dose varies from 4·0 to 8·0 g total daily, for urinary infections, to 20 to 30 g total daily, for septicæmia.

Cephalosporins

Cephalosporins were first obtained from a mould cultured from the sea near a Sardinian sewage outfall in 1945. Development of semi-synthetic forms has followed. Cephalosporins are related to the penicillins in so far as they also have a beta-lactam ring. This ring gives the penicillins and cephalosporins a similar mode of action, and a spectrum similar to ampicillin. But vulnerability to beta-lactamase enzymes (penicillinase, cephalosporinase) is substantially less. Staphylococci resistant to methicillin (drug-tolerant forms) are also relatively resistant to cephalosporins. There is partial cross allergenicity between penicillins and cephalosporins, i.e. patients allergic to penicillin can often, but not invariably, be safely treated with a cephalosporin.

Cephalosporins are chiefly used for penicillin-resistant (drug-destroying) staphylococci and in Gram-negative urinary tract infections.

Cephaloridine is given i.m. (painfully) or i.v., 250 mg to about 1·0 g 6 hrly: renal toxicity occurs at higher doses and in those with reduced renal function (e.g. age); toxicity is enhanced by diuretics or by other nephrotoxic antibiotics. **Cephalothin** is similar to cephaloridine (including dose); it is probably less toxic to the kidney. **Cephalexin** (250 mg) is absorbed when swallowed; oral dose 250 mg to 1·0 g, 6 hrly. **Cephaloglycin** is useful only in urinary infections. See also **Probenecid.**

Aminoglycosides

Streptomycin

Streptomycin was the first important antibiotic discovered in the deliberate search that followed the demonstration of the clinical efficacy of penicillin. It is obtained from Streptomyces griseus which was cultured by Waksman in 1944, from a heavily manured field and also from a chicken's throat. It was soon introduced into medicine for its bactericidal activity against Myco. tuberculosis and other penicillin-insensitive organisms. It acts by interfering with protein synthesis.

Uses. Streptomycin is most important in therapy of tuberculosis, tularæmia and plague, but it can also be useful against E. coli, Proteus vulgaris, Ps. æruginosa, H. influenzæ, Br. abortus and Kl. pneumoniæ. But gentamicin is generally preferable as less toxic.

In urinary infections the urine should be made alkaline as this enhances the antibacterial action and, since bacterial resistance may develop in a

matter of hours, heavy doses (0·5 g, 8 hrly.) may be used for a maximum of three days. Even this may cause eighth nerve damage in the elderly. If the patient is not then better streptomycin should be stopped unless the organism can be shown to have retained its sensitivity in which case the dose must be halved to avoid toxicity. In the treatment of tuberculosis, streptomycin is always combined with other drugs (isoniazid, PAS) as each prevents the proliferation of strains resistant to the others since the drugs act at different metabolic sites.

Although there were theoretical objections, circumstances forced the trial of intermittent streptomycin therapy in tuberculosis—frequent intramuscular injections are impracticable outside hospital—and it has been found effective. This may be because streptomycin is bactericidal, and the organism is slow growing.

Bacteria sometimes become dependent on streptomycin for growth, but it is not known whether this ever has practical clinical importance.

Drug resistant organisms rapidly dominate when streptomycin is used alone, see above, and except in tuberculosis streptomycin is best used in short vigorous courses. There is partial cross-resistance with neomycin, kanamycin and paromomycin.

Pharmacokinetics: *absorption* from the intestine is negligible and streptomycin is used to destroy intestinal bacteria. For systemic use it is given i.m. *Distribution* is throughout the extracellular fluid. It penetrates poorly into the cerebrospinal fluid and the eye, moderately into the pericardium and joints, and readily into the peritoneal cavity. It crosses the placenta. Streptomycin is *excreted* unchanged by the kidney. If renal function is poor the drug will accumulate and cause serious toxicity with ordinary doses; this must be especially remembered when treating renal tuberculosis in which twice-weekly serum assays are desirable to establish correct dosage. Streptomycin should not be used in the absence of information on renal function. Blood levels above 3 mcg/ml 24 hours after injection foreshadow danger to the eighth cranial nerve.

Toxicity is marked with high doses and is a serious drawback to the use of streptomycin. The gravest toxic effect is eighth cranial nerve damage which increases with the size of the dose and the duration of treatment and the age of the patient above 40 years. With 2 g a day over half the patients develop symptoms during the fourth week and with 1 g a day a sixth of the patients develop symptoms during the sixth week of treatment. Vestibular damage predominates and dizziness (often only when upright at first), headache, nausea, vomiting, nystagmus and ataxia occur at first. The symptoms may then settle down and only be noticeable on sudden movement. Recovery generally occurs over weeks or months but it is often incomplete especially in those above 40 years who are also liable to develop serious toxic effects at lower doses. They should not be given streptomycin where there is a reasonable alternative. In tuberculosis streptomycin may be essential. If symptoms of ototoxicity occur it must be stopped.

Without postural sense swimming becomes dangerous. Caloric tests of vestibular function may enable vestibular damage to be detected before serious symptoms occur. The auditory division of the eighth nerve is less vulnerable but tinnitus followed by deafness can occur and may be permanent. The location of the damage, in the eighth nerve, at the end-organ, neurone or in the central connections has not been settled. Streptomycin should obviously be stopped, if possible, before symptoms of eighth nerve dysfunction occur. However, symptoms can first occur after the drug has been stopped and if they occur during therapy they can progress after its cessation.

Large amounts of streptomycin instilled into pleural or peritoneal cavities after surgery have been followed by respiratory paralysis due to neuromuscular block.

The use of streptomycin to destroy vestibular function (bilaterally) in the treatment of Ménière's syndrome (unilateral), while interesting as applied pharmacology, is hardly therapeutics.

Allergic reactions occur, particularly rashes and fever with eosinophilia; hyposensitisation is possible. Albuminuria occurs rarely, it is reputed to herald no danger. Vague feelings of paræsthesiæ of the lips, headache, lassitude, dizziness may occur after each injection; they are less common if the patient is kept at rest after an injection, and it has been demonstrated that muscular activity hastens absorption after i.m. injection, so that higher plasma concentrations occur. Pain at the injection site is common.

Dihydrostreptomycin was introduced in an attempt to avoid the vestibular toxic effects of streptomycin, but it was soon found to be very toxic to the auditory division of the eighth nerve. A mixture of equal parts of streptomycin and dihydrostreptomycin (streptoduocin, Dimycin) has been used in an attempt to reduce the toxicity to the eighth nerve, whilst retaining therapeutic efficacy. Its superiority has not been proved and the drug has been generally abandoned.

Preparations and dosage

Streptomycin Sulphate Injection, B.P. is given i.m. (painfully), a usual dose being 1 g a day as a single dose or 0·5 g twice a day. Occasionally 3 g a day is given for two or three days only.

Intrathecal injection is rarely indicated. Streptomycin is irritant to the meninges and neurotoxicity is enhanced by using this route. The dose is 20 to 50 mg in at least 10 ml. Solutions should be freshly prepared for each injection and should contain no preservative. They may also be used in the pleural and peritoneal cavities.

Oral streptomycin tablets, 1 g 6 hrly for three days, may be used prior to bowel surgery and for dysentery.

Application of streptomycin to the skin, either therapeutic, or accidental when preparing injections, should be avoided as sensitisation is liable to occur.

Other Aminoglycosides

These resemble streptomycin in many ways, including 8th cranial nerve toxicity.

Gentamicin (0·8 mg/kg i.m., 8 hrly) is safer than streptomycin. It affects the vestibular branch of the 8th cranial nerve primarily; auditory damage is rare. Gentamicin is chiefly used against Ps. æruginosa, E. coli, Proteus and staphylococci. It is also used topically. It is often effective against organisms resistant to kanamycin and neomycin. Its half-life is 3–6 hrs. **Tobramycin** is specially active against Ps. æruginosa. **Kanamycin** is less active against Ps. æruginosa and more toxic to hearing.

Neomycin (0·5 g) is principally used topically in combination with another antimicrobial to prevent drug resistance, e.g. neomycin + bacitracin (Neobacrin), and for its antibacterial action in the bowel, for which it is preferred above streptomycin because it is more effective against coliforms (E. coli, Proteus, Ps. æruginosa) and because drug resistance is slower to develop.

Prolonged oral use causes a malabsorption syndrome (food and drugs are affected) with characteristic intestinal mucosal changes.

Dosage, as an intestinal antiseptic before surgery, 1 g 4 hrly for one or two days; for dysentery, for up to five days. It may be combined with bacitracin or a non-absorbed sulphonamide. Neomycin is the best antibiotic for oral use in hepatic failure, 4 to 6 g daily total. Enough absorption does occur to cause eighth nerve damage especially if there is renal failure. Kanamycin may then be preferred as being less ototoxic.

Bacteria resistant to this group of minor antibiotics are often resistant to streptomycin, but, curiously, the reverse is less constant.

Paromomycin and **framycetin** are similar to neomycin in use (bowel infections and "sterilisation" and topical application) and in toxicity. These aminoglycosides are very ototoxic and enough may be absorbed with topical use on raw surfaces to produce this effect. They are also nephrotoxic to differing degrees.

Chloramphenicol (*7, 27, 44*)

Chloramphenicol was obtained in 1947 from a streptomyces found in a soil sample from a mulched field in Venezuela and from a compost heap in Illinois, U.S.A. It was soon made synthetically. Chloramphenicol was the first antibiotic with a wide range of activity against common organisms which was also reliably absorbed from the intestine. It was also dramatically effective against organisms hitherto immune from therapy, salmonellæ and rickettsiæ. Unfortunately its use in trivial infections soon became widespread with tragic results for some. Chloramphenicol is bacteristatic; it inhibits protein synthesis.

Uses. Chloramphenicol is chiefly active against **H. influenzæ, H. pertussis,** salmonellæ and other **coliforms (E. coli, Proteus, Klebsiella),**

streptococci, brucellæ and rickettsiæ. Its systemic use is dominated by the fact that it can cause, though rarely, fatal aplastic anæmia; apart from this it would be a drug of choice for common infections, e.g. bronchitis. The danger of aplastic anæmia is remote enough for a physician habitually to prescribe chloramphenicol for such diseases and yet not to see a case of aplastic anæmia during his career. This has led some to discount the risk (about 1 : 50,000 courses), but to many it is intolerable that trivial disease should be treated with chloramphenicol. "A girl of four years had an attack of bronchitis with asthma for which she received 1 g chloramphenicol daily for four days. Six months later she developed a sore throat, which was treated with a further course of chloramphenicol, 1 g daily for four days. Three days after completing this course a purpuric rash appeared and in spite of blood transfusion she died two weeks later." Aplastic anæmia was found at necropsy.*

Chloramphenicol therefore should only be used where the infection is insensitive to other drugs† and this situation is only likely to arise in severe H. influenzæ infections (meningitis, pneumonia) and in typhoid fever, where it is superior to ampicillin. Urinary tract infections should not nowadays require chloramphenicol.

Drug resistance rarely occurs *during* treatment. Resistant S. typhi occur.

Pharmacokinetics: *absorption* from the alimentary tract is almost complete. It is metabolised in the liver and *excreted* in the urine where only 10% is active drug.

Distribution is approximately even throughout the body but concentrations in the pleural space and cerebrospinal fluid, in the absence of inflammation, are about half the plasma concentration. In meningitis the concentrations in cerebrospinal fluid approximately equal those in the plasma.

Toxicity. Apart from the soreness of the mouth, alimentary tract symptoms due to alteration of normal flora are less common than with tetracyclines because of the more complete alimentary absorption. Rashes are rare; central nervous system disturbances occur. Chloramphenicol had been in clinical use for three years before its most serious toxic effects, blood disorders, were reported. The blood disorder may be thrombocytopenia, granulocytopenia or, worse, aplastic anæmia, any of which may be fatal. Aplastic anæmia is more likely to occur after repeated or prolonged or heavy courses of treatment though it is not closely dose-related. It may be detected at an early and recoverable stage by repeated examination of the blood. The danger level is a total leucocyte count below 4,000/cu. mm. This may be the only situation where repeated blood examinations offer a real safeguard against unpredictable marrow depression.

Victims of aplastic anæmia are likely to die of it, or, if they do not, to develop leukæmia.

* GAIRDNER, D. (1954). *Brit. med. J.*, **2**, 1107.

† It may be thought justifiable to use it more freely in the aged.

Aplastic anæmia is probably an idiosyncrasy (which see), but there is also a reversible and directly dose-related bone marrow depression (anæmia, reticulocytopenia) that can be regarded as a normal pharmacological effect of the drug.

Chloramphenicol is the commonest cause of drug-induced aplastic anæmia.

Optic nerve damage occurs very rarely.

Another serious toxic effect of chloramphenicol was discovered as a result of routine use of chemoprophylaxis in premature babies born 24 hours or more after spontaneous rupture of the fetal membranes (*46*). Their mortality was high and demanded investigation. A controlled experiment seemed the only ethical way to clear up the confusion caused by the uncontrolled introduction of chemoprophylaxis.

Babies were allocated to four treatment groups:

1. No drug treatment	32 babies	19% died
2. Chloramphenicol	30 babies	60% died
3. Penicillin + streptomycin	33 babies	18% died
4. Penicillin + streptomycin + chloramphenicol	31 babies	68% died

The cause of death was circulatory collapse (grey syndrome) with high chloramphenicol plasma concentration due to failure of the liver to conjugate, and of the kidney to excrete, the drug.

Had the controlled experiment, with measurement of plasma concentrations, been made at the outset, the uncontrolled experiment, with its loss of life, would never have been made.

Biochemical investigation of the fate of drugs in the immature can alone predict safe dosage schedules. However, it is easy to be wise after the event.

Dosage. *Chloramphenicol Caps., B.P.* (250 mg) 250 to 750 mg may be given orally 6 hrly. The dose should be as low as is reasonable and medication should not extend beyond 14 days. Parenteral preparations are available.

Topical applications for eye, ear and skin are available and seldom cause allergy. However bactericidal drugs that are not used systemically, bacitracin, neomycin, polymyxin, chlorhexidine, are generally preferable.

The Tetracyclines

Tetracyclines (1948 and after) have the broadest antimicrobial spectrum of all. They are obtained from soil streptomyces. The differences between them are small and tetracycline serves for general use. Demethylchlortetracycline is an alternative. They are bacteristatic, though, with i.v. injection, weakly bactericidal blood levels can be achieved. They interfere with bacterial protein synthesis.

Uses. Tetracycline is active against nearly all Gram-positive and Gram-negative pathogenic bacteria except for most strains of Proteus and Ps.

æruginosa. It can therefore be the drug of choice for many common infections, particularly if these are mixed or if therapy must be "blind". e.g. peritonitis, bronchitis, bronchopneumonia. Tetracycline does not replace penicillin where the latter is indicated, because penicillin is both less toxic and bactericidal. Tetracycline is also useful against large viruses and rickettsiæ and is used in combination or as a second choice in numerous infections: see table of drug choice.

Since teeth provide a permanent record of tetracycline given during their development (*25*: see below), they can be used for epidemiological studies of prescribing. Examination (under ultra violet light) of 400 first permanent molars extracted during normal treatment in a local authority dental clinic revealed that more than half the children aged 3 to 15 yrs had had a tetracycline during the first 10 yrs of life. The youngest children showed the highest incidence (over 70%). Discoloration visible to the naked eye occurred in 15% of the youngest and 7% of the older children.

Drug resistance is now a common problem in virtually all species of organism. Cross-resistance within the group is complete.

Pharmacokinetics: the tetracyclines are only partially *absorbed* from the alimentary tract, enough remaining in the intestine to alter the flora and to give rise to troublesome and sometimes dangerous complications. They are *distributed* throughout the body, but i.v. administration is needed to get high levels in the cerebrospinal fluid. They are *excreted*, largely unchanged, in the urine. The half-life of tetracycline is about 8 hrs and this is increased in renal failure to as much as 108 hrs. Serious deterioration of renal function due to increased antianabolic effect (below) may occur. The half life of doxycycline is not increased in renal failure (it is metabolised) and it should be used in such cases.

Adverse reactions. Heartburn, nausea and vomiting due to gastric irritation, are common. Attempts to reduce this with milk or antacids reduce absorption. Loose bowel motions occur, due to alteration of the bowel flora, and this sometimes develops into diarrhœa.

Superinfection may be due to C. albicans (with sore mouth, diarrhœa and pruritus ani), Proteus, Pseudomonas or staphylococci. The last can cause a fulminating and fatal enteritis and is most likely to do so where the drug is used in heavy and prolonged dosage after gastric and intestinal surgery. Its occurrence when tetracycline is given i.v. is probably due to biliary excretion of the drug. When superinfection occurs the tetracycline should be withdrawn, but substitution of another antibiotic should be delayed, if possible, until the superinfecting organism is shown to be sensitive to it. In the case of C. albicans, nystatin is used but it may be doubted whether the routine incorporation of nystatin or amphotericin B into oral preparations of tetracyclines (Mysteclin) is useful. But patients particularly disposed to superinfection (which see) who need prolonged therapy may reasonably be given nystatin in addition from the outset. Withdrawal of the tetracycline as soon as definite diarrhœa occurs is probably the wisest course; spontaneous recovery is then usual. Admini-

stration of a purgative to a patient with abnormal bowel flora is risky, as it is liable to precipitate diarrhœa.

Disorders of epithelial surfaces, perhaps partly due to vitamin B complex deficiency and partly to mild superinfection with yeasts or moulds, lead to sore mouth and throat, black hairy tongue, dysphagia and peri-anal soreness. There is some evidence that administration of vitamin B preparations may prevent or arrest alimentary tract symptoms. It is probably wise to give these vitamins routinely if tetracycline therapy is to be prolonged.

Tetracyclines provide another example (see chloramphenicol) of an important unwanted effect of a drug with valuable actions first being noticed years after widespread clinical use. Whenever this occurs the question whether the effect could and should have been predicted must always be asked. Being wise after the event provides a pleasantly easy basis for criticism of others, especially if it can be represented as championing the sick or helpless. However, in this case the developers of the tetracyclines cannot reasonably be blamed for lack of foresight.

Tetracyclines are selectively taken up in **growing bones and teeth** of the fetus and children, due to their chelating properties with calcium phosphate. This causes dental enamel hypoplasia with pitting, cusp malformation, yellow or brown pigmentation and increased susceptibility to caries. The severity and pattern of changes varies with the dose of the tetracycline and the age of the child.

After the fourteenth week of pregnancy and in the first few months of life even short courses can be damaging. The second dentition is not affected in utero. Avoidance of discoloration of the permanent front teeth requires avoidance of tetracyclines from birth to 4 years, and of other teeth until 8 years of age. Prolonged tetracycline therapy can also stain the fingernails at all ages.

The effects on bones after they are formed in the fetus are of less clinical importance, because pigmentation has no cosmetic disadvantage and a short spell of delayed growth may not matter. Whether serious deformity can result from administration in early pregnancy is not yet known. No serious growth disorders have yet been reported amongst children with chronic respiratory disease taking a tetracycline continuously, though both dentitions can be affected.

Oxytetracycline may be less likely to interfere with the teeth than others, but ampicillin, the other important broad-spectrum antibiotic may be preferable during pregnancy and the period when teeth are developing.

Tetracyclines are also bound to peptides in tumour tissue where, as with teeth and bones, they fluoresce. Attempts have been made to put this to practical diagnostic use.

Tetracyclines cause a negative nitrogen balance due to inhibition of protein synthesis, **antianabolic effect.** This can be clinically important in the presence of renal failure, in post-operative and injured patients and in those in poor general nutrition.

Tetracyclines also induce photosensitisation and other rashes. Liver and pancreatic damage can occur, especially in pregnancy and with renal disease, when the drugs have been given i.v. and rarely benign intracranial hypertension.

Preparations and dosage

Tetracycline Caps. or Tabs., B.P. (250 mg). Usual oral dose 250 mg 6 hrly, but a total daily dose of 4 g may be used if indicated. In severe infections a loading dose of 1 g can be given, and more drug is absorbed if frequency of administration is increased to 3 hrly than if the 6 hrly dose is doubled.

Demethylchlortetracycline Caps., B.P. (150 mg) is absorbed from the gut more completely and is excreted by the kidney more slowly than is tetracycline so that it has the convenience of less frequent administration. 300 mg orally 12 hrly is equivalent to the usual dose of tetracycline above. It may be more likely to induce photosensitisation.

Parenteral administration is best by intermittent i.v. infusion of tetracycline or oxytetracycline (chlortetracycline is unstable) in 0·9% sodium chloride or 5% dextrose solutions. About 1 g a day is given in two to four doses. Since strong solutions cause thrombophlebitis, the solution should not contain more than 10 mg/ml and since too rapid infusion may make the patient feel ill, rate of flow should not exceed 2 ml/min. A slow continuous infusion may be used instead. Injection i.m. is feasible and preparations contain procaine to reduce the pain.

Alternatives to tetracycline and demethylchlortetracycline include chlortetracycline; oxytetracycline; lymecycline which has the advantage that it can be given parenterally in smaller volume, methacycline, rolitetracycline, clomocycline, doxycycline.

Macrolide Group of Antibiotics
Erythromycin, Oleandomycin, Spiramycin

The antibacterial spectrum of this group, of which erythromycin (1952) is the most important, is similar to penicillin; they are bacteristatic. When erythromycin was introduced it was hoped that it would solve the problem of penicillin-resistant staphylococci, but it was soon found that these and other organisms readily developed resistance to it if therapy lasted more than a week. Erythromycin was therefore generally held in reserve, particularly in hospitals. for use in otherwise untreatable infections. Now that the penicillinase-resistant penicillins are available as well as numerous other antibiotics, the importance of erythromycin is less.

Uses. Its chief place at present is in treating streptococcal and pneumococcal infections where, because of allergy, patients cannot be given penicillin. If used for more than a week it should be given in combination to delay development of drug resistance. There can be few if any occasions where there is no alternative to erythromycin.

Pharmacokinetics: *absorption* after oral administration is incomplete and is best with erythromycin estolate which, however, can damage the liver, especially if given for above 10 days which is seldom necessary. Erythromycin is *distributed* throughout the body and *excreted* in the urine.

Toxicity. Erythromycin is remarkably non-toxic, but the estolate can cause cholestatic hepatitis with pain and fever. This is probably an allergy, and recovery is usual. Other allergies are rare.

Gastro-intestinal disturbances, particularly diarrhœa, occur but the antibacterial spectrum being narrower than with tetracycline super-infection is less troublesome.

Preparations and dosage

Erythromycin Estolate Caps., B.P. (250 mg). Usual oral dose 250 mg 6 hrly, or twice this in severe infection.

Erythromycin Tabs., B.P. (250 mg), dose as for the estolate. Tabs. are enteric-coated as erythromycin, though not the estolate, is destroyed by gastric acid.

Parenteral preparations are available.

Oleandomycin is similar to erythromycin except that it is a little less effective. Combination with tetracycline (Sigmamycin) provides no demonstrated advantage. **Triacetyloleandomycin**, though more active than oleandomycin is also more hepatotoxic. **Spiramycin** is less effective than erythromycin though it persists for longer in the tissues. But this is not important in routine therapy.

There is limited bacterial cross-resistance between the macrolides.

Minor Antibiotics

These antibiotics, and some above, are included because:

1. They may be used topically without serious risk of allergy.
2. They may be required in the uncommon event of an organism being or becoming resistant to all the antibiotics previously described.
3. They have a spectrum extending beyond the antibiotics already described.
4. Their use is limited by their toxic effects.
5. They are new and their place has not yet been assessed.

Novobiocin (1957) is a bacteristatic reserve drug chiefly for treatment of resistant staphylococci. It has lost much of its importance since the introduction of penicillinase-resistant penicillins.

Novobiocin Tabs., B.P. (250 mg) are readily absorbed when taken orally (250 to 500 mg 4 to 6 hrly). Its toxic effects include allergies (rashes, fever) and gastro-intestinal upsets. It may interfere with conjugation of bilirubin and so cause kernicterus in the newborn.

Vancomycin is too toxic to be used except as a last resort in, say, resistant enterococcal endocarditis or staphylococcal infection. It must be given i.v. to obtain a systemic effect (i.m. injection causes necrosis).

Polypeptide antibiotics: polymyxin, colistin, bacitracin, gramicidin.

Colistin (polymyxin E) and **polymyxin B** are second choices to gentamicin and carbenicillin against Pseudomonas infections. They are nephrotoxic. Colistin is preferable where parenteral therapy is needed. They are not absorbed from the gut.

Bacitracin. In 1943, an antibiotic-producing bacillus was isolated from a compound fracture of the tibia in a 7-year-old girl, Margaret Tracey, during an investigation of the bacterial flora of contaminated accidental wounds. The antibiotic was named after her.

Like the other polypeptide antibiotics bacitracin is nephrotoxic and now need never be given parenterally. It is not absorbed when taken orally. It is used for topical application and in the bowel, generally in combination. Allergy and drug resistance are not troublesome.

Gramicidin is obsolete. Tyrothricin is a mixture of gramicidin and tyrocidine.

Fusidic acid is a steroid antibiotic. It is active against penicillinase-producing staphylococci though these fairly rapidly became resistant and so it may be best to combine it with erythromycin or novobiocin. It can either antagonise or potentiate benzylpenicillin according to a variety of complex circumstances. It is active against a moderate range of organisms, but it is not a drug of first choice. It is well absorbed when swallowed, but can cause gastro-intestinal upset.

Clindamycin is a synthetic variant of **lincomycin**. They are similar in antibacterial spectrum to erythromycin (with which there is partial cross-resistance) and to benzylpenicillin. Clindamycin is better absorbed from the gut. They penetrate bone relatively well. The chief use is where benzylpenicillin is contraindicated. Colitis can occur.

Anticancer antibiotics. See chapter on malignant disease.

Antituberculosis drugs. See under *tuberculosis*.

Antifungal Antibiotics

Nystatin (1954) (named after the New York State Department of Health) is active against yeasts and other moulds, but not against bacteria. It may be needed in patients whose life is endangered by superinfection such as occurs with the tetracyclines. Routine use of nystatin along with tetracycline need only be considered in infants, diabetics, the pregnant and immunosuppressed or debilitated patients, who are especially liable to monilial superinfection. It is relatively non-toxic and is poorly absorbed from the alimentary canal. Although enough may be absorbed to control systemic candidiasis, amphotericin B is superior. It may be used locally. Injections have not been successful as nystatin is very insoluble and causes pain. For pulmonary candidiasis a suspension of the powder is inhaled from a suitable machine.

Amphotericin B (1958) is the drug of choice for systemic fungal and candida infections (see table). It is poorly absorbed from the gut and must be given by i.v. infusion. It can also be given intrathecally.

Amphotericin B is toxic (vomiting, fever, renal damage, thrombophlebitis at the injection site, anæmia, rashes), and it should only be given where a firm diagnosis demands it.

Natamycin has been found capable of controlling aspergillosis and candidiasis.

Griseofulvin (125 mg) is the first drug to be effective, taken orally, against superficial fungus infections in man. It is produced by a penicillium mould, but has no antibacterial effect.

Griseofulvin was discovered in 1939, but was not introduced into clinical practice until 1958 because big doses are toxic to animals, although it had been used some years earlier to control moulds on vegetables grown in glasshouses. Its great insolubility had seemed a bar to clinical efficacy. It is carcinogenic in animals.

Griseofulvin is effective against all superficial ringworm (dermatophyte) infections. It is taken into keratin, including hair, and exercises its fungistatic effect there. Griseofulvin is especially valuable in ringworm of the finger nails and hair, for which treatment was previously unpleasant and difficult. The toenails tend to resist treatment and may still require avulsion. Adverse reactions include gastrointestinal and CNS symptoms, transient leucopenia, alcohol intolerance.

Griseofulvin should not be used for trivial infections, for these are often amenable to topical applications. Duration of therapy is from weeks to months, depending on the rate of growth of the infected organ. Disease of the nails needs the longer period, and so may hair infection, for griseofulvin does not kill fungus already established, it merely prevents infection of new keratin, so that re-infection will occur if treatment is stopped whilst infected keratin is still on the body. Local hygiene therefore remains important. Treatment must continue for a time after both visual and microscopic evidence of infection has disappeared.

Griseofulvin is ineffective in pityriasis versicolor, candidiasis and in systemic mycoses. Dose: a single oral dose of 0·5 g/day.

Antivirus Drugs (*24*)

Although no substantial success has been achieved against the small viruses, the following drugs are mentioned as evidence that prospects of both prophylaxis and therapy are brightening.

Since viruses are intracellular parasites that take part in metabolism of host cells they present a more difficult problem of chemotherapy than do bacteria. They can be attacked before they enter the cells or during passage from cell to cell or else prevented from entering the cell. It is now even possible to interfere with them within the cell. But an important difficulty is that virus multiplication has often passed its peak before symptoms occur. The best hope therefore probably lies in prophylaxis, though identification of contacts for treatment during incubation periods is often impracticable.

Idoxuridine competes with thymidine during synthesis of DNA. It

interferes with the multiplication of herpes simplex virus which needs DNA, but, of course, it also interferes with mammalian cells, especially bone marrow.

It has been found useful applied topically (1 to 2 hrly) against superficial and early herpes simplex ocular keratitis, but it does not benefit deep or late infection. Idoxuridine i.v. has been tried in generalised zoster; results are uncertain and it is toxic, as is to be expected from its mode of action; but topical application for a few days may help.

Amantadine probably blocks the entry of virus into the host cell. It is useful for prophylaxis of influenza A2 infection, but must be taken continuously throughout the period of risk. At present it is probably only indicated in epidemics and in high risk patients, e.g. those with cardio-respiratory diseases. Adverse effects include sleepiness, depression, anxiety and other CNS effects, especially in the old.

There is slight therapeutic effect once influenza has developed. The duration of fever is reduced, but not that of other symptoms. Immunity develops normally. It may mitigate herpes zoster if given early.

Interferon is a protein made by cells as a response to virus infection. It has been found capable of inhibiting virus replication. Its clinical potential is being explored.

Methisazone (*47*), a thiosemicarbazone, has been shown capable of protecting man against variola virus when given in the incubation period. It does not seriously suppress variola vaccination and both can be used together to protect contacts and to prevent generalised vaccinia in those specially liable, e.g. eczema subjects, immune deficients. It can cause severe vomiting.

There are many more antimicrobials and it is convenient to describe some whose use is particularly restricted along with the treatment of the disease in which they are used, e.g. some urinary antibacterials, anti-malarials, etc. It is to be expected that new antimicrobials will continue to be introduced, chiefly as alternatives to the established drugs, but occasionally extending the scope of chemotherapy to parasites hitherto immune.

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Chapter 8

CHEMOTHERAPY OF INDIVIDUAL DISEASES

SINCE there is commonly more than one antimicrobial which could be used in any disease, the principal infections will now be discussed chiefly from the point of view of choice of drug. Doses are those given in the independent description of each drug except where otherwise stated. It would be repetitious to discuss alternative therapies which might be chosen in the light of bacteriological reports or after failure of the apparent drug of choice. In such cases treatment will follow the general principles already discussed. The table in the preceding chapter is also relevant to this chapter.

General

Usually antimicrobials given orally should be taken on an empty stomach before meals for optimal absorption. However, this is not important with sulphonamides, phenethicillin, phenoxymethylpenicillin or chloramphenicol; but it is important with cloxacillin.

Some of those best given before meals may cause vomiting due to local irritation (tetracyclines, erythromycin, griseofulvin, PAS, nitrofurantoin) and may then have to be given with, or after, meals.

All antibiotic preparations should be kept cool. Temperatures above 80°F, which may be met inside closed cars even in temperate countries, cause rapid loss of potency.

Staphylococcal Infections (*11*, *12*, *14*, *15*)

Benzylpenicillin is the drug of choice, for it is potent and bactericidal against sensitive organisms. Unfortunately resistant strains are becoming more and more common and in the absence of bacteriological sensitivity tests, cloxacillin should be used.

If a penicillin cannot be used, due to allergy, clindamycin may be substituted. If the infection is likely to be resistant for any reason then a combination of two drugs, e.g. erythromycin, fusidic acid, novobiocin, etc., should be used.

Nasal carriers of staphylococci present a problem in surgical wards of hospitals and nasal creams containing gentamicin or vancomycin have been found effective. Neomycin resistance occurs. Eradication is often only temporary.

Skin carriers may be treated with hexachlorophane (liquids or soaps). Excessive use of strong preparations can lead to absorption of enough to damage the CNS.

Sore Throats and Streptococcal Infections

Sore throat may be endemic or epidemic. In the endemic form 50 to 75%, and in an epidemic 100%, may be due to Strept. pyogenes, which is always sensitive to benzylpenicillin. Unfortunately streptococcal sore throats cannot be clinically differentiated from the non-streptococcal with any certainty. Prevention of complications is more important than relief of the symptoms, which seldom last long.

There is no general agreement whether chemotherapy should be employed in mild endemic sore throat; the disease usually subsides in a few days, septic complications are uncommon and rheumatic fever rarely follows. It is reasonable to withhold penicillin unless streptococci are cultured. In severe or epidemic sore throat penicillin should be given to prevent these complications. In a closed community penicillin prophylaxis of unaffected people to stop an epidemic may be considered, for instance phenoxymethylpenicillin 125 mg by mouth, twice a day, for a period depending on the course of the epidemic, or a single injection of 900 mg (1·2 megaunits) of benzathine penicillin.

The occurrence of sore throat in any patient who has had rheumatic fever or nephritis is an indication for immediate penicillin therapy.

That penicillin therapy reduces the likelihood of rheumatic fever following streptococcal infection is now agreed; one clinical trial (*3*) in a closed community of young men gave the following result:

	Number of Patients	
	Penicillin treated	*Controls*
Total number of patients with streptococcal sore throat	978	996
Definite rheumatic fever	2	28
Possible rheumatic fever	3	7

Sulphonamides (bacteristatic) are less effective against sore throat, do not prevent late complications and may leave a carrier state. Penicillin cures carriers at least temporarily.

Antimicrobial lozenges are ineffective in sore throat and may cause resistant organisms and yeasts to appear as well as inducing an allergy which may be mistaken for worsening of disease and lead to intensification of the offending therapy. Gargles may have a comforting placebo value for the patient, but this is more than counterbalanced by the annoyance and disgust caused to others. Yeast infections require topical treatment. Local anæsthetic lozenges can cause allergy and should only be used if there is severe dysphagia, but too extensive local anæsthesia is, of course, hazardous (risk of inhalation).

The gap dividing what *can* be achieved from what generally *is* achieved is illustrated by the following report.*

Of 110 patients with a first attack of rheumatic fever 96 (87%) had

* GROSSMAN, B. J., *et al.* (1963). *J. Amer. med. Ass.*, **183**, 985.

a history of antecedent infection, 62 (56%) were taken to a doctor and of these 50 (81%) received antibiotic therapy, though this was considered adequate in dose and duration (10 days) in only 10 (16%). Of the 110 patients, 54 had residual cardiac involvement when they left hospital. It was estimated that 84% of these cases were preventable if they had both been to a doctor and been treated properly.

In scarlet fever and erysipelas the infection is inevitably streptococcal and benzylpenicillin should be used even in mild cases, to prevent rheumatic fever and nephritis.

Chemoprophylaxis of streptococcal infection (*2*, *36*) should be undertaken in patients who have had an attack of rheumatic fever. It is continued for at least 5 years, or until aged 18, whichever is the longer period, although some hold that it should continue for life, for histological study of atrial biopsies shows that the cardiac lesions may progress despite absence of clinical activity. Chemoprophylaxis should be continued for life after a second attack of rheumatic fever.

A single attack of acute nephritis is not an indication for chemoprophylaxis (which see) but in the rare cases of nephritis in which recurrent hæmaturia occurs after sore throats, chemoprophylaxis may be used. It is sometimes also used in the nephrotic syndrome, as infections may be followed by increased albuminuria.

Ideally, prophylaxis should continue throughout the year, but if the patient is unwilling to submit to the routine, at least the winter months should be covered.

Relatively low doses of penicillin and sulphonamides have been shown to be effective prophylactics.

Suitable regimens include: benzathine penicillin, 900 mg i.m. monthly (probably the most effective) or phenoxymethylpenicillin, 125 mg orally, 12-hrly. If there is penicillin allergy a sulphonamide (e.g. sulphadiazine) 1·0 g orally, 12-hrly (adults) or 0·5 g (children < 30 kg).

Adverse effects are uncommon. The choice between daily oral or monthly penicillin injections will depend chiefly on convenience to the patient and whether he can be relied on to take daily doses.

Patients taking penicillin prophylaxis are liable to have penicillin-resistant Strept. viridans in the mouth so that during dentistry there is a particular risk of bacterial endocarditis in those with any residual rheumatic heart lesion. Any but the most trivial dentistry, and also other surgery, therefore needs special chemoprophylaxis, see *endocarditis*. Patients taking penicillin are also liable to carry resistant staphylococci.

Acute infections of the middle ear and nasal sinuses commonly respond to benzylpenicillin. In children a single big dose may be given i.m. (300 to 600 mg according to size), or a mixture of benzylpenicillin with slow release forms (e.g. Triplopen) if oral therapy is impracticable.

Chemotherapy has not removed the need for myringotomy in later cases, for sterilised pus may not be completely absorbed, and may leave adhesions that impair hearing.

Chronic middle ear and sinus infections require surgical attention. Antimicrobials are adjuvants only.

Vincent's angina responds readily to benzylpenicillin; a single i.m. dose of 600 mg is often enough except in a mouth needing dental treatment, when relapse may follow. Metronidazole (200 mg 8-hrly for 7 days) can be effective.

Diphtheria. Antitoxin, 20,000 to 100,000 units, i.m. or i.v. (after a test dose) according to the severity of the disease, is given as soon as the diagnosis is even suspected. Erythromycin or penicillin is also used, to prevent the production of more toxin by destroying the bacteria.

Respiratory Infections (*7, 17, 19–21*) (*for tuberculosis, see later*)

Bronchitis. The principal organisms responsible are Strept. pneumoniæ and H. influenzæ, and for *acute bronchitis* tetracycline, ampicillin or co-trimoxazole are best.

In *chronic bronchitis* suppressive chemotherapy, generally only needed during the winter, should be considered for patients with symptoms of pulmonary insufficiency, recurrent acute exacerbations or permanently purulent sputum. Whether therapy should be continuous or intermittent is still uncertain, and so it would seem reasonable to try intermittent therapy first and only continuous therapy if it fails. The main effect of continuous therapy is to reduce the duration of acute exacerbations rather than their number, perhaps because the exacerbations are initiated by virus infection which promotes secondary bacterial invasion.

Suitable regimens would be tetracycline (0·25 g 6-hrly or 0·5 g 12-hrly) or demethylchlortetracycline (0·3 g 12-hrly). Lower doses are less effective. Ampicillin (0·5 g 12-hrly or even 1·0 g 6-hrly) or co-trimoxazole (1 tab. 12-hrly) are alternatives.

Should the sputum remain purulent then therapy should be changed, preferably in the light of bacteriological tests.

For intermittent therapy the patient is told to take the drug in full dose at the first sign of a "chest" cold and to stop it in 3 days if the disease does not follow the familiar course. Otherwise he should continue until he is well again. If he remains ill for more than 10 days he will need investigation.

That there are so many conflicting results of therapeutic trials may be due to dominant pathogens varying in the same place in different years as well as from place to place.

"Firm insistence that cigarettes will shorten the patient's life and that he must stop smoking is often effective and will do more for him than years of chemotherapy."*

Expectorants, antitussives and mucolytics are of little, and enzyme (trypsin) preparations are probably of no use. If there is airway obstruction, it should be treated by bronchodilators but it may become necessary to consider the use of an adrenal steroid, though these are less effective

* Editorial (1960). *Lancet*, **2**, 1286.

than in asthma. There is no doubt that an adrenal steroid can improve ventilation in some bronchitic patients, but benefit tends to diminish with time and there may be an added risk of spreading infection. If there is no obvious benefit within a week there will be none, and the steroid should be stopped. It is not a treatment to undertake without very strong reason or unless objective measurement of respiratory function is practicable. Cromoglycate helps a minority of such patients.

Bronchiectasis provides a similar problem to that of chronic bronchitis from a chemotherapeutic aspect.

Whooping-cough, Bordetella pertussis (*1*). Chemotherapy is needed in children who are weak, have damaged lungs or are under 3 years old. Ampicillin, erythromycin or tetracycline is given; they are safer than chloramphenicol. Chemotherapy is useless unless begun in the first week of illness, nor is it dramatically effective, which is why it is not advocated in all cases. Vomiting may render chemotherapy difficult and it will be rare that parenteral therapy is justified.

Atropine methonitrate is dubiously claimed to have a special antitussive effect in whooping-cough. The usual antitussives may also be tried.

Bacterial pneumonias. For *acute lobar pneumonia*, which is virtually always due to pneumococci, penicillin is always effective. If there is allergy, erythromycin, clindamycin or co-trimoxazole can be used.

Bronchopneumonia is caused by a variety of organisms. Bacteriological identification is desirable and, if the fever does not fall in two days, essential as a guide to treatment, but in its absence tetracycline or ampicillin may be used. For *staphylococcal pneumonia* treatment will be needed for 3 weeks after the temperature is normal. Cloxacillin plus fusidic acid may be used for urgent initial treatment.

Virus and rickettsial pneumonias are unaffected by antimicrobials with the exception of psittacosis, Q fever and Eaton-agent which are sensitive to tetracycline. Chemotherapy may be needed to control bacterial complications.

Empyema is treated according to the organism identified and by aspiration and drainage. If the empyema occurs in an untreated patient benzylpenicillin is satisfactory, but if the patient has developed the empyema whilst on chemotherapy, it is wise to change to a different drug. Vigorous systemic chemotherapy is essential and an intrapleural antibiotic can be added when the pus is aspirated for diagnosis, e.g. benzylpenicillin 0·6 g, streptomycin 1·0 g, or ampicillin 0·5 g. Intrapleural therapy may be given daily or less frequently as a commonsense view of the patient's progress counsels.

If the pleural fluid is thick with fibrin or pus so that aspiration is difficult and loculation seems likely, surgery is best, but streptokinase-streptodornase mixtures can sometimes successfully liquefy the effusion.

Pulmonary abscess is treated similarly to bronchopneumonia and with surgery as required.

Virus upper respiratory tract infections (*17*). The practice of giving

antibacterial drugs at the outset, especially in children, to prevent or shorten secondary bacterial invasion confers little or no benefit and carries a slight risk of promoting a drug-resistant infection. It is better to watch for complications and to treat those that need it on clinical grounds early and vigorously. Shortening of the purulent stage of the common cold can be achieved, but it is doubtful whether such therapy is justified routinely. Claims that ascorbic acid usefully prevents or reduces severity of coryza require further substantiation.

The use of mixtures of sympathomimetics and antihistamines, antipyretics and analgesics for symptomatic relief of the common cold may give a little relief to some and can prove dangerous to those in whom any of the ingredients are contraindicated, e.g. patients taking antihypertensives or monoamine-oxidase inhibitors. Many of these remedies are sold directly to the public. There is no evidence proving that they do more good than harm.

Infective Endocarditis (*5, 10, 16*)

Bacterial identification is important, but treatment must not be delayed once blood has been taken for culture (say three times in one day), because grave cardiac (usually valvular) damage can occur.

Choice of drug is best made with the help of detailed sensitivity tests. The organism is most commonly Strept. viridans group, Strept. fæcalis or Staph. aureus or albus.

High doses of *bactericial* drugs are needed because the organisms are not only relatively inaccessible in avascular vegetations, but the host reaction is negligible and contributes little to cure so that use of bacteristatic drugs is more liable to be followed by relapse.

Treatment may be chosen thus:

Staphylococcus. For Staph. aureus, see above. Staph. albus may be best treated similarly.

Streptococcus very sensitive to penicillin. At least 1·2 g (2 megaunits) of benzylpenicillin i.m. a day in divided doses.

Streptococcus moderately sensitive to penicillin. At least 2·4 g benzylpenicillin i.m. a day in divided doses *plus* streptomycin 0·75 g twice a day. The dose of penicillin should be adjusted in the light of quantitative bacteriological sensitivity tests, the aim being to achieve blood levels at least five times as high as the concentration needed to *kill* the organism *in vitro*. Sometimes as much as 18 g benzylpenicillin i.m. per day may be necessary, particularly with Strept. fæcalis, when streptomycin would be used too. Where high doses are needed i.v. therapy may be preferred, chiefly for comfort.

Probenecid may be used to delay renal tubular excretion of penicillin, with an exceptionally resistant organism, with oral therapy and in children whose muscle bulk may be insufficient for the injections. Excretion of

other antibiotics is not blocked, so there is no added danger of streptomycin toxicity.

Miscellaneous organisms. Treatment depends on identification and sensitivity tests.

Unidentified organism. Penicillin (2·4 g benzylpenicillin i.m. a day) plus streptomycin may be used. If a good clinical response is not obtained within a week the penicillin dose should be increased to 18 g benzylpenicillin i.m. a day.

Duration of treatment should be at least 4 weeks after clinical cure, although an occasional embolus does not necessarily mean the infection is still active. Streptomycin may be given for only 1–2 weeks in older patients. A low grade fever may be caused by frequent large i.m. injections.

Shorter treatment than that advised here can be successful, but the consequences of failure are so grave that it is hard to justify any increased risk of relapse. The same reasoning operates against oral therapy, but several weeks of frequent i.m. injections are a severe ordeal and it may be unreasonable not to give penicillin orally for part of the time or even for sole treatment (phenoxymethylpenicillin) where the organism is highly sensitive.

Teeth should not be extracted during treatment; a very resistant infection can result.

Prophylaxis. Any surgical manœuvre, especially dental extraction and including urinary tract instrumentation, may cause a bacteræmia. This is liable to result in endocarditis in patients with acquired valvular or congenital heart disease. Chemoprophylaxis with benzylpenicillin (penicillin plus streptomycin in the case of the urinary tract) should always be undertaken in such patients. It should be started just before the operation with only sufficient time allowed for the chosen preparation to produce adequate blood levels (oral penicillin 60 minutes, i.m. procaine penicillin 1 to 3 hours, soluble penicillin i.m. 15 minutes). One dose may be enough but caution may dictate continuing therapy for 36 hours, or longer if tissue trauma is extensive, especially after operations in the mouth, which is normally inhabited by Strept. viridans group. To begin prophylaxis days before the operation encourages resistant organisms in the body, especially Strept. viridans group in the mouth, and may be followed by drug-resistant endocarditis. For the same reason surgery during penicillin administration, e.g. in patients taking prophylaxis against rheumatic fever, should be covered by a different antibiotic, e.g. streptomycin, a cephalosporin or erythromycin. Bactericidal drugs are preferable.

Meningitis (*22*)

Accurate bacteriological diagnosis may be the main factor in determining the fate of the patient. (For tuberculous meningitis, see later.)

Even in the presence of an epidemic there cannot always be complete certainty when the patient is first seen, so there is something to be said for

injecting penicillin into the subarachnoid space when the initial essential lumbar puncture is performed, if the fluid is turbid and the patient very ill.

The volume of an injection into the lumbar subarachnoid space should be about 10% (10–12ml) of the total adult cerebrospinal fluid volume if, in the absence of mechanical block, it is to provide substantial concentration in the basal cisterns. This volume can include cerebrospinal fluid that is taken for mixture with a smaller volume of drug solution. Withdrawal and re-injection does not get the drug up to the brain. To reach the ventricles an injection would probably need to be 30 ml.*

Adrenal steroid therapy is needed only if there is evidence of adrenocortical insufficiency (Waterhouse–Friderichsen syndrome in meningococcal septicæmia). Intrathecal therapy to reduce inflammatory blocks in the subarachnoid space where there is evidence of these, is rational, but proof of its value is hard to get. There is no case for routine use of adrenal steroids in meningitis. The intrathecal dose of hydrocortisone is 10 mg, along with any antimicrobials: do not mix in syringe.

Meningococcal meningitis. Sulphonamide resistant organisms are increasing and benzylpenicillin is now the drug of choice (900 mg, i.m. 6-hrly, with probenecid). Intrathecal injections are probably unnecessary and also carry disadvantages. Penicillin passes inflamed meninges well. Oral penicillin may be used as soon as it is plain the patient is recovering.

Prophylaxis in an epidemic can be achieved by ampicillin, erythromycin or rifampicin.

Pneumococcal meningitis is treated by benzylpenicillin in high doses i.m. (14·5 g, 24 megaunits) and intrathecally (6 mg, 10,000 units) daily, plus sulphadiazine. Cure is less easy than with meningococcal infection. Cephaloridine is an alternative.

Hæmophilus influenzæ meningitis is treated by ampicillin in large dose in preference to chloramphenicol (because of danger of blood disorder). Unfortunately as inflammation subsides the penetration of ampicillin through the meninges declines markedly. Careful clinical watch is vital so that if improvement ceases a change to chloramphenicol can be made. Alternatively, intrathecal ampicillin (10 mg) can be used.

Coliform and pseudomonas meningitis require bacteriological help for efficient therapy. Intrathecal treatment is necessary, e.g. gentamicin (5 mg), cephaloridine (50 mg).

Meningitis due to other organisms is treated on general principles discussed earlier.

Duration of therapy depends on the usual clinical criteria and on examination of the cerebrospinal fluid, though this latter may be dispensable in uncomplicated meningococcal cases as treatment is generally so successful. Therapy is commonly needed for 14 days.

Phenobarbitone may be given to prevent convulsions.

In **meningeal tuberculosis** (*44*) it is essential to use isoniazid, which penetrates well into the cerebrospinal fluid.

* Rieselbach, R. E., *et al.* (1962). *New Engl. J. Med.*, **267**, 1273.

An effective regimen (in mg/kg/day in divided doses) is isoniazid 20, streptomycin 40, PAS 250. Duration is as for other forms of tuberculosis.

Intrathecal therapy is only essential in a minority of cases, but as it is impracticable to select these early, some advocate at least 10 days intrathecal therapy in all, e.g. streptomycin, 10 to 50 mg/day according to size. In relapse, during or after cessation of treatment, intrathecal isoniazid (10 to 50 mg according to size) may be added.

A systemic adrenal steroid may be needed if there is cerebral œdema from this as from other causes. It may also prevent block of cerebrospinal fluid paths by reducing inflammatory exudate.

Of the alternative drugs, rifampicin, ethionamide and cycloserine readily enter the cerebrospinal fluid from the blood.

Intestinal Infections (*32–36*)

Infective diarrhœa is best treated by choosing the drug in the light of bacteriological identification and sensitivity tests. In the absence of such help a severe case be treated by a drug that is absorbed (tetracycline, sulphadiazine, ampicillin) plus one that is confined to the bowel when given orally (neomycin, streptomycin, polymyxin, etc.). Drug-resistant organisms are common and treatment may have to be changed empirically. With severe dehydration even the poorly absorbed sulphonamides carry danger of crystalluria.

Milder cases may be treated with oral neomycin or a non-absorbed sulphonamide (with streptomycin resistance develops quickly).

Shigella infection can be treated as above. With Sh. sonnei multiple drug resistance is common, but mild cases do not need antimicrobials. Infections with Sh. flexneri need treatment and tetracycline, ampicillin and chloramphenicol are commonly effective. Treatment has ordinarily been given for 7 days, but it seems likely that a single dose of tetracycline 2·5 g orally, is as good, or even better. Chemoprophylaxis with a non-absorbed drug may be used in an epidemic, e.g. colistin, kanamycin.

Enteropathogenic E. coli, see table on drugs of choice.

Staphylococcal enteritis should be assumed to be due to penicillinase-producing organisms unless the contrary is shown. Cloxacillin (orally and i.m.) is effective.

Salmonella infections. In the acute stage chloramphenicol is superior to ampicillin because it subdues the infection quicker. Treatment should last for at least a week after subsidence of fever. Co-trimoxazole is also effective.

In severe cases hydrocortisone is believed by some to help. The risk of bowel perforation due to suppression of inflammation and healing is reputedly slight.

A *carrier state* may be more common after chloramphenicol than after ampicillin. The bactericidal ampicillin or co-trimoxazole may be superior to the bacteristatic chloramphenicol in its treatment, for there is no local defence reaction to eradicate the immobilised organism, and relapse occurs on withdrawal of a bacteristatic drug. Ampicillin dosage may need to be

heavy and prolonged (1 to 3 months), especially for urinary carriers. Surgical treatment may be needed, e.g. cholecystectomy. Ampicillin is concentrated in the bile, chloramphenicol is not. Efficacy of co-trimoxazole may be comparable.

Candidiasis is treated by nystatin.

Cholecystitis and cholangitis are treated by a wide-spectrum antibiotic that is concentrated in bile, e.g. tetracycline, ampicillin.

Suppression of bowel flora or bowel "sterilisation" prior to colonic surgery in order to prevent postoperative sepsis is commonly practised. "This must be one of the most extraordinary concepts in chemotherapy ever to have gained general currency."* If the drugs have any effect this will be to deprive the patient of the flora with which he has an equilibrium. The results of this "are frequently disagreeable and may be dangerous. The postoperative patient can ill afford to lose his normal bowel flora since it constitutes one of the major protections against occupation of the bowel by undesirable organisms."* Evidence of benefit from preoperative antimicrobials is not convincing and the subject deserves further study. A variety of regimens is used, e.g. neomycin plus phthalylsulphathiazole for 2 days before surgery.

But suppression of bowel flora is more certainly useful in **hepatic insufficiency.** Here, absorption of products of bacterial breakdown of protein in the intestine can lead to cerebral symptoms and even to coma. In acute coma neomycin (6 g daily) is essential and it should be used as a prophylactic (4 g daily) in patients with protein intolerance who fail to respond to dietary protein restriction. Kanamycin is preferable in cases with renal failure because neomycin may cause ototoxicity, the ordinarily negligible amounts absorbed becoming important in these cases.

In **blind-loop syndrome** it is desired to eliminate bacteria which are using up vit. B_{12} and altering bile salts so that steatorrhœa results. After an initial course of ampicillin or tetracycline, therapy can be intermittent, say 3 days a week, to prevent recolonisation.

For similar reasons antimicrobial therapy is used in initial treatment of **tropical sprue.**

Peritonitis. A broad-spectrum drug (tetracycline) or a combination (gentamicin plus clindamycin) is used as infection is usually mixed. Antimicrobials may be put in the peritoneal cavity at operation. Large doses of streptomycin and of neomycin (5 to 10 g) used thus can cause neuromuscular block, especially if the patient has recently had a non-depolarising neuromuscular blocking drug. Smaller doses are safer. Kanamycin 1·0 g may be preferable as it has relatively little neuromuscular blocking effect.

Clioquinol (Entero-Vioform), which has a wide range of *in vitro* antibacterial effect as well as being an amœbicide, is popular as a prophylactic and treatment of mild infective enteritis. Its value has been much debated and no generally agreed conclusion has been reached. Large

* O'Grady, F. W. (1972). Chemoprophylaxis in medicine and surgery. *J. Roy. Coll. Phycns. Lond.*, 6, 203.

doses of clioquinol can cause unpleasant subacute myelo-optico-neuropathy (SMON). This has occurred principally in Japan and may be influenced by genetic or environmental factors. Dosage of clioquinol should be limited to 7·0 g over not less than 14 days and a course should only be repeated after an interval of 4 weeks.

Furazolidone (Furoxone) is a nitrofuran active against shigellæ and salmonellæ. At present it would seem only to be indicated where the organisms are resistant to well-tried antimicrobials. Toxic effects include vomiting, headache and rashes; it is, incidentally, a monoamineoxidase inhibitor.

In superinfection diarrhœa attempts to colonise the bowel with harmless organisms (by giving lactobacilli by mouth), or to restore normal flora (by enemas of normal fæces) have not been notably successful.

Symptomatic treatment of diarrhœa, see index.

Urinary Tract Infections (*23–27*)

Identification of the causative organism and its sensitivity to drugs are very important because of the large range of organisms which may be responsible and the prevalence of resistant strains. Most of the causative organisms are Gram-negative, but Strept. fæcalis (Gram-positive) is common.

In infections of the lower urinary tract it is the concentration of antimicrobial in the urine rather than in the tissues that matters, and as many are concentrated in the urine the administered dose may be relatively low. However, it is the concentration in the tissues that matters in infections of the substance of the kidney and here doses as for any systemic infection are needed.

Correction, if possible, of predisposing anatomical abnormalities, such as an enlarged prostate, bladder diverticula, congenital abnormalities of the renal pelvis or ureters, or removal of renal calculi is important for success. If correction is not possible chemoprophylaxis may help prevent recurrent infections.

A high fluid intake reduces the danger of crystalluria when full doses of sulphonamides are used but obviously it also reduces the concentration, and so the effectiveness of the antimicrobial drug. A urinary output of 1·5 litres a day is adequate.

Elimination of infection is hastened by moderately copious urine volume (about 1·5 l/day) and by frequent micturition. Antimicrobials are well concentrated in the urine and a moderate diuresis will not significantly diminish their efficacy.

Renal function in relation to treatment. Some drugs are particularly liable to cause toxic effects in the presence of renal failure as a result of reduced excretion and hence higher plasma concentrations. As a general guide, tetracyclines and nitrofurantoin should be avoided in renal failure, and plasma concentrations should be monitored with gentamicin, kanamycin, cephalosporins and colistin. Defective glomerular

filtration and diminished tubular reabsorption of water may also cause low urinary concentration. Potassium salts, commonly used to make the urine alkaline, and acidifying agents, are dangerous in renal failure.

Some drugs can damage the kidney and should only be used if demonstrably essential and for a maximum of 5 days, e.g. polymyxin.

Where the function of one infected kidney is very poor, treatment is especially difficult, since most of the antimicrobial is excreted by the better kidney and the concentration in the urine from the worse side may be low.

Choice of drug. In all cases of **acute urinary infection** it is desirable to have a specimen of urine sent for bacteriological investigation before treatment begins. However, it is not always necessary to await the result of the examination before beginning treatment. The commoner causative organisms are E. coli, Proteus, Pseudomonas, Strept. fæcalis and coliforms.

In an acute infection due to an unidentified organism and with an *acid* urine it is reasonable to start with a sulphonamide or co-trimoxazole. If symptoms persist after 3 days it is probable that the organism is resistant and a change should be made to nitrofurantoin or ampicillin. Better still, bacteriological help should be sought.

If the infected urine is *alkaline*, the organism may well be Proteus, and co-trimoxazole or ampicillin should be tried first. A cephalosporin, tetracycline or chloramphenicol may also be effective. Proteus is usually resistant to nitrofurantoin.

If an infection does not respond rapidly to such blind treatment, bacteriological and anatomical investigation are then vital. Recurrence or relapse also demands such investigation. Relapse is probably more common with drugs that are effective in urine but not in tissues (nitrofurantoin, low doses of sulphonamides).

Urinary pH can have an important influence on efficacy of some drugs.

Acid pH enhances tetracyclines, nitrofurantoin, fusidic acid, methicillin, cloxacillin, novobiocin.

Alkaline pH enhances streptomycin, gentamicin, clindamycin, lincomycin, cephalosporins and erthromycin.

pH is clinically unimportant with benzylpenicillin, colistin, chloramphenicol and vancomycin.

An acid urine is essential if hexamine is used, and pH must be kept below 5·5.

Dysuria is also relieved by altering urinary pH from acid to alkaline.

The urine can be made **alkaline** with sodium bicarbonate 3 g 2-hrly orally until the pH exceeds 7·0 to universal indicator paper; the dose is then adjusted to keep it alkaline. Sodium or potassium citrate, lactate or acetate 3 to 6 g orally at least 6-hrly can also be used (they are converted into carbonates in the body), but they are nauseating and a potassium salt is particularly dangerous in renal failure as it can cause fatal hyperkalæmia. Hyoscyamus is still sometimes combined with agents to alter pH in the hope that this parasympatholytic will help to alleviate dysuria.

The urine can be made **acid** by ascorbic acid (0·2 g) 4 g orally daily in divided doses or by methionine (3 to 10 g orally daily in divided doses). An indicator should be used. Methionine is the more unpleasant to take. It is a sulphur-containing amino-acid that is metabolised in the body and is largely excreted as acid inorganic sulphate. Use of acidifying agents in the presence of renal failure can produce dangerous acidosis and treatment must be carefully controlled. For alternative acidifying agents see Ch. 20.

If the urine is alkaline because the infecting organism, e.g. Proteus, is a urease producer and is splitting urea to liberate ammonia in the urine, then acidifying drugs will not alter urinary pH and should not be forced as they will only cause dangerous systemic acidosis.

In chronic and recurrent urinary infections, bacteriological help is essential for drug resistance is common and mixed infections occur. If the initial pathogen is still present after two weeks it is futile to persist with the initial treatment.

Duration of treatment after apparent cure. This is a subject of disagreement.

Some, impressed by the frequency with which chronic symptomless infection may persist after an acute infection with serious, and even fatal, late consequences, would advise as long as 3 months on a lower dose if there has been substantial parenchymal invasion, say sulphadimidine 0·5 g, or nitrofurantoin 50 mg twice a day. But, if an acute infection is mild and it is certain that it is not a flare-up of a chronic infection treatment for 2 to 3 weeks may be enough. For a first attack of cystitis 7–10 days is adequate.

In recurrent or chronic infection treatment should probably continue for 6 months. Urine should be cultured during and at the end of treatment and 2–3 months later.

Chemoprophylaxis of urinary infections is sometimes undertaken in patients liable to recurrent attacks or acute exacerbations of an ineradicable infection. A sulphonamide (0·5 g twice a day) or nitrofurantoin (50–100 mg nightly) are suitable. However, if recurrences are due to relapse of an infection that has been merely suppressed by a drug, then choice of drug must be made with bacteriological help.

Gut bacteria are a principal cause of urinary infection. Therefore it is desirable that a drug used for urinary chemoprophylaxis should be well absorbed from the upper gut so that it does not reach the colon or give sufficiently high plasma concentrations to alter colonic flora and induce drug resistance. This can be achieved because, though relative concentrations in plasma (and so in glomerular filtrate) are low, the enormous reabsorption of water in the kidney gives relatively high and effective urine concentrations.

Nitrofurantoin (Furadantin) is a synthetic bactericidal antimicrobial useful only against urinary infections because it is rapidly excreted and concentrated in the urine. Rapid metabolism in the liver prevents effective

plasma concentration being reached without toxicity. But renal tubular reabsorption occurs and renal tissue levels are higher, though they cannot be depended on sufficiently to make nitrofurantoin a suitable drug for acute pyelonephritis. Its spectrum is similar to that of chloramphenicol; acquired bacterial resistance is not a problem. It is used against E. coli and Proteus when these are resistant to other drugs. It is more active, more soluble and more completely excreted in an acid urine. Metabolites may turn the urine dark brown. Nitrofurantoin (50, 100 mg) is taken orally, after food since it is a gastric irritant, in a dose of 50–100 mg 6-hrly as therapy; for prophylaxis, see above. The gastric effects are claimed to be minimised by combining nitrofurantoin with deglycyrrhinizated liquorice (Ceduran).

Excretion is reduced in cases of renal insufficiency so that the drug is both more toxic and less effective.

Toxic effects include nausea, diarrhœa, peripheral neuritis (the drug should be stopped at the earliest symptom), hæmolytic anæmia (same mechanism as for primaquine), pulmonary infiltration, rashes and other allergic effects.

Nalidixic acid (Negram) has a spectrum similar to nitrofurantoin. It may prove useful in Proteus infections. Its place in therapy is otherwise uncertain. It causes a positive reaction to urinary tests with Benedict's solution and Clinitest. It is toxic to skin, central nervous system and bowel.

Hexamine (Methenamine) mandelate (Mandelamine) (0·5 g) is a combination of two urinary antiseptics, hexamine and mandelic acid. It is taken orally and excreted in the urine where, provided the pH is 5·5 or less, the active antibacterials, mandelic acid and formaldehyde (to which all bacteria are sensitive), are liberated; it therefore has no systemic antibacterial effect. Methenamine is rarely needed for acute infections and is only used in chronic or recurrent infections when other drugs fail. It can be continued indefinitely and acquired bacterial resistance is not troublesome. Urinary acidification is essential, and this may be impossible with urea-splitting (ammonia-producing) organisms. It should not be used where there is renal insufficiency. Overdose can cause a chemical cystitis. Gastric upset may occur. The dose is 1 to 1·5 g 6-hrly to treat an infection and 1 g 8-hrly for prophylaxis.

Drugs Used in Tuberculosis (*37–43*)

Streptomycin and **dihydrostreptomycin** have been discussed earlier.

Sodium* aminosalicylate (para-aminosalicylic acid, PAS)

In 1940 it was reported that salicylic acid increased the oxygen consumption and carbon dioxide production of tubercle bacilli. It seemed that this acid or some other benzoic acid derivative might play an important part in the metabolism of the tubercle bacillus, analogous to that of para-

* The calcium salt can be used where sodium is unwanted, e.g. in cardiac disease, but it is less well absorbed.

aminobenzoic acid in the streptococcus. In 1946 fifty related compounds were studied in the hope of finding one which would interfere with the metabolism of the tubercle bacillus sufficiently to offer therapeutic possibilities and as a result PAS was introduced into clinical practice.

PAS is well absorbed from the alimentary tract, is distributed throughout the body water, though penetrating only partially into the cerebrospinal fluid. The serous cavities are readily accessible. PAS interferes with absorption of rifampicin and doses of these drugs should be widely separated.

Toxic effects are seldom serious, although nausea, vomiting and diarrhœa due to local irritation are common. These are less with the sodium salt than with the free acid. Crystalluria, agranulocytosis and allergies (especially fever, rash, enlarged lymph glands and encephalitis) occur. The PAS should be stopped if anything more serious than a mild rash occurs. Desensitisation is generally practicable, see below. Goitre with hypothyroidism, diabetes and hepatitis can occur. Impaired renal function enhances the toxicity of PAS as of so many drugs.

PAS is only used in the treatment of tuberculosis, and always in combination with one or two other drugs (isoniazid, streptomycin), because this delays the development of bacterial resistance. Indeed so important is this that isoniazid is incorporated in the PAS cachets (Sodium Aminosalicylate and Isoniazid Cachets, B.P.C.), to make it impossible for the patient to take one without the other; the convenience of having to take only one preparation is only a secondary consideration. It is better that the patient should be without both drugs rather than without one; also, half dose of the two drugs allows resistant organisms to appear.

If patients baulk at the official cachets, as some do (for dose see below), both because of their size and because the irritant drug is released in the stomach (it is best taken with food) then one of the more elegant proprietary coated granules may be found superior. It is clear that patients *must* be persuaded of the necessity of taking their drugs as prescribed, and despite side-effects, provided these are at all tolerable.

Isoniazid (INH, INAH, isonicotinic acid hydrazide)

Isoniazid was introduced as a tuberculostatic agent in 1952. Its discovery was the result of attempts to combine the known antituberculous effects of nicotinamide and the thiosemicarbazones.

Isoniazid is more effective against Myco. tuberculosis than both streptomycin and PAS; it probably acts by interfering with bacterial respiration. It is either bacteristatic or bactericidal according to concentration and temperature. Isoniazid is well absorbed from the alimentary tract and is distributed throughout the body water, penetrating easily into the cerebrospinal fluid. It should always be given in cases where there is special risk of meningitis (miliary tuberculosis and primary infection). It is active against intracellular organisms, whereas streptomycin is not.

There are great differences in the rate at which people inactivate the drug and it has been found that this depends on a single gene. People are either slow inactivators (autosomal homozygous recessive) or rapid inactivators (heterozygotes and homozygous dominants). In fixed-dose treatment regimens the proportion of slow inactivators achieving bacteriological quiescence is slightly higher than for rapid inactivators. On the other hand slow inactivators get more peripheral neuritis.

After the initial peak concentration, which is similar in slow and fast inactivators, the plasma concentration in fast inactivators is less than half that in slow inactivators. The half-life of isoniazid in slow inactivators is 2·5 times that in fast inactivators (i.e. 45–80 min against 140–200 min).

Slow inactivators comprise about 5% of Eskimos, 15% of Chinese, 60% of Asian Indians, 45% of American Negroes, 45% of Europeans and 65% of Jews.

Isoniazid enters milk in about the same concentration as in the blood.

Isoniazid interferes with pyridoxine metabolism, and induces pyridoxine deficiency; pyridoxine output in the urine is increased. The principal effects are peripheral neuropathy, and, more rarely, anæmia, and pellagra (in the malnourished). They are nearly confined to slow inactivators and those with renal insufficiency. They can be prevented by giving pyridoxine 50–100 mg orally/day. Other adverse effects include mental disturbances, convulsions, incoordination, encephalopathy, alcohol intolerance and a variety of allergic effects.

When isoniazid is used alone drug resistance develops in all cases within 5 months.

The usual oral dose of isoniazid (50, 100 mg) is 100–300 mg 12-hrly. It can be given i.m. and intrathecally.

PAS increases the isoniazid blood level as both are acetylated and there is competition for this metabolic path.

Alternative or reserve drugs are used where there are problems of drug intolerance and bacterial resistance. They are in this class because of either greater toxicity or lesser efficacy. Selection and management is best left to specialists. They include: *thiacetazone* and *ethambutol* (generally used in patients intolerant of PAS): *rifampicin* (about as effective as isoniazid; causes jaundice and thrombocytopenia): *pyrazinamide ethionamide, prothionamide, cycloserine, viomycin, kanamycin, capreomycin.*

Chemotherapy of Tuberculosis (*37–43*)

Chemotherapy of tuberculosis can be considered as having two stages:

1. **Initial triple** drug therapy.
2. **Continuation double** drug therapy.

Chemotherapy of tuberculosis is initiated with three drugs because:

1. Resistance develops against all antituberculosis drugs if they are used singly.
2. Resistance can be delayed or prevented by using more than one drug.

3. Initial resistance to two of the standard drugs is rare.
4. Bacterial sensitivity tests take 8 to 12 weeks.

Triple therapy is given until the results of the sensitivity tests are known and therapy continued with two drugs to which the organism has been found sensitive. If bacteriological tests fail, then continuation therapy must be decided according to local knowledge of the likely pattern of drug resistance of the organisms; in Britain isoniazid and PAS are generally continued.

Relapses during or after treatment obviously present a special problem of choosing two drugs to which the organism is sensitive. Reserve drugs are likely to be needed.

Respiratory tuberculosis (*Prof. John Crofton generously provided this account*)

Knowledge of the sensitivity of the organism to antituberculosis drugs is useful, but bacteriological tests take weeks to perform and so the information is not usually available before treatment is begun. Before the proper use of drugs was known drug resistance commonly occurred and some patients passed on resistant organisms to others. The increasing use of reliable combinations of drugs is making drug resistance much less of a problem in economically developed countries. Initially the patient is given all three standard drugs, streptomycin, PAS and isoniazid. Three drugs are given in case he has been infected with tubercle bacilli resistant to one of them. The other two will then not only be active against the disease but will prevent further resistance developing. Infection with bacilli resistant to two of the main drugs is fortunately rare.

In patients under the age of 40 the routine treatment consists of streptomycin 1 g daily together with sodium PAS 5 g twice daily and isoniazid 100 mg twice daily. Vestibular disturbances from streptomycin are more likely to occur over the age of 40. Over this age streptomycin is now commonly given in a dose of 0·75 g daily though in older patients it is wise to check the plasma concentation of streptomycin and reduce the dose or the frequency of injections if the level is more than 1 mcg/ml after 24 hours.

Resistance tests on cultures taken before the start of treatment become available in 2 or 3 months. If the bacilli prove to have been sensitive to all three drugs PAS may then be omitted and daily streptomycin and isoniazid carried on so long as the patient is in hospital.

When a patient is discharged from hospital there are at present two possible regimens for further treatment. The standard combination is 5 g of sodium PAS and 100 mg of isoniazid, both given twice daily. This has the advantage of oral administration but it has been found in practice that a number of patients fail to take their drugs and may therefore later relapse. For patients who are judged not likely to be reliable in taking their therapy it is safer to use a combination of streptomycin and

isoniazid twice weekly, both drugs being administered under supervision. This combination is also useful in patients who have difficulty in tolerating PAS. Streptomycin is given in a dose of 1 g twice weekly, say Mondays and Thursdays, and at the same time a single dose of isoniazid, 14 mg/kg, is swallowed under supervision. To prevent isoniazid toxicity pyridoxine 10 mg is given simultaneously. This regimen has been found, in studies in Madras (India) in association with the Medical Research Council (UK), to be at least as effective as PAS with isoniazid.

Patients with mild disease, who may be allowed to continue with a normal life apart from therapy, should also receive all three standard drugs for the first 3 months, though it is sufficient to give the streptomycin three times weekly. After 3 months the streptomycin is stopped but PAS and isoniazid are continued. If the patient is thought to be unreliable the twice weekly regimen of streptomycin and isoniazid, as outlined above, can be substituted.

Recently ethambutol and rifampicin, two powerful and relatively non-toxic antituberculosis drugs, have become available. It seems possible that one of these may, after further trials, come to be used instead of PAS in the standard treatment of new cases. Certainly either can be substituted if the patient has any severe toxic reaction from PAS or streptomycin. There is a suggestion that rifampicin combined with isoniazid may result in earlier conversion of the sputum to negative than occurs with standard drugs, but rifampicin is expensive (1972) and for this reason alone not at present justifiable for routine treatment.

The dose of ethambutol is 25 mg/kg/day in a single daily dose for the first 6 weeks, followed by 15 mg/kg/day. Rifampicin is normally given in a dose of 600 mg in a single dose daily. Both drugs are given orally.

Chemoprophylaxis is the giving of chemotherapy to prevent tuberculous disease. "Primary" chemoprophylaxis, the use of chemotherapy in previously uninfected individuals, is seldom justified; protection can normally be obtained by other means, e.g. segregation. "Secondary" chemoprophylaxis is the use of chemotherapy in infected, but symptom-free, individuals. A positive tuberculin test may be the only manifestation of tuberculosis; chemotherapy is certainly justifiable in children under the age of three, in whom the risk of disseminated disease is high, and sometimes at older ages. Chemotherapy is increasingly given to patients whose X-rays show evidence of probably quiescent disease, as a number of these patients later relapse. In both these groups the risk of emergence of drug resistance is small and isoniazid has often been given alone; nevertheless a two-drug treatment with both isoniazid and PAS is probably safer.

Patients with drug-resistant organisms. Choice of treatment depends on careful assessment of the patient's previous chemotherapy and his reaction to it. Deterioration in sputum positivity or X-ray while receiving a drug suggests that the bacilli have become resistant to it. Confirmation by resistance testing is desirable, but, as resistance tests

take 8 weeks or more, the decision has often to be made on clinical grounds. The treatment of patients with bacilli resistant to the three standard drugs has become very much easier since the introduction of ethambutol and rifampicin drugs which are both well tolerated and very effective. It is desirable to add a third drug. Prothionamide or ethionamide (which have equal effects though prothionamide is perhaps slightly less toxic) are best if tolerated; if not pyrazinamide seldom causes subjective upset though it has potential liver toxicity.

Allergic reactions. Drug allergy is common and usually occurs between the second and fifth week of therapy. The commonest manifestation is fever with or without a rash. Treatment should be stopped until the reaction has subsided. Test doses should then be given. If the reaction has been mild the test dose could be half the full dose, i.e. 50 mg for isoniazid, 0·5 g for streptomycin and 2·5 g for PAS. These should be administered in that order on successive days. If the patient is allergic, fever or rash appears within a few hours. Even if there is a reaction one should continue with testing to the other drugs as multiple allergy, especially to streptomycin and PAS, is common. If there is no reaction to the lower dose a full dose should be given before deciding that the patient is not allergic to that drug.

If the initial reaction was severe a smaller initial test dose should be given, followed by the larger dose if there is no reaction.

If there is allergy to only one drug the other two should be given in full doses, with twice daily ascending doses of the offending drug. With a moderate or slight reaction the initial dose for streptomycin should be 0·1 g increasing by 0·1 g in successive doses; for PAS 0·5 g with 0·5 g increments and for isoniazid (allergy to which is rare) 10 mg, with 10 mg increments. With severe reactions the initial dose should be correspondingly decreased and the increments smaller.

If there is allergy to more than one drug an effective combination of reserve drugs must be given until desensitisation is completed.

Rarely, with multiple allergy, an attempt may be made to continue therapy whilst using an adrenal steroid to suppress the allergy.

Non-respiratory tuberculosis

The principles of treatment, rest, chemotherapy, surgery and prolonged follow-up are the same as for respiratory tuberculosis. In only a few cases is surgery now necessary. It should always be preceded and followed by chemotherapy.

Many chronic tuberculous lesions may be relatively inaccessible to drugs as a result of avascularity of surrounding tissues and treatment frequently has to be prolonged, and dosage high, especially if damaged tissue cannot be removed by surgery. Tuberculosis of **bones** provides an example.

In **renal** tuberculosis with impaired renal function the dangers of increased toxicity due to defective excretion of drugs should be remem-

bered and the dose lowered if necessary. Measurement of plasma concentrations of the drugs is often required.

Meningeal tuberculosis: see *meningitis*.

Tuberculosis of the skin, particularly lupus vulgaris, usually responds well. Some physicians have given isoniazid alone but it is preferable to give two drugs.

Duration of antituberculosis treatment

All patients with tuberculosis should be treated with drugs for 18 months to 2 years depending on severity. In one study of 295 patients with pulmonary tuberculosis, those treated for 3 months had a relapse rate of 36%, for 3 to 5 months, 17% and of more than 100 treated for a year or more only one relapsed (*12*). Experiments with intensive treatment with triple bactericidal combinations suggest that periods as short as 6 months may be adequate (*51*).

Adrenal steroids and tuberculosis

In pulmonary tuberculosis these should be given to severely ill or moribund patients. They reduce the reaction of the body to tuberculoprotein and buy time for the drugs to take effect. They also cause the patient to feel better much more quickly. Adrenal steroids are also useful in tuberculous pleural effusion, meningitis, miliary disease and in renal disease where there is any risk of developing stenosis in the ureter. They reduce inflammatory exudate and formation of adhesions.

In the absence of effective chemotherapy an adrenal steroid will cause tuberculosis to extend and it should never be used alone, say for another disease, if tuberculosis is suspected.

Continuous versus intermittent chemotherapy (*38–43*)

The success rate of daily chemotherapy over 2 years is much higher in formal therapeutic trials than it is in routine medical practice. This is largely because patients do not follow the instructions reliably and daily supervision is impracticable once the patient has left hospital. Patient "disobedience" can be as high as 25% and is liable to increase with passage of time, especially as the patient may be feeling perfectly well for the greater part of the 2 year course.

It is practicable to supervise drug administration if it is sufficiently infrequent.

Twice-weekly *supervised* chemotherapy gives overall results as good as conventional self-administered daily chemotherapy; even better where the patient is known to be unreliable.

Once-weekly chemotherapy is inferior, especially in fast isoniazid inactivators. This is because therapeutic effect with this regimen is related to *duration* of an adequate isoniazid plasma concentration, whereas with more frequent administration it is related to *peak* plasma concentration. *Peak* plasma concentrations after a dose are, as expected, unaffected by the patient's status as a slow or fast inactivator. A dose

of isoniazid sufficient to provide sufficient duration for efficacy, given once a week in a fast inactivator, has to be so high as to cause acute toxicity due to excessive peak concentration. Development of slow-release formulations may render once-weekly chemotherapy generally practicable.

Chronic toxicity of isoniazid is related to *duration* of exposure to adequate concentrations so that with daily or twice-weekly therapy it has proved possible to find dose regimens that provide the effective peak concentrations with minimum risk of toxicity in even the slow inactivators.

Thus in routine therapy it is not necessary to distinguish between slow and fast inactivators.

It would be difficult to find a better example of the utility of pharmacokinetic studies in designing safe and effective dosage schedules.

Fortunately, recovery of reproductive capacity of Myco. tuberculosis after exposure to drugs is slow enough to allow widely spaced doses which would be inadequate in many acute infections.

The choice between daily and intermittent chemotherapy will depend on a variety of factors including patient attitude and availability of supervision in hospital or home.

Eye Infections

Superficial infections are treated by a variety of antibiotic drops (1 to 2-hrly, or every few minutes in severe cases) and ointments where drops are inconvenient, e.g. at night; neomycin, chloramphenicol, framycetin, tetracycline, polymyxin, are superior to sulphonamides (usually sulphacetamide). They are often used in conjunction with hydrocortisone or prednisolone, but this combination is risky as the steroid masks the progress of the infection and, should it be applied with an antimicrobial to which the organism is resistant, may make the disease worse. Local chemoprophylaxis is used to prevent secondary bacterial infection in virus conjunctivitis. Hydrocortisone can make virus infections worse, and delay the healing of some corneal ulcers. Herpes simplex virus infection may be helped by idoxuridine.

Local allergy may be confused with persisting infection and treatment uselessly continued.

Intra-ocular infections are treated by systemic and subconjunctival injection. The latter provides high intraocular concentration by direct diffusion.

Trachoma is due to a large virus; a tetracycline is applied to the eye though it is not certain that the virus is sensitive to the drug.

Venereal Infections

Gonorrhœa. Penicillin resistance, and therefore the doses recommended, are increasing. Effective treatment requires exposure of the organism briefly to a high concentration of drug. Single dose regimens

are practicable as well as being obviously desirable for social reasons. Dosage must be higher in women because the complexity of the parts of their anatomy that are infected has pharmacokinetic implications (achievement of adequate concentrations at infected sites). 2·4 g procaine penicillin i.m. will cure most uncomplicated cases in the male; females need 3 g benzylpenicillin (in 10 ml 0·5% lignocaine to reduce pain); both 30 mins after probenecid 2·0 g orally. Complicated cases need a course of treatment. There is a variety of other effective regimens.

Whilst penicillin treatment of acute gonorrhœa at current doses may cure a simultaneously contracted syphilis, it may also mask it so that the primary infection is not seen and a disastrous late syphilis occurs; this may be more a theoretical than a practical risk. But, a serological test for syphilis should be done 3 months after treating gonorrhœa.

Alternative drugs for gonorrhœa include kanamycin, co-trimoxazole, spectinomycin, tetracycline. Kanamycin and spectinomycin are inactive against syphilis.

Chemoprophylaxis with penicillin has been successfully practised in military camps.

Syphilis. Treponema pallidum never becomes resistant to penicillin.

Primary and secondary syphilis is effectively treated by 600 mg procaine penicillin i.m. daily, for 10 days. If it is suspected that the patient may not present himself for this course, a single i.m. injection of 1·8 g (2·4 megaunits) benzathine penicillin may be given.

Tertiary syphilis should have the same treatment prolonged to 3 weeks. The cerebrospinal fluid does not return to normal for months, and sometimes never. A second course of penicillin is advisable if the spinal fluid is still abnormal after 6 months.

Congenital syphilis in the newborn may be treated with 100 mg procaine penicillin i.m. for 10 days. Topical application of hydrocortisone to the eyes helps to reduce interstitial keratitis.

A pregnant woman with syphilis should be treated as for primary syphilis, in each pregnancy some advocate, in order to avoid all danger to the children.

Therapy is best given between the third and sixth months as there may be a risk of abortion if it is given earlier.

Results of treatment of syphilis with penicillin are excellent, virtually 100% cure is achieved in seronegative cases, but the cure rate is lower in seropositive cases.

Follow-up of all cases is essential, for 5 years if possible, with annual serological tests and a final examination of the cerebrospinal fluid. Relapses are rare and it is hard to distinguish these from re-infections. One study found the "relapse rate" amongst patients on identical treatment to be related to social status, which suggests that most relapses are really re-infections.

Chemoprophylaxis of syphilis may be practised with oral penicillin, but is not absolutely reliable and there is a risk of contracting an infection,

the early signs of which may be masked. Masking of gonorrhœa does not occur. Chemoprophylaxis is not to be recommended under normal social conditions. A patient who is known to have been exposed to syphilis recently may be treated as though he has syphilis, but there is no agreement as to the clinical merits of this, although social requirements may occasionally demand it.

Patients allergic to penicillin may be treated with a tetracycline 3 g a day for 2 to 3 weeks, but with this dose adverse reactions are likely. Smaller doses may be effective but it is not known for certain.

There is wide variance in dosage used in different clinics. As long-term follow-up results become available, dosage will be standardised. Arsenic certainly, and bismuth perhaps, have been rendered obsolete by penicillin. Iodides, under whose sole influence gummata will heal without any concomitant cure of the disease, add nothing to the efficacy of penicillin in late syphilis.

Pyrexial therapy by deliberate infection with malaria or by heating the patient in a box, is now only used in the most advanced cases with optic atrophy or apparently treatment-resistant neurosyphilis. The treatment has dangers and may confer no benefit when given after a full course of penicillin, but in the absence of definite evidence it is reasonable to retain such desperate measures for such desperate cases (see bismuth sodium thioglycollate).

The Herxheimer (or Jarisch-Herxheimer) reaction may be due to the massive slaughter of spirochætes resulting in the release of toxic substances. As pyrexia it is common during the few hours after the first penicillin injection. It is usually mild, but in neuro- or cardiovascular syphilis there may be a sudden worsening of the condition due to inflammatory reaction at the site of the lesions. It cannot be prevented by graduating the doses of penicillin, and probably not by using bismuth or mercury first. An adrenal steroid may stop it and should probably be given if a reaction is specially to be feared, starting 2 days before and continuing for 1 day after the antibiotic is given (prednisolone 40 mg/day orally will serve).

Non-gonococcal urethritis is a heterogeneous group and often responds to a tetracycline. For trichomonas urethritis metronidazole is used, see below.

Chancroid is due to Hæmophilus ducreyi, it is susceptible to co-trimoxazole and tetracycline (10-day course).

Lymphogranuloma venereum, due to a large virus, is probably best treated by a tetracycline (3 weeks). Early treatment is obviously desirable in the hope of avoiding the dangerous scar formation characteristic of the disease.

Granuloma inguinale, due to a virus, may respond to a course of tetracycline (3 weeks).

The use of the tetracyclines in the last four diseases may mask syphilis, so long-term follow-up is desirable.

Vaginal Infections

Bacterial vaginal infections are treated according to general principles of chemotherapy. Resistant infections sometimes respond if a small dose of an œstrogen is given orally for a month. Local allergy to locally applied drugs is common and may be difficult to distinguish from exacerbation of the infection. There are numerous causes of failure to cure and numerous practical details of therapy that are beyond the scope of this book, but which are vital for success. Gynæcological sources should be consulted.

Trichomonas vaginitis (and urethritis) is treated by **metronidazole** (Flagyl) (200 mg) 200 mg orally 8-hrly for 7 days. About 10% of cases recur and up to 2 g total/day for 3 to 4 days may then be tried. Apparent relapses may be re-infections and so it is wise to inspect the sexual partner. If there are repeated recurrences he should be treated even if he appears to be free from infection. Co-existing gonorrhœa or candidiasis are causes of failure of treatment.

Metronidazole is also effective in amœbiasis, Vincent's infection and giardiasis of the alimentary tract.

It is effective and seems to be safe in pregnancy, though caution may suggest that it is wiser not to use it late in the menstrual cycle. Although excreted in the milk it is harmless to the baby.

Adverse effects are seldom troublesome. They include gastro-intestinal upset, rashes, dizziness, headache, an unpleasant taste and a weak disulfiram-like interaction with alcohol.

Nimorazole and nifuratel are alternatives.

Candidiasis is treated by Nystatin Pessaries (B.N.F.) inserted once or twice a day for 14 days with nystatin powder or ointment on surrounding skin. Failure may be due to a concurrent intestinal infection causing re-infection and Nystatin Tablets (B.N.F.) may be given orally 8-hrly with the local treatment. The male sexual partner may use nystatin ointment for his benefit and for hers (re-infection).

Non-specific vaginitis may be helped by restoring the vaginal pH to its normal acid state with Lactic Acid Pessaries (B.P.C.). "With such an uncomfortable and socially distressing condition as vaginitis, there is no place for perfunctory investigation or treatment. These patients require careful clinical and laboratory investigation and merit the full attention of the gynæcologist."*

Genital warts can be treated with podophyllin (cytotoxic resins from the notorious drastic purgative plant podophyllum peltatum).

Other Infections

Burns (*18*). Infection may be substantially reduced by compresses of silver nitrate solution (0·5%), silver sulphadiazine or by maphenide.

* Editorial (1964). Vaginitis. *Lancet*, **2**, 848.

Substantial absorption can occur from any raw surface and use of aminoglycoside (e.g. neomycin) preparations can cause ototoxicity.

Gas gangrene (*28*). The skin between the waist and knees is normally contaminated with anaerobic fæcal organisms. However assiduous the skin preparation be for orthopædic operations or thigh amputations it will not kill spores. Surgery done for vascular insufficiency where tissue oxygenation may be poor is liable to be followed by infection. Cl. welchii is sensitive to penicillin and such operations should be accompanied by penicillin prophylaxis.

Wounds. Systemic chemoprophylaxis is necessary for several days at least in dirty wounds, where sutures have to be left below the skin, and in penetrating wounds of body cavities. Benzylpenicillin is probably best, but in the case of penetrating abdominal wounds tetracycline or ampicillin should be added.

There are many antimicrobial preparations for local use, e.g. hexachlorophane, chlorhexidine, and antibiotics, see B.N.F.

Iodine solution is an effective skin antiseptic where the patient is not allergic. However it is inactivated by serum so that its painful application to wounds is punishment, not therapy.

Abscesses and infections in bone and serous cavities are treated appropriately to the organism concerned but require high doses because of poor penetration. Local instillation of the drug may be needed.

In osteomyelitis early treatment is urgent to prevent bone necrosis. Bacteriological identification is of great importance and blood for culture (50% of cases are positive) should be taken before therapy begins, indeed aspiration of the bone to get the organism has been advocated.

As the organism is commonly Staph. aureus initial treatment should be benzylpenicillin, plus cloxacillin lest it be a penicillinase-producer. Therapy should continue for 3 weeks after pyrexia has ceased. Surgery is often needed in late cases; in early cases its place is controversial.

Skin sepsis in chicken pox, small pox and some other diseases may be severe enough to demand chemotherapy. Benzylpenicillin, ampicillin or a tetracycline will serve.

Brucellosis responds to tetracycline (2 g/day for 3 weeks) plus, in severe cases, streptomycin (1 to 2 g/day for 2 weeks). Relapses are treated similarly. Mild Herxheimer reactions may occur at the start of treatment.

Actinomycosis. The organism is sensitive to a range of drugs, but access is poor because of granulomatous fibrosis. High doses of benzylpenicillin, 3 to 6 g/day, are given for several weeks. Tetracycline can be tried. Surgery is likely to be needed. **For other fungus diseases,** *see* table of choice of antimicrobials (Chap. 7).

MAINLY TROPICAL DISEASES

Amœbiasis (*48*)

Both bowel lumen-dwelling and tissue-invading forms of amœbæ are present where there is active disease. Metronidazole will kill both forms,

and for routine purposes it replaces the complex multiple drug regimens previously necessary. For metronidazole see above.

Acute amœbic dysentery can be treated by metronidazole 800 mg orally, 8-hrly for 5–10 days. If unusally severe tetracycline (250 mg orally, 6-hrly for 10 days) and diloxanide (500 mg orally, 8-hrly for 10 days) may be added.

Hepatic amœbiasis can be treated by metronidazole 400 mg 8-hrly.

Asymptomatic intestinal amœbiasis (carriers) can be treated by metronidazole (400 to 800 mg 8-hrly for 5 to 10 days) or by one of the amœbicides that is largely confined to the gut lumen, e.g. diloxanide, di-iodo-hydroxyquinoline, and they can be used for *prophylaxis* where it is appropriate to attempt this.

Emetine is used only in the most severe cases.

Notes on amœbicides

Emetine is an alkaloid from ipecacuanha (a South American plant). Apart from its traditional use, e.g. in Dover's powder, ipecacuanha is obsolete. Emetine is obsolete as an emetic, because of toxicity and unreliability, but it retains its unsuitable name. It is too irritant to be given orally for systemic effect and it is given i.m. which is less painful than s.c. It is slowly excreted by the kidney. Injected emetine is concentrated in the liver and is highly effective in hepatic amœbiasis, but is useless against infection confined to the bowel lumen.

Toxicity comprises local inflammation, nausea, occasional vomiting, and diarrhœa (by an action on intestinal muscle) which may be confused with diarrhœa due to the disease. Weakness and fatigue occur.

Emetine is toxic to the myocardium (tachycardia, hypotension, precordial pain, conduction defects and arrhythmia). Changes in the electrocardiogram may occur during the course of emetine or up to 3 weeks afterwards. These are common and may persist for several weeks. Patients should be kept in bed when on systemic emetine and should not exercise vigorously for a further 3 weeks.

Emetine should be stopped if conduction defects, arrhythmia or more than a slight tachycardia occur.

In the presence of cardiac disease and perhaps during pregnancy emetine should be avoided if at all possible.

The *dose* is 60 mg i.m. daily (for 5 to 10 days). After a 10-day course two weeks must pass before more emetine is given, and then only for 6 days.

Dehydroemetine is probably less cumulative, less toxic and as effective as emetine, so that it may be superior. But emetine is safe if used carefully. Dosage is similar to emetine. A slow release form for use in the intestine is made.

Emetine bismuth iodide (EBI) (60 mg) liberates emetine in the large intestine and so is useful against amœbæ in the bowel. Toxicity is largely limited to gastro-intestinal symptoms, which may be severe. An anti-emetic may be needed. Rarely, enough emetine is absorbed to cause systemic effects and so vigorous exercise should be prohibited during and for a week after administration. The dose is 60 to 180 mg orally nightly.

Diiodohydroxyquinoline (Diodoquin) (300 mg) is almost unabsorbed

from the gut and toxic effects (diarrhœa, nausea, rashes, iodism) are rare. The dose is 650 mg orally 8-hrly.

Chloroquine is effective in hepatic but not in intestinal amœbiasis. It is concentrated in the liver. For toxicity see below. The oral dose of chloroquine is 300–600 mg base/day in 3 doses (250 mg chloroquine phosphate or 200 mg of the sulphate = 1 tablet B.N.F. = approx 150 mg base.)

Erythromycin and tetracycline are not direct amœbicides but alter the bowel flora on which amœbæ are partly dependent, making the environment uncongenial. They are particularly advocated if there is extensive infected ulceration. A direct amœbicide should be used concurrently or relapse will follow.

Diloxanide furoate (500 mg) is chiefly useful in asymptomatic intestinal amœbiasis although it is well absorbed and excreted in the urine. Unwanted effects are trivial and largely gastro-intestinal. Dose, 500 mg orally, 8-hrly for 10 days or more.

For relapses or failures of treatment, varying combinations may be chosen from the above and from the following incomplete list of luminal amœbicides: acetarsol (Stovarsol), carbasone, glycobiarsol (Milibis), chiniofon (Yatren), clioquinol (Vioform), paromomycin (Humatin).

Cholera (*29*)

The infection causes fluid and electrolyte loss (average about 0·5 l/hour, but this may rise to 1·5 l/hour) and this is the cause of death. Tetracycline (3 to 4 g/day, initially i.v.) gives definite reduction in diarrhœa in less than 24 hours. Although it is vibriocidal, carrier states may follow in about 3% of patients. Furazolidone is a second choice drug. For maximal detection of carrier states, examination of stools after magnesium sulphate purgation is used.

Malaria (*45, 46*)

To understand the chemotherapy of malaria it is necessary to know the principal features of the parasites' life cycle, because complete cure will not result unless both the blood and tissue (liver) cycles in man are attacked. As this cannot at present be done by a single drug, two drugs must be used, except in falciparum malaria in which the liver cycle is non-persistent. The correct choice is important.

Quinine as cinchona bark was introduced into Europe from South America in 1633. It was used for all fevers, amongst them malaria. Further advance in the chemotherapy of this disease was delayed until 1880, when Laveran finally identified malarial parasites in the blood. His views were not generally accepted and six years later, Osler, at a meeting in the U.S.A., expressed grave doubts of the relevance of Laveran's "bodies". The subsequent discussion so impressed him that he put off his holiday in Canada to investigate the blood of malarial patients. He saw the parasites and said that he "had been taught the folly of scepticism based on theoretical considerations".

The mode of spread of malaria was still uncertain when in 1894 Manson

while walking along Oxford Street, London, told Ross to "look for the parasite's dung in the mosquito's stomach". Ross returned to India with a microscope, followed this advice and soon provided the final link in the malarial parasite's life cycle.*

Quinine was the principal antimalarial drug available until 1930, when as a result of research based on Ehrlich's work on dyes, mepacrine (Atabrine or Quinacrine), a dye derivative, was introduced. It did not displace quinine until in 1942 the Japanese armies captured South East Asia and the Pacific Islands, which had supplanted South America as the source of quinine. This shutting off of quinine supplies from the Allied forces precipitated a military crisis and mepacrine was hastily manufactured to meet it. The proper use of mepacrine reduced the malaria rate amongst Australian troops in New Guinea from 740 cases per thousand soldiers per annum in November 1943 to 26 cases per thousand soldiers per annum one year later. So important was the prevention of clinical malaria to the prosecution of the war that the daily taking of mepacrine was made a matter of military discipline. Fairley writes how some soldiers with malaria were found to have low levels of mepacrine in their blood and how, after having excluded other causes, the "suggestion" that they would be kept "in the North" until their malaria stopped was followed by a dramatic rise of mepacrine blood level and cessation of malaria.

It was vital that the dosage of mepacrine necessary to enable troops to fight in hyperendemic areas without serious casualties from malaria should be found quickly. At a base in North Queensland, Australia, extensive experiments were carried out. Physical stress is believed to promote malarial relapses and so the trials of mepacrine were carried out on volunteers under conditions simulating those of jungle warfare. Volunteers were first exposed to the bites of infected mosquitoes. They were then injected with adrenaline or insulin, put half-naked into, and kept immobile in, a refrigerator at −9°C for one hour or "worked or exercised in a tropical climate at the hottest time of the year to a point verging on physical exhaustion". Some were "taken over hills for 6–10 miles, induced to swim against a stream until they were tired out, and were then walked back over the hills at as fast a pace as possible by a specially trained sergeant-major". Others marched 80–85 miles over mountains in 3 days or were put into a decompression chamber. Mepacrine was an effective prophylactic under all these conditions.†

Since this time numerous antimalarial drugs have been made and there is a wide choice of remedies.

Antimalarials and immunity

Repeated attacks of malaria confer partial immunity and the disease often becomes no more than an occasional inconvenience. Unfortunately

* Russell, P. F. (1953). *Lancet*, **2**, 944.
† Fairley, N. H. (1945). *Trans. Roy. Soc. Trop. Med. Hyg.*, **38**, 311.

it has not yet proved possible deliberately to confer active immunity to malaria, and prevention depends on drugs and on casually acquired immunity. The partially immune should generally not take a prophylactic for, owing to the resulting absence of the red cell cycle, they will slowly lose their immunity so that, should they then cease to use the prophylactic

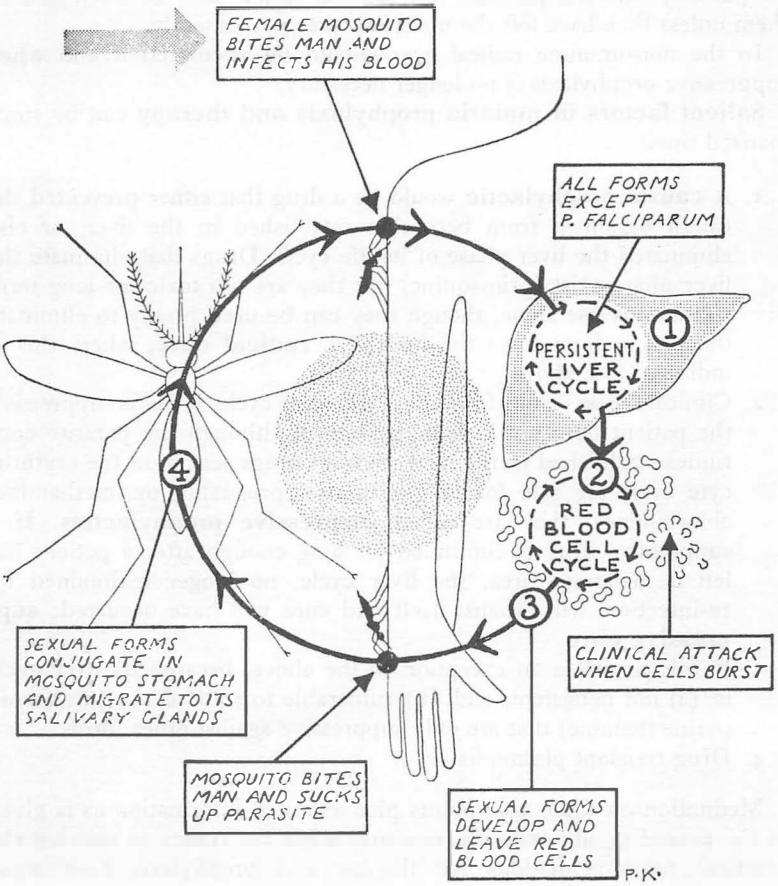

FIG. 5. Life-cycle of the malaria parasite. The numbers are referred to in the text.

they are left highly vulnerable to the disease. They should only take a prophylactic in the following circumstances: if it is virtually certain that they will never abandon it; if they go to another malarious area where the strains of parasite may differ; during the last few months of pregnancy in areas of P. falciparum to avert the risk of miscarriage; also, the very young may be given "incomplete" prophylaxis to preserve health and yet to

allow immunity to develop,* despite the risk of encouraging development of drug-resistant plasmodia if low doses are used.

The non-immune should receive continuous prophylaxis in malarious areas. Drugs will be chosen in the light of local knowledge of drug-resistant strains.

In therapy of the acute attack a single dose of chloroquine is enough for partially immune patients. Nor should radical cure be attempted in them unless they have left the malarious area permanently.

In the non-immune radical cure should be attempted if and when suppressive prophylaxis is no longer necessary.

Salient factors in malaria prophylaxis and therapy can be summarised thus:

1. A **causal prophylactic** would be a drug that either prevented the causal organism from becoming established in the liver, or else eliminated the liver phase of its life cycle. Drugs that eliminate the liver phase exist (primaquine) but they are too toxic for long-term continuous use alone, though they can be used briefly to eliminate the plasmodium from the body, i.e. **radical cure,** where this is indicated (see above).
2. Clinical illness results from the erythrocyte cycle. If this is suppressed, the patient does not become acutely ill although the parasite continues established in the liver. Several drugs acting on the erythrocyte cycle are safe for long-term use (proguanil, pyrimethamine, chloroquine); they are called **suppressive prophylactics.** If a suppressive drug is continued for long enough after a patient has left a malarious area, the liver cycle, no longer maintained by re-infection, will exhaust itself and cure will have occurred: **suppressive cure.**
3. P. falciparum is an exception to the above, because its liver cycle is, (a) not persistent, and, (b) vulnerable to some drugs (proguanil, pyrimethamine) that are only suppressive against other forms.
4. Drug resistant plasmodia occur.

Meditation on these four points plus as much information as is given in the preceding life-cycle diagram may allow the reader to see that the practical recommendations for therapy and prophylaxis have some rational basis.

These features can be expressed in a different fashion, thus—

Sites of action of drugs in plasmodial life-cycle

Erythrocyte cycle (site 2 in diagram) *suppressive prophylactic and suppressive cure:* 4-aminoquinolines (chloroquine), proguanil, pyrimethamine (see above for exceptional qualities of P. falciparum).

* SCHOFIELD, F. D. (1962). *Practitioner*, 188, 62.

Hepatic cycle (site 1 in diagram) *radical cure and causal prophylactic:* 8-aminoquinolines (primaquine).

Sexual forms: *in man* (site 3 in diagram) *prevent transmission:* primaquine: patient becomes non-infective.

in mosquito (site 4 in diagram), *prevent transmission:* proguanil, pyrimethamine: parasite fails to develop in mosquito.

Mechanism of action and drug resistance

Pyrimethamine and proguanil inhibit the enzyme that converts folic to folinic acid (dihydrofolate reductase), having an affinity for it in the parasite far greater than for the same enzyme in man. Trimethoprim is similar, but in its case the selectivity is greatest for bacterial enzyme (see co-trimoxazole) though it also has antimalarial activity. Cognoscenti use the term "antifols" for these drugs. They can also be potentiated by sulphonamides for malarial therapy, e.g. pyrimethamine plus sulfadoxine (Fanasil).

Chloroquine acts by interfering with the parasites' ability to digest haemoglobin, which deprives it of essential amino acids, and eventually leads to interference with DNA.

Primaquine acts by interfering with plasmodial mitochondria.

Drug resistance is a growing problem. It develops more readily to the antifols than to the 4-aminoquinolines (chloroquine). This difference may be due to the fact that the antifols (proguanil, pyrimethamine) block one metabolic site whereas the 4-aminoquinolines (chloroquine) block a series. There is cross-resistance within each group.

Resistance to the 8-aminoquinolines (primaquine) is not a clinical problem though research workers, unable to let well alone, have managed to induce it experimentally.

When to start suppressive prophylaxis. It is unnecessary to start prophylaxis until the day before exposure.

When to stop suppressive prophylaxis. In order to allow liver forms to pass into the erythrocyte cycle and be killed by the drug, i.e. to achieve suppressive cure, the drug should be continued at least 4 weeks after cessation of risk of infection. But relapses may occur after this time.

Interaction. Mepacrine and proguanil (but not chloroquine) inhibit the metabolism of 8-aminoquinolines (primaquine, etc.) to an extent that can lead to serious toxicity of the latter. Simultaneous administration should be avoided. But the effect can occur weeks after mepacrine administration has ceased because mepacrine is stored in the tissues.

Drug combinations are being used for drug-resistant strains, e.g. chloroquine plus pyrimethamine (Daraclor): amodiaquine plus primaquine (Camoprima): pyrimethamine plus dapsone (Maloprim), etc.

Depôt preparations for i.m. injection clearly have a place where patients cannot be relied on to swallow tablets, e.g. cycloguanil embonate (painfully i.m.) may protect as long as 3 months.

Notes on individual drugs

4-aminoquinolines (chloroquine, amodiaquine). Chloroquine is readily absorbed from the gut, is about 50% plasma protein bound and is concentrated up to several hundred times in various tissues (e.g. liver, spleen, kidney, eye). The plasma half-life of a single weekly dose is about 3 days, but with daily administration and resulting tissue accumulation it increases to more than twice that time, and some of the drug remains in the body for months. Because of the diversion into tissues and the plasma protein binding, a priming dose is used in order to achieve adequate free plasma concentration in the treatment of the acute attack of malaria though it is not generally used for prophylaxis.

Chloroquine is partly metabolised but is largely excreted unchanged in the urine; this can be enhanced by urinary acidification. Corneal deposits of chloroquine occur with prolonged therapy, but retinal toxicity is more serious and occurs chiefly with the higher doses over long periods used in rheumatoid arthritis (which see). Because of the storage in tissues ocular toxicity can progress, and even begin, after administration of the drug has stopped. Blurred vision can result from defective ocular accommodation due to accumulation of chloroquine in the iris. Other adverse reactions include rashes, and other allergic effects, mental disturbances, bleaching of hair and gastrointestinal symptoms. After i.v. injection cardiac arrhythmias may occur due to its quinidine-like action (it has also been tried in treatment of cardiac arrhythmias). Other uses include hepatic amœbiasis, and employment of its anti-inflammatory effect in rheumatoid arthritis, and in discoid and disseminated lupus erythematosus. *Hydroxychloroquine* and *amodiaquine* are similar.

Mepacrine, an acridine derivative, is obsolete for malaria except where i.m. injection is needed. It is used as an anthelmintic and amœbicide.

Proguanil (chloroguanide), a biguanide, is moderately well absorbed from the gut; it is heavily bound to plasma protein, but little to the tissues, so it is not stored in the body and must be given daily when used as prophylaxis. The kinetics of **pyrimethamine** (a diaminopyrimidine) are similar except that tissue binding is stronger and once weekly administration is enough for prophylaxis.

Apart from alimentary tract symptoms, adverse reactions are uncommon, despite their "antifol" activity.

8-aminoquinolines (primaquine, pentaquin), though chemically so close to the 4-aminoquinolines, act at a different site in the plasmodial life cycle (see above). Although they have a property (action on hepatic cycle) to provide *causal* prophylaxis, they are too toxic for prolonged sole use for this purpose. Primaquine is well absorbed from the gut; it is only moderately concentrated in the tissues; it is rapidly metabolised. Adverse effects include alimentary tract symptoms, methaemoglobinæmia and hæmolytic anæmia, especially in subjects with a genetic deficiency of erythrocyte glucose-6-phosphate dehydrogenase. See also *interaction*, above.

Quinine is described more fully below.

Sulphonamides and **sulfones** have a small, but perhaps an increasing place in treating resistant forms of malaria.

Bismuth sodium thioglycollate (Thio-Bismol) is the only antimalarial bismuth salt. Its sole use is to regulate malaria induced for therapeutic purposes, which, if induced by injecting infected blood, is liable to cause daily bouts of fever. It should, if given during the fever on one day, prevent fever the following day, and so is useful if the patient is too weak to stand more. Other antimalarials cannot be relied on to stop the next attack. The dose is 100 to 200 mg i.m. Relapse occurs after 1 to 3 days.

Dosage of antimalarial drugs (oral unless otherwise stated)

For suppression: one of the following—

pyrimethamine (25 mg):	25 mg once a week (a first choice).
chloroquine phosphate (250 mg):	500 mg once a week (a second choice)
chloroquine sulphate (200 mg):	400 mg once a week (a second choice).
amodiaquine (200 mg):	400 mg base once a week (a second choice).
proguanil (25, 100 mg):	100 mg daily* (a drug of second choice).
quinine (300 mg):	300 to 600 mg daily, if no other drug available.

Mass prophylaxis using cooking salt to which suppressives have been added has been tried in Brazil.

For treatment of overt attack in non-immunes: one of the following—

chloroquine phosphate (250 mg): or equivalent of sulphate	1·0 g, then 0·5 g 6 hrs later, then 250 mg daily for 2 days (first choice drug).
amodiaquine:	600 mg, then 400 mg daily for 2 days (first choice drug).
quinine:	600 mg 3 times a day for 7 days.

In the partially immune a single dose will serve.

For emergency treatment: one of the following—

chloroquine (first choice): 200 to 300 mg base i.m. and repeated 6 hours later. Infusion i.v. is feasible (300 mg base in 500 ml 0·9% sodium chloride over 1 hour) but liable to cause hypotension. Children should probably be given less than the dose as ordinarily calculated, as they may have convulsions.

* Many find it easier to remember to take a tablet daily rather than weekly.

mepacrine (second choice): 300 mg i.m. and repeated 6 hours later. Like chloroquine it can cause convulsions in children and a lower dose may be desirable.

quinine dihydrochloride (only in severe falciparum infection): 600 mg i.v. at a rate not exceeding 60 mg/min, up to 3 times a day. Injection i.m. causes necrosis.

For radical cure: *primaquine* (7·5 mg base): 15 mg daily for 14 days (first choice), plus therapy for overt attack, see above.

Pyrimethamine and proguanil provide radical cure for falciparum infection. Any suppressive drug continued for 4 to 6 weeks, because of the short duration of the liver cycle, will also eradicate P. falciparum.

The reason some tablet weights and doses are expressed as "base" is because these drugs are offered as several salts whose doses vary accordingly, e.g. *chloroquine phosphate* 250 *mg* = 155 *mg base: sulphate* 200 *mg* = 146 *mg base.*

Quinine

Quinine, which is obtained from the cinchona tree, has lost much of its therapeutic importance. It is usually described, vaguely, as a "protoplasmic poison" which term conceals a wide variety of actions. Quinine has numerous effects in the body, many of which are of no therapeutic use. It is well absorbed from the alimentary tract, although it is a strong irritant, and causes vomiting by local gastric effect as well as by stimulating the vomiting centre. Intramuscular injections are liable to form abscesses; i.v. injections are dangerous, see below.

Uses. Dilute solutions are used for their bitter taste in tonics and as aperitifs. The antimalarial action of quinine has already been mentioned, its mechanism may be the same as the 4-aminoquinolines. It is more toxic and less effective than the synthetic alternatives. It is also used in myotonia and cramps.

On the central nervous system quinine acts as a feeble antipyretic and analgesic and is included in numerous proprietary mixtures. It interferes with the second and eighth cranial nerves (see under toxicity).

On the heart quinine acts similarly to its optical isomer quinidine (which see), but is less potent.

On skeletal muscle quinine increases the refractory period; this is made use of in patients with myotonia (300 mg of bisulphate 8-hrly) or nocturnal muscle cramps (300 to 600 mg of bisulphate at night), sometimes with worthwhile benefit. Procainamide is also effective and may be superior to quinine in myotonia, and prednisone has been found useful. The symptoms of myasthenia gravis may be made worse by quinine and this has been tried as a diagnostic test in doubtful cases, but it is unreliable.

On the pregnant uterus quinine has a stimulant effect which increases as pregnancy advances. It is widely known to the general public as an abortifacient, and cases of poisoning are seen as a result. But it is unreliable even in lethal doses.

On the blood. Quinine may cause hæmolysis (blackwater fever) in

some patients with chronic falciparum malaria and in pregnancy; it causes thrombocytopenia and agranulocytosis rarely. These are probably allergic effects, due to auto-immune mechanisms, as are rashes and asthma. This is well shown by the following bold experiment (*13*):—

A woman who was in the habit of taking proprietary analgesics containing quinine had episodes of epistaxis and purpura and hæmatemesis. Eventually the quinine was suspected and an oral test dose of 5 mg was given. 1½ hours later she felt ill with headache and pyrexia. The blood platelet count fell from 400,000 to 17,600/cmm in 3½ hours. The bleeding time was 12 minutes (normal 2 to 5 minutes). It was decided to infuse 200 ml of her plasma into a normal volunteer who had just taken quinine and who was known not to be allergic to it. An hour later the volunteer felt ill and soon had two rigors with cyanosis, nausea and vomiting. His platelet count fell from 850,000 to 5,400/cmm, he developed petechiæ and his gums bled. The bleeding time was over 18 minutes. He was given oral cortisone and corticotrophin i.v., and made a complete recovery although the platelet count took a week to return to normal. A later transfusion of the patient's serum into the volunteer in the absence of quinine caused no reaction.

It is suggested that quinine forms a complex with platelets and that this becomes antigenic in some people. In the experiment the antibodies formed in the patient were transferred to the volunteer and destroyed his platelets in the presence of quinine.

Toxic effects. Some toxic effects of quinine are common to quinidine, salicylates and cinchophen and the term cinchonism is used to describe them. They consist of interference with the auditory nerve causing tinnitus, deafness and vertigo, and of visual impairment and even complete blindness, the onset of which may be very sudden. The cause of this is disputed; it is probably due to direct toxicity on the retinal cells and not to vascular spasm. In addition quinine causes rashes, nausea, vomiting and diarrhœa with abdominal pain, also fever, hypotension, convulsions and respiratory depression. Ventricular tachycardia happens very rarely and i.v. injections should be very slow. Treatment of quinine poisoning consists in encouraging renal excretion by increasing urinary output and making it acid, which may double the rate of elimination, and in treating symptoms as they occur. Vasodilators and vitamins in cases of blindness are probably valueless, though it may be worth trying stellate ganglion block. Loss of sight can be permanent, but partial or complete restoration is usual. Allergy to quinine sometimes, but not always, means the patient is allergic to quinidine.

Trypanosomiasis

African form. Suramin or pentamidine are used in early cases without CNS involvement since they do not penetrate the CNS. If there is CNS involvement the more toxic arsenicals are required (melarsoprol, melarsonyl). Nitrofurazone is a less effective alternative, used where

there is allergy to other drugs. Pentamidine may be used as a prophylactic.

South American form. Treatment is less satisfactory: a nitrofuran (nifurtimox) is used.

Leprosy (*47*)

Effective treatment of leprosy is complex and requires much experience if the best results are to be got. As with tuberculosis, treatment must be prolonged.

Sulphones, e.g. dapsone (diaminodiphenylsulphone, DDS), are the drugs of choice. They were found to be effective against common bacterial infections in animals during the flood of research that followed the discovery of the sulphonamides, but they were more toxic than these and so were not used clinically. In 1941 the tuberculostatic effect of sulphones was noted and, as a result, they were tried against leprosy in rats. Successful clinical trial followed in 1943.

Other antileprotics include thiambutosine, clofazimine and rifampicin.

Exacerbations during therapy, allergic "lepra" reactions, respond to an adrenal steroid and, interestingly, to thalidomide, which has anti-inflammatory or immunosuppressive actions.

Other Infections

Leishmaniasis (kala-azar) is treated with organic pentavalent antimony (sodium stibogluconate) and aromatic diamidines (pentamidine).

Anthrax may be treated by benzylpenicillin, 1·8 g a day, perhaps plus streptomycin. Tetracycline, 4 g a day may be effective.

Tularæmia and plague may be treated by streptomycin, tetracycline, sulphonamides or chloramphenicol.

Rickettsial infections, e.g. typhus, respond to tetracycline and to chloramphenicol. Relapses are common but are amenable to a further course of chemotherapy.

Psittacosis is due to a large virus and responds to tetracycline.

Non-syphilitic spirochætoses

Yaws is cured by penicillin or tetracycline.

Relapsing fever and rat-bite fever respond to penicillin or tetracycline.

Leptospirosis is only usefully affected if treated very early in its course. Heavy doses of penicillin or tetracycline can be tried.

Chemotherapy of Helminthiasis (*49, 50*)

In the past, the successful eradication of worms in the gut lumen has depended on careful adherence to detailed schedules of drug administration integrated with starvation (to expose the parasite to the drug) and purgation (to expel both parasite and drug). This was because the drugs used were about equally poisonous to both host and parasite, and selective

toxicity to the worm was obtained by therapeutic regimen and not by biochemical specificity. This still obtains to some extent, e.g. with tapeworms, but newer drugs are more selective and so are less tiresome and unpleasant to take. For example, in both Ascaris and man acetylcholine is the transmitter of the nerve impulse to muscle. But curare, which blocks the neuromuscular junction in man has little effect on Ascaris and piperazine which blocks it in Ascaris has little effect in mammals. Both drugs act competitively, though probably not identically, and the selectivity is presumably due to a difference in the nature of the myoneural receptors. The neuromuscular block prevents the worm from maintaining its position in the gut and it is removed by normal peristaltic activity.

On the other hand there is evidence that drugs that stimulate activity in the worm also interfere with the orientating mechanisms, and can be successful anthelmintics.

Helminths have complex life-cycles, special knowledge of which is required by those who treat infestations. The following notes must suffice here. Drug resistance has not so far proved to be a clinical problem, though it has occurred in animals on continuous chemoprophylaxis.

Factors contributing to the choice of safe and effective treatment of **schistosomiasis** include: (1) variety of parasite; (2) need for mass therapy, i.e. cheap drugs that are safe enough to be given with little or no medical supervision; (3) difficulties in assessing cure, e.g. elimination of egg excretion does not prove cure, and resumption of egg excretion may be either relapse or reinfection; (4) difficulties in giving serial doses of drugs to scattered populations, i.e. a need for single dose treatment; (5) host factors modifying drug response, e.g. race, immunity, nutritional status, renal and hepatic function; (6) control of reinfection, e.g. vector control, agricultural practices, education.

The subject will not be considered in detail here, for anti-schistosomiasis programmes vary with circumstances and are commonly in the hands of local health authorities.

Drugs used include antimony compounds which probably act by inhibiting the enzyme phosphofructokinase in the parasite. Preparations include antimony Na or K tartrate, sodium antimonylgluconate, antimony dimercaptosuccinate and stibophen. They are toxic to the cardiovascular system and can cause sudden death; they can also cause severe vomiting, and arthritis, pneumonia, and anaphylactoid reactions; they are more hazardous if there is hepatic or renal insufficiency.

Schistosomes have cholinergic neuromuscular mechanisms which differ sufficiently from those in man to allow anticholinesterase drugs to be useful and relatively safe (e.g. metrifonate).

Other drugs include niridazole, lucanthone and hycanthone which interfere with gonadal function in the schistosomes.

In **filariasis,** due to six different parasites, diethylcarbamazine kills microfilariæ; it induces an unpleasant allergic Herxheimer reaction due to the products of disintegration of the dead parasites; antihistamine

or adrenal steroid therapy may be needed. Suramin which is chiefly active against the adult worms is also used.

Trichiniasis. In early cases thiabendazole may help, but there is no drug effective against worms that have migrated to the muscles. Adrenal steroid therapy may be necessary during the acute illness caused by the migration.

For **strongyloidiasis,** thiabendazole: for **dracunculiasis** (guinea worm), niridazole or thiabendazole. For **trichuriasis** (whipworm), thiabendazole, and hexylresorcinol if it fails.

For **tæniasis,** fluid diet for 24 hours: mag. sulph. purge at night to ensure the worm will not be protected by food: next morning give niclosamide (2 g) or dichlorophen (6 g) orally, crushed tablets: repeat next day: slight colicky diarrhœa may occur. The worm is killed and may be digested, so that a hunt for its head in the fæces is not worth the unpleasantness incurred. With T. solium there is risk of regurgitation of eggs into the stomach leading to cysticercosis, so give antiemetic before dose. Look for segments in stool at 3-month follow-up. These drugs replace mepacrine and male fern extract.

Ascariasis. Piperazine citrate 3·5 g (solid and fluid preps available) orally on two consecutive days: no special bowel ritual: malaise, vomiting may occur. Alternatives are tetramisole, levamisole and hexylresorcinol.

Enterobiasis (threadworm). Viprynium, single oral dose 5 mg *base*/kg up to maximum of 250 mg: no special bowel ritual: turns stool red: minimal toxicity, malaise, vomiting: precautions against reinfection by self or family improve chance of cure: repeat after 2 weeks if necessary. Piperazine may be used.

Ankylostomiasis (hookworm). Bephenium (Alcopar) 5 g sachet orally before breakfast: same dose all ages: no special bowel ritual. Toxicity virtually absent: also effective against concurrent ascariasis. Tetrachlorethylene (0·1 ml/kg up to maximum of 5 ml) is an alternative: fluid diet 24 hours before drug, avoiding fat and alcohol which promote absorption of drug: mag. sulph. purge night before and again 2 hours after taking drug in morning: starve until purge works: do not repeat for 10 days: toxicity slight if correctly used: headache, vertigo. Chenopodium oil is obsolete.

Giardia lamblia can be removed, if desired, by metronidazole or mepacrine.

Guide to Further Reading

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Chapter 9

CORTICOTROPHIN, ADRENAL STEROIDS, AND ANTAGONISTS

History. In 1855 Dr. Thomas Addison, assisted in his observations by three colleagues, published his famous monograph "*On the constitutional and local effects of disease of the suprarenal capsules*". All four have given their names to diseases unrelated to the adrenal cortex; Addison to pernicious anæmia, Bright to nephritis, Gull to myxœdema and Hodgkin to lymphadenoma. In the following year a physiologist whose principal fame also lies elsewhere made a contribution to the study of the adrenal glands. Brown-Séquard performed bilateral adrenalectomy in animals and demonstrated that the glands were essential to life, but his work was discounted because, it was said, the animals would die of such surgery whether the glands were removed or not.

Before the end of the 19th century attempts were being made to treat patients with Addison's disease by adrenal gland extracts. By 1896, Osler, using glycerin extracts of fresh hog adrenals given orally, had treated six cases with improvement in one.

The fact that the secretions of the adrenal cortex differed from that of the medulla was not appreciated in 1901 when adrenaline was first isolated, so that the failure of attempts to maintain life in adrenalectomised animals and to benefit Addison's disease with the newly discovered adrenaline was a great disappointment.

It was not until the 1920's that the vital importance of the adrenal cortex was appreciated and the distinction between the hormones secreted by the two parts of the gland became clear. At this time it was said "the literature so-called of the physiology and pathology of the adrenal bodies presents a very confused and baffling picture, which only begins to clear somewhat when it is recognised that no mean proportion of the total mass of printed matter, and the portion which contributes most to the haze, can and ought to be stricken from the record on internal evidence alone. . . . Nowhere, perhaps, in experimental work is it more necessary to remember the difference between *post hoc* and *propter hoc*. Anyone who looks into the literature will see how often this rule has been neglected."*

By 1929, a year of grave economic upheaval, a reliable adrenal cortical extract was being prepared and its potency determined on cats. This involved injecting, over a period, some five hundred U.S. dollars' worth of material into each cat. These valuable beasts "were viewed with some economic misgiving by those of us who, as graduate students in the

* STEWART, G. N. (1924). *Physiol. Rev.*, **4**, 163.

Princeton laboratories at the time, were not sharing in the alleged prosperity of early 1929."* However, the first clinical trial of this extract reassured any doubters by rapidly reviving a moribund patient suffering from Addison's disease.

By 1936, numerous steroids were being crystallised from cortical extracts, but not enough could be obtained to provide supplies for clinical trial.

The first steroid to be synthesised was deoxycortone (DOCA, DCA) in 1937, and this was done before it had been isolated from cortical extracts, in which only very small amounts occur.

In 1948 cortisone was made from bile acids in quantity sufficient for clinical trial, and the dramatic demonstration of its power to cause remission in cases of rheumatoid arthritis was published in the following year. Since then an embarrassingly large number of steroids have been made and offered to the clinician. They are made by a complicated process from natural substances (chiefly plant chemicals), the constitution of which approach most nearly to that of the steroids themselves. A principal aim in research is to produce steroids with more selective action than cortisone, which commonly induces a greater variety of effects than are desired in any patient who is not suffering from adrenal insufficiency.

About the same time as cortisone was introduced, corticotrophin became available for clinical use.

In 1927 it had been shown that removal of the pituitary gland in animals was followed by atrophy of the adrenal cortex. In 1933 it was found that administration of pituitary gland extracts to animals was followed by hypertrophy of the adrenal cortex. In the 1940's the pure substance in the pituitary, corticotrophin, was isolated, and in the 1960's it was synthesised.

CORTICOTROPHIN

(Adrenocorticotrophic Hormone, ACTH)

Natural corticotrophin is a polypeptide, consisting of a chain of 39 amino-acids, secreted by the anterior pituitary gland.

The biological activity resides in the first 24 amino-acids (which are common to many species) and most immunological activity resides in the remaining 15 amino-acids.

The pituitary output of corticotrophin responds rapidly to physiological requirements and, since the plasma half-life of corticotrophin is 15 min, and the adrenal cortex responds rapidly (within 2 min) it is plain that adjustments of steroid output can be made quickly.

Synthetic corticotrophins have the advantage that they are shorter amino-acid chains and so are less likely to cause serious allergy, though

* Gaunt, R., and Eversole, W. J. (1949). *Ann. N.Y. Acad. Sci.*, **50**, 511.

this can happen. In addition they are not contaminated by animal protein which is a potent allergic hazard.

Tetracosactrin consists of the biologically active first 24 amino-acids of man and animals and so it has similar properties, e.g. 15 min half-life. Other synthetic corticotrophins in which amino-acids are substituted in the active first 24 are being made, and some of these show useful prolongation of action due to slower destruction.

Actions. Corticotrophin is responsible for stimulating the synthesis and/or release of corticosteroids (of which the most important is hydrocortisone) and to a lesser extent of androgens, by the cells of the adrenal cortex. It has only a minor effect on aldosterone production which can proceed independently. In the absence of corticotrophin the cells of the inner cortex atrophy.* The release of natural corticotrophin by the pituitary gland is controlled by the hypothalamus by a mechanism which is probably neurohumoural (corticotrophin releasing factor) and which is influenced by environmental stresses as well as by the level of circulating hydrocortisone. High blood levels of any steroid with glucocorticoid effect prevent release of corticotrophin which in turn results in adrenal hypofunction. This is the reason why catastrophe may follow sudden withdrawal of steroid therapy. The steroid must be tailed off to give time for the normal pituitary production of corticotrophin to be resumed and, in the case of prolonged therapy, for the recovery of the atrophied suprarenal gland.

Corticotrophin is of little or no use in restoring suppressed pituitary-adrenal function after withdrawal of prolonged steroid therapy. This is because the limiting factor in recovery is the pituitary or hypothalamus not the adrenal cortex. Attempts to use it to prevent the consequences of adrenal suppression during steroid therapy have also failed for the same reason.

But if corticotrophin is used as sole therapy, hypothalamic-pituitary-adrenal responsiveness to stress is substantially maintained, and this constitutes a definite advantage. The reasons for this may be that blood corticosteroid levels do not reach the heights that are usual with orally administered steroids, and there is some evidence that smaller amounts of corticotrophin from a recovering pituitary produce adequate output from a hypertrophied adrenal, but have little effect on the atrophied cortex induced by prolonged exogenous steroid therapy.

Corticotrophin suppresses growth less than do exogenous steroids and so it is preferred for long-term therapy in children (*11*).

The **effects** of corticotrophin are those of the steroids (hydrocortisone, androgens) liberated by its action on the adrenal cortex. Prolonged heavy dosage causes a clinical picture resembling Cushing's syndrome.

Corticotrophin is used both in diagnosis and in treatment. It is inactive if taken orally.

* But not of the outer cortex (zona glomerulosa) which secretes aldosterone and which is not under pituitary control.

Diagnostic use: as a test of the function of the adrenal cortex in cases suspected of Addison's disease, hypopituitarism, Cushing's syndrome or the adrenogenital syndrome.

One technique useful for diagnosis of Addison's disease in the Out-patient Dept. is to inject 0·25 mg Tetracosactrin Inj B.N.F. i.v. and to compare plasma 17-oxogenic steroids before and 30 min after. A more reliable test involves Tetracosectrin Zinc Inj i.m. (a depot preparation) and takes 48 hrs.

Characteristic responses to adrenal stimulation in different kinds and degrees of insufficiency are shown in Fig. 6. Here the metabolites of the steroids are measured since the work was done before it was possible to

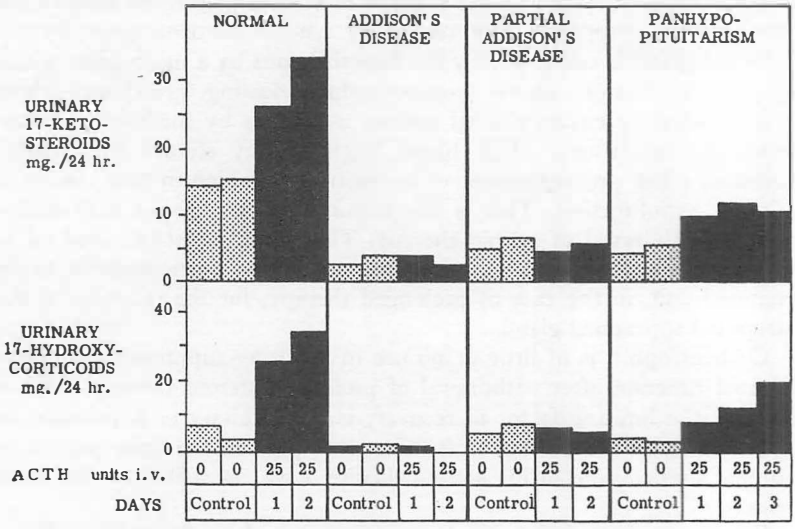

Fig. 6. Response to corticotrophin in adrenal insufficiency.*

measure the actual hormones. The glucocorticoid (chiefly hydrocortisone) metabolites are measured as 17-oxogenic steroids (17-hydroxycorticoids); the androgen (anabolic steroids) metabolites are measured as 17-oxo-steroids (17-ketosteroids).

It is convenient here to summarise some tests for integrity of the hypothalamic-pituitary-adrenal system that are available to the physician wishing to establish the site and magnitude of disorder whether due to natural disease or therapy (pituitary irradiation). But first a **physiological note:** changes in plasma concentration of hydrocortisone (cortisol), stress, etc., affect the *hypothalamus* to modify production of cortico-trophin-releasing factor (CRF): this factor acts on the *pituitary* and the released corticotrophin acts on the *adrenal cortex* to secrete hydrocortisone which is monitored by the *hypothalamus* by a feed-back mechanism.

* By courtesy of Dr. George Thorn and the Editor of *J. Amer. med. Ass.* (1958) **168,** 2130.

Defects in this cycle can be isolated by stimulating or suppressing it at these different sites and measuring the consequences (corticotrophin or steroids in the blood or steroids in the urine):

1. Tests acting initially via the hypothalamus

(a) *Dexamethasone suppression.* Dexamethasone acts on the hypothalamus (like hydrocortisone), to reduce CRF output. Dexamethasone is used because it is so potent (only 2 mg orally is given) that metabolites in the urine are not enough to interfere with measurement of hydrocortisone metabolites.

(b) *Insulin hypoglycæmia* stimulates the hypothalamus to release CRF.

2. Tests acting initially on the pituitary

(a) *Lysine-vasopressin* directly stimulates the pituitary to release corticotrophin. CRF itself is not available at present.

3. Tests acting initially on the adrenal cortex

(a) *Corticotrophin* administration (see above).

(b) *Metyrapone* blocks the final step in hydrocortisone synthesis (see below).

Example: a failure to respond to insulin hypoglycæmia with a positive response to lysine-vasopressin would indicate hypothalamic failure, and so on.

Therapeutic use: either, (*a*), when adrenocortical hormone effects are desired to treat a disease or, (*b*), when it is desired to stimulate inactive adrenal glands.

a. The aim is to produce intense adrenocortical stimulation to provide high blood levels of hydrocortisone. Corticotrophin has the disadvantage that it must be given by injection and the effectiveness of the adrenal response remains uncertain unless blood or urine steroid levels are measured. But it does not stunt growth in children.

b. To stimulate an adrenal cortex which has atrophied as a result of hypopituitarism or suppression of the anterior pituitary gland by steroid therapy. This is not useful during withdrawal of the steroid, but can be used if these patients have an infection or other severe accidental stress during the succeeding 1 to 2 years when pituitary responsiveness may still be inadequate.

The effects of exogenous corticotrophin differ from those of exogenous adrenal steroid administration in some important respects:

1. Corticotrophin causes an increased adrenal secretion of anabolic steroids (androgens) as well as of catabolic steroids (e.g. hydrocortisone). Exogenous corticosteroids are solely catabolic and inhibit the pituitary,

resulting in adrenal suppression, so that even the normal amount of anabolic steroid is not produced; there is thus an increase in urinary 17-oxogenic steroids (metabolites of hydrocortisone, etc.) and a *decrease* in oxosteroids (metabolites of androgens). Muscle wasting and osteoporosis are thus less likely to occur with corticotrophin, and this is important in the treatment of muscle wasting diseases, e.g. dermatomyositis, polymyositis.

2. Adrenocortical atrophy occurs with exogenous steroid, due to pituitary inhibition, but adrenocortical hypertrophy occurs with exogenous corticotrophin.

3. Suppression of endogenous pituitary corticotrophin secretion occurs with exogenous steroid and this is the chief reason for the adrenal insufficiency that may follow sudden cessation of therapy, for recovery of pituitary function can be slow and steroids *must* be withdrawn gradually to avoid acute adrenal insufficiency.

Exogenous corticotrophin therapy, however, causes much less pituitary suppression (see above).

Whatever the reason, the patient receiving corticotrophin is less likely to suffer acute adrenal insufficiency as a result of intercurrent illness or other stress, or following withdrawal of treatment than is the patient on exogenous steroid therapy.

4. Corticotrophin cannot be used to obtain selective anti-inflammatory effect, for it principally increases endogenous production of hydrocortisone. Therefore electrolyte disturbances, such as sodium retention, are inevitable with vigorous therapy.

5. With corticotrophin, the amount of adrenal stimulation is limited by the capacity of the gland to about four times the resting output, whereas with exogenous steroid there is no upper limit. This fact may contribute to the lower incidence and lesser severity of some toxic effects in clinical practice. Overdosage with oral steroid is only too easy.

6. With long-term exogenous corticotrophin therapy there is a *lesser* incidence and severity of the following unwanted effects—osteoporosis and muscle wasting (see 1 above), bruising, gastric upset, peptic ulcer and growth arrest in children, but a *higher* incidence of acne (because of androgen secretion) and of hypertension (because selective anti-inflammatory effect cannot be got—see 4 above).

7. Because even to synthetic corticotrophin immunological resistance is liable to develop, it is necessary to watch the effect of therapy by measuring urinary 17-oxogenic steroids or plasma hydrocortisone.

Choice between corticotrophin and an orally-active steroid for therapy. To justify abandoning the convenience of oral therapy for the inconvenience and unpleasantness of twice-weekly, i.m. injections, even if self-administered, there must be strong reasons. The *advantages* of corticotrophin are that hypothalamic-pituitary-adrenal response to stress and some unwanted effects are less common, though some others are more common (see 6 above). The risk of chronic overdose is also less

and withdrawal is safer and easier (see 3 above). These considerations may sometimes cause corticotrophin to be preferred in individual patients. Otherwise the indications and contra-indications for corticotrophin are similar to those for exogenous steroid, excepting, of course, in cases where the adrenal cortex itself is diseased.

It is important to use the minimum dose for the required response in order to avoid unwanted effects. General contra-indications for corticotrophin therapy are the same as those for adrenal steroids. Dosage of corticotrophin cannot be expressed in equivalence with oral steroid.

Preparations. *Tetracosactrin Injection, B.N.F.* is a powder dissolved in water immediately before injection i.m. or s.c., 0·25 mg. It is used for diagnostic tests only as it has such a short half-life (15 min).

Tetracosactrin Zinc Injection, B.N.F. (Synacthen Depot) in which the hormone is adsorbed on to zinc phosphate from which it is slowly released. This is the form used in therapy, for it can be given i.m. twice a week (0·5 to 1·0 mg) and the doses then spaced according to response.

Corticotrophin preparations from animals (mixed with carboxymethylcellulose or gelatin for prolonged effect) remain available, but synthetic preparations are always preferable to biological preparations.

Corticotrophin CMC (carboxymethylcellulose) Inj. and *Corticotrophin Gelatin* Inj. (B.N.F.) are animal preparations which have to be biologically standardised. The doses are expressed in units.

ADRENAL STEROIDS AND THEIR SYNTHETIC ANALOGUES

Hormones normally produced by the adrenal cortex include hydrocortisone (cortisol), corticosterone, aldosterone and some androgens and œstrogens, but not cortisone, most of which, when administered, is converted by the body into hydrocortisone. Unless so converted, cortisone is biologically inert. Numerous other steroids have been isolated from the gland and many more have been made in the laboratory.

Adrenal steroids are chiefly used in medicine for their anti-inflammatory effects. These are only obtained when the drugs are given in doses far above those needed for physiological effect. Their metabolic effects, which are of the greatest importance to the normal functioning of the body, then become "unwanted", "toxic" or "side" effects. Much successful effort has gone into separating glucocorticoid from mineralocorticoid effects and some steroids (prednisolone, dexamethasone) have virtually no mineralocorticoid effect. But it has not yet proved possible to separate some of the glucocorticoid effects from each other, so that if a steroid is used for its anti-inflammatory action the risks of osteoporosis, hæmatemesis, diabetes, etc., remain.

In the account that follows, the effects of hydrocortisone will be described and then other steroids insofar as they differ. In the context of this chapter "adrenal steroid" means a substance with hydrocortisone-like activity. Androgens are described elsewhere.

The effects of hydrocortisone are as below. Naturally there is a distinction between replacement therapy (physiological effects) and the higher doses of pharmacotherapy.

On inorganic metabolism (**mineralocorticoid** effects): increased retention of sodium by the renal tubule, and increased potassium excretion in the urine. At the same time there is increased glomerular filtration rate which tends to promote sodium excretion by allowing less time for ion exchange in the tubule. But sodium retention ordinarily dominates.

On organic metabolism (**glucocorticoid** effects):

On carbohydrate metabolism: gluconeogenesis is increased and peripheral glucose utilisation (transport across cell membranes) may be decreased (insulin antagonism) so that hyperglycæmia and sometimes glycosuria results. Latent diabetes becomes overt, and this has been used as a test for the prediabetic state.

On protein metabolism: anabolism (conversion of aminoacids to protein) is decreased but catabolism continues unabated or even faster, so that there is a negative nitrogen balance with muscle wasting. Osteoporosis (reduction of bone protein matrix) occurs, growth slows in children, the skin atrophies and this, with increased capillary fragility, causes bruising and striæ. Healing, of peptic ulcers or of wounds, is delayed, as is fibrosis.

On fat deposition: this is increased on shoulders, face and abdomen.

Inflammatory response is depressed, regardless of its cause so that as well as being of great benefit in "useless" or excessive inflammation steroids can be a source of danger in infections by limiting useful protective inflammation.

Allergic effects are suppressed. The antigen–antibody interaction is unaffected, but its injurious inflammatory consequences do not follow.

Antibody production is reduced by heavy doses.

Lymphoid tissue is reduced.

Renal excretion of uric acid is increased.

Blood eosinophils are reduced in number, and this has been used as a test of activity.

Euphoria or psychotic states may occur, perhaps due to CNS electrolyte changes.

Anti-vitamin D action, see calciferol.

Reduction of hypercalcæmia chiefly where this is due to excessive absorption of Ca from the gut (sarcoidosis, vit D intoxication).

Urinary calcium excretion is increased and renal stones may form.

Growth reduction in children: the mechanism is uncertain.

Suppression of hyothalamic-pituitary-adrenocortical system occurs with high doses, so that sudden withdrawal leaves the patient in a state of adrenocortical insufficiency. The normal daily secretion of hydrocortisone is 15 to 25 mg; 40 to 80 mg hydrocortisone, or 50 to 100 mg cortisone or its equivalent in other preparations, is needed daily for complete cortical suppression and for useful anti-inflammatory effect. A suppressed adrenal continues to secrete aldosterone.

Notes on Individual Adrenal Steroids

All except deoxycortone and aldosterone are usefully active when swallowed. Some details of preparations and equivalent doses are given in the table. Injectable and topical forms are available (creams, suppositories, eye drops, etc.).

Hydrocortisone (cortisol) is the principal naturally occurring steroid. A soluble salt can be given i.v. (as Hydrocortisone Sodium Succinate Inj. B.P.) for rapid effect in emergency. A suspension of the insoluble Hydrocortisone Acetate Inj. B.P. can be given i.m. for prolonged effect, and also intra-articularly. It is preferable to cortisone because it is the natural hormone.*

Cortisone can also be given orally or i.m. It is biologically inactive and is converted to hydrocortisone in the liver, so it is unsuitable for topical application. Though satisfactory as replacement therapy in many patients, hepatic insufficiency renders it partially ineffective, so that it is probably better to use hydrocortisone as routine substitution therapy in Addison's disease.

Choice of parenteral preparation for systemic effect: the soluble Hydrocortisone Sodium Succinate (or Phosphate) Inj. is used for quick (1–2 hr) effect. Hydrocortisone or Cortisone Acetate Inj. (a suspension) for slower but more prolonged effect.

RELATIVE POTENCIES OF ADRENAL STEROIDS

Compound	*Size of Oral Tablet*	*Approximate Relative Potency*		*Equivalent Dosage (for Anti-inflammatory Effect)*
		Anti-inflammatory (Glucocorticoid) Effect	*Sodium-retaining (Mineralocorticoid) Effect*	
cortisone	25 mg	1	1	100 mg
hydrocortisone	20 mg	1·2	1	80 mg
prednisolone and prednisone	5 mg	5	0·8	20–25 mg
methyl prednisolone	4 mg	6	minimal	16–20 mg
triamcinolone	4 mg	6	none	16–20 mg
dexamethasone	0·5 mg	37	minimal	2–4 mg
betamethasone	0·5 mg	40	negligible	2–3 mg
paramethasone	2 mg	10	negligible	10 mg
deoxycortone	—	negligible	50†	—
fludrocortisone	0·1 mg	10–20	150	—
aldosterone	—	none	500‡	—

† Sublingual administration.
‡ Injected.

* Cortisone is at present substantially cheaper than hydrocortisone, and may be preferred for that reason alone wherever there is certainty that the patient will reliably effect the conversion to hydrocortisone. In general, cost is ignored in this book, not because it is unimportant, but because it is liable to dramatic changes.

Prednisolone is predominantly anti-inflammatory and has little sodium retaining activity.

Prednisone is converted into prednisolone in the liver.

Methylprednisoline is similar to prednisolone.

Triamcinolone has virtually no sodium retaining effect, but has the disadvantage that muscle wasting may occasionally be severe and anorexia and mental depression may be more common at high doses.

Dexamethasone, betamethasone and paramethasone are similar, powerful, predominantly anti-inflammatory steroids.

Fludrocortisone has a very great sodium-retaining effect in relation to its anti-inflammatory action, and only at high doses need the non-electrolyte effects be considered. It is used to replace aldosterone in Addison's disease.

Deoxycortone (DCA, DOCA) has exclusively mineralocorticoid effects. It is destroyed on passage through the liver and so is ineffective when swallowed. It has been superseded by fludrocortisone.

Aldosterone, the main natural salt-retaining hormone, can be given i.m. (0·5 mg) several times a day. After oral administration it is rapidly inactivated and it has no place in routine therapeutics, as fludrocortisone is as effective and is active orally. *Spironolactone* is a competitive aldosterone antagonist and blocks the mineralocorticoid effect of other steroids.

Pharmacokinetics. Absorption of the synthetic steroids given orally is rapid. The *half-life* of most in plasma is 1½ to 3 hrs but the maximum biological effect occurs later, 2 to 8 hrs. They are usually given three times a day. They are metabolised principally in the liver and are excreted by the kidney. The half-life is prolonged in hepatic and renal disease.

Conversion in the liver of cortisone to hydrocortisone is much less efficient than that of prednisone to prednisolone. Liver disease must be severe to prevent the conversion.

In the blood adrenal steroids are carried in the free (pharmacologically active) form (5%) and also bound (95% in the case of hydrocortisone) to *transcortin* (a globulin with high affinity, but low binding capacity) and, when this is saturated, to albumin (80% in the case of hydrocortisone). The concentration of the transcortin is increased by œstrogens (e.g. pregnancy, oral contraception, other œstrogen therapy), so that if plasma hydrocortisone concentration is measured the *total* will be found raised, but the amount of *free* hydrocortisone may be normal (though it can be raised), being controlled by the normal feedback mechanism. Patients may be wrongly suspected of Cushing's syndrome if the fact that they are taking œstrogen is unknown and only the *total* concentration is measured.

In patients with low serum albumin steroid doses should be lower than usual owing to the reduced binding capacity. In addition, the low albumin concentration may be caused by liver disease which also potentiates steroids by delaying metabolism (half-life of prednisolone may be doubled) (*15*).

Various spaced-out dosage schedules have been used in the hope of

reducing pituitary-adrenal suppression by allowing the plasma steroid concentration to fall enough between doses to allow some pituitary recovery. None has been both successful in avoiding suppression at the same time as it was successful in controlling symptoms (*9*).

Choice of Adrenal Steroid

For replacement therapy in adrenocortical insufficiency, hydrocortisone or cortisone. In Addison's disease a small dose of a hormone with only mineralocorticoid effect (fludrocortisone) is normally needed in addition.

For anti-inflammatory and anti-allergic effect, prednisolone, prednisone, triamcinolone or dexamethasone. It is not possible to rank these in firm order of merit. One or other may suit an individual patient best, especially as regards incidence of side-effects such as mucle wasting.

For pituitary-adrenocortical suppression, e.g. in adrenal hyperplasia, prednisolone or dexamethasone.

Unwanted Effects of Adrenal Steroids

These consist of too intense production of the physiological or pharmacological effects listed under effects of hydrocortisone.

Unwanted effects do not occur with one or two doses. They follow prolonged administration and are sufficiently frequent and dangerous to warrant serious consideration by the physician whether "the disease which he is attempting to suppress is more dangerous to the patient than the Cushing's syndrome which he might induce" (*6*). The undesired effects recounted below should never be experienced in replacement therapy, but only when the steroid is used as a "drug". Naturally, the nature of unwanted effects depends on the choice of steroid. Fludrocortisone in ordinary doses does not cause osteoporosis and prednisolone does not normally cause œdema. With this in mind, the principal evil effects of chronic administration are **iatrogenic Cushing's syndrome:** *moon face*, *characteristic deposition of fat on the body*, *œdema*, *hypertension*, *striæ*, *bruising*, *acne*, *hirsutism*, *muscle wasting and osteoporosis* (with fractures of ribs and vertebræ rather than of long bones). It is not known whether addition of a small dose of anabolic steroid can usefully prevent osteoporosis and muscle wasting. *Diabetes mellitus* may appear.

Depression and psychosis can occur, sometimes with suicide, especially in those with a history of mental disorder; *insomnia* occurs.

Gastric ulcer occurs particularly in patients taking an adrenal steroid plus drugs known to cause gastric bleeding, e.g. aspirin, a frequent combination in rheumatoid arthritis. Gastric bleeding and ulcer in patients on steroid alone is probably not increased; but adrenal steroids may delay the healing of pre-existing peptic ulcer.

Other horrors include posterior subcapsular *lens cataract* (if the dose exceeds 10 mg prednisolone/day or equivalent for above a year), *glaucoma*, *raised intracranial pressure and convulsions*, *blood hypercoagulability*, *menstrual disorders and fever*. *Delayed tissue healing* is seldom important,

but it can disagreeably complicate deep radiotherapy. Major *skin damage* can result from minor injury.

Suppression of the inflammatory response to infection and immunosuppression cause some patients to present with atypical symptoms and signs and quickly to deteriorate. The incidence of infection may not be increased, but it can be more severe when it occurs. Tuberculosis may develop insidiously.

The incidence of unwanted effects depends on dosage and duration of therapy but can be as high as 50% of cases.

Hypothalamic-pituitary-adrenal suppression occurs in all cases of prolonged therapy: it may be substantial within a week.

Precautions during chronic adrenal steroid therapy. The patient's daily weight is a useful guide to detection of fluid retention before œdema is clinically obvious. Other precautions include a monthly urine test for glucose and measurement of the blood pressure, and a 6-monthly spine X-ray for osteoporosis. Hypokalæmia may occur and a potassium supplement may be necessary.

Patients must be given a card giving details of their therapy, to carry always, and they *must* be instructed on the importance of taking their steroid regularly; also, on what to do if they develop an intercurrent illness—to double their next dose and to tell their doctor.

Treatment of intercurrent illness, particularly infections, is urgent, and the dose of steroid should be doubled during the illness and gradually reduced as the patient improves. Effective chemotherapy of bacterial infections is specially important (see above).

Virus infections contracted during steroid therapy can be overwhelming because the immune response of the body may be largely suppressed. But a steroid may sometimes be useful in therapy after the disease has begun (thyroiditis, encephalitis) and there has been time for the immune response to occur. It then acts by suppressing unwanted effects of immune responses and excessive inflammatory reaction, but see also under adrenal steroids in severe illness.

In the event of the misfortune of **surgery** being added to that of adrenal steroid therapy the patient should receive 100 to 200 mg hydrocortisone i.m. with premedication. If there is any sign suggestive that the patient may collapse, e.g. hypotension, during the operation, i.v. hydrocortisone (50 to 100 mg) should be infused at once. The immediate post-operative period is specially dangerous. An uneventful recovery may be covered by 12-hrly i.m. injections of hydrocortisone (100 mg, 50 mg, 50 mg, 25 mg). An emergency operation should be covered by 200 mg hydrocortisone i.m. before, and 100 mg in an i.v. infusion of 500 ml saline during operation, with similar postoperative care.

Minor operations, e.g. dental extraction, may be covered by 50 to 100 mg hydrocortisone orally 2 to 4 hrs before operation and the same dose afterwards. An i.v. infusion should be available for immediate use in case that is not enough.

Unless they have been shown to respond to corticotrophin, patients who have had suppressive doses of adrenal steroid within the past year (i.e. more than 30 mg hydrocortisone or 40 mg cortisone daily, or its equivalent, for more than a week) should be treated similarly because their pituitary-adrenal system, though adequate for ordinary life may fail to respond to severe stress. If steroid therapy has been prolonged, these precautions should be taken for 2 years after stopping it. This will mean that some unnecessary treatment is given, but collapse due to acute adrenal insufficiency can be fatal and the ill-effects of short-lived increased dosage of steroid are less grave, being confined to possibly increased incidence and severity of infection. However some regard this risk of infection as serious enough to warrant confining steroid administration, as far as practicable, to those who, having ceased steroid therapy now fail to respond to a corticotrophin test.

Adrenal steroids and pregnancy. Although a relationship between steroid therapy and cleft palate and other fetal abnormalities has been suspected, there is no doubt that women taking a steroid throughout have both conceived and borne normal babies. Adrenal insufficiency due to pituitary suppression in the newborn probably only occurs with high doses. Dosage during pregnancy should be kept as low as practicable. Fluorinated steroids should be specially avoided as they may be more teratogenic (dexa, beta and paramethasone, various topical steroids, e.g. fluocinolone).

Adrenal steroids and cancer. It is possible, though unproved, that growth and metastasis of some cancers is enhanced by steroid therapy.

Dosage and routes of administration. Dosage depends very much on the purpose for which the steroid is being used and on individual response. It is impossible to suggest a schedule that will suit every case.

The following commencing doses can be used:

For a disease such as dermatomyositis which may be fatal: prednisolone 60 to 75 mg a day, or its equivalent of another steroid. The dose is then increased if necessary until the disease is controlled or toxic effects occur; as much as 300 mg prednisolone a day can be needed.

For a chronic, less dangerous disease, such as rheumatoid arthritis: 10 to 17·5 mg of prednisolone daily, adjusted later according to the response.

In some special cases, including adrenal insufficiency, dosage is mentioned in the account of the treatment of the disease.

Equivalent doses of the various steroids will be found on page 9.9.

For continuous therapy the minimum amount to produce the desired effect must be used. Sometimes imperfect control must be accepted by the patient because full control, e.g. of asthma, though obtainable, involves use of doses that must lead to long-term toxicity, e.g. osteoporosis.

In general, serious unwanted effects are unlikely if the daily dose is

below the equivalent of 50 to 75 mg hydrocortisone or 10 to 15 mg prednisolone.

A variety of injectable preparations for systemic effect is available (see above).

Topical applications (creams, snuff, inhalations, enemas) are used in attempts to obtain local, whilst avoiding systemic, effects whenever possible, and solutions are injected into joints and subconjunctivally. Cortisone and prednisone are not used as local tissues will fail to convert them to their active forms. However, all these can, with heavy dose, be sufficiently absorbed to suppress corticotrophin production. Individual preparations are mentioned in the text where appropriate.

Contra-indications to the use of adrenal steroids for suppressing inflammation are all relative, depending on the advantage to be expected. They should only be used for serious reasons in patients with diabetes, a history of mental disorder or peptic ulcer, epilepsy, tuberculosis, hypertension or heart failure. The presence of any infection demands that effective chemotherapy be begun before the steroid, but there are exceptions (some virus infections, see above).

Steroids containing fluorine (see above) intensify diabetes more than others and so should be avoided in diabetes.

Tissue damage due to deep radiotherapy may be enhanced.

Prolonged use of adrenal steroids in children presents essentially the same problems as in adults except that growth is retarded roughly in proportion to the dose. This is unlikely to be important unless therapy exceeds 6 months; there is a spurt of growth after withdrawal.

Some other problems loom larger in children than in adults. Common childhood virus infections may be more severe, and if a non-immune child taking an adrenal steroid is exposed to one, it is wise to try to prevent it with gamma globulin.

Smallpox vaccination is unsafe, as generalised vaccinia may occur (this may be preventable by a concurrent injection of anti-vaccinial gamma globulin), but active immunisation with killed vaccines or toxoids will give normal response unless the dose of steroid is high, when the response may be suppressed.

Children may develop raised intracranial pressure more readily than adults. They probably absorb triamcinolone better than other orally active steroids; this may cause overdosage, which is specially important as triamcinolone can produce severe muscle wasting.

Fixed-dose combinations of adrenal steroids with other drugs in one tablet are objectionable as it is always important to adjust the steroid dose to the minimum that produces the desired effect so that the dose of the other drug is altered, not on the patient's need for it but on his need for steroid.

Mixtures of a steroid and aspirin are available. They are peculiarly objectionable because of the dangers of peptic ulcer and bleeding, though they can be therapeutically effective.

Indications for Use of Adrenal Steroids

1. **Replacement.**
2. **Inflammation suppression.**
3. **Immunosuppression.**
4. Pituitary suppression (uncommon).

Nabarro (*4*) summarises the place of adrenal steroids in therapeutics:

"The addition of physiological amounts of cortisone has greatly improved the replacement therapy available for patients with Addison's disease or hypopituitarism. Larger or pharmacological amounts of steroids have been used in the treatment of diseases unrelated to the adrenal gland. Steroids of the cortisone group inhibit the inflammatory reaction of connective-tissue cells, but in many instances the inflammatory reaction is part of the body's defence mechanism and is to be encouraged rather than inhibited. It has, however, become apparent that there are diseases which are really due to the body's reaction being quite disproportionate to the noxious stimulus. The manifestations of the disease are, in fact, those of an exaggerated or inappropriate inflammatory response, and if steroid therapy can inhibit this inappropriate response the manifestations of the patient's disease will be suppressed. The underlying condition is not cured, though it may ultimately burn itself out.

"The anti-inflammatory action of steroids is used for this purpose in allergic conditions and diseases like rheumatoid arthritis, rheumatic carditis, disseminated lupus erythematosus, and polyarteritis nodosa. Large doses of steroid will also inhibit antibody production and help in the management of auto-immune conditions like some of the hæmolytic anæmias and thrombocytopenic purpuras. Steroid therapy may also be used to suppress the patient's adrenal glands; the doses required, however, are nearer the physiological levels. This may be needed in cases of adrenal dysfunction where abnormal androgenic steroids are being made, or in cases of disseminated breast cancer to inhibit adrenal secretion of œstrogens, the so-called medical adrenalectomy.

"When large doses of steroids are given for their pharmacological action, the result will be to produce an iatrogenic Cushing's syndrome. There is a tendency to forget that Cushing's syndrome is a serious illness with a grave prognosis—so serious, in fact, that one has no hesitation in advising total adrenalectomy for its treatment. Admittedly, treatment with high doses of steroid may in some situations be life-saving, or produce a temporary remission in an incurable disease. There has been a tendency to overlook the dangers of treatment with cortisone and the newer synthetic steroid hormones and to use them in cases where the treatment may prove more dangerous or disabling than the original disease" (*4*).

An account of the use of steroids in some individual diseases follows.

Acute adrenal insufficiency (Addisonian crisis)

This is an emergency and 100 mg hydrocortisone sodium succinate should be given i.v. immediately it is diagnosed. An i.v. infusion of

0·9% sodium chloride solution is set up and a second 100 mg of hydrocortisone is added to the first litre, which may be given over 2 hrs. At the time the infusion is started 100 mg hydrocortisone are given i.m. After the infusion the patient should receive 50 mg hydrocortisone i.m. or orally, 8-hrly for 24 hrs, then 12-hrly for 24 hrs and then a total of 50 to 75 mg a day orally in two or three doses. Other treatment to restore electrolyte balance will depend on the circumstances. Blood transfusion with or without vasoconstrictor drugs may be needed in addition, to help restore the blood pressure. The cause of the crisis should be sought and treated; it is often an infection. When the dose of hydrocortisone falls below 60 mg a day, supplementary mineralocorticoid (fludrocortisone) may be needed (see below).

Chronic primary adrenocortical insufficiency (Addison's disease)

Hydrocortisone or cortisone orally are used (20 to 40 mg total daily) with two-thirds of the total dose in the morning to mimic the natural *circadian rhythm* of secretion. Some patients do well on hydrocortisone alone, with or without added salt, but most patients require a small amount of mineralocorticoid as well (fludrocortisone, 0·1 to 0·2 mg once a day, orally). If the dose of fludrocortisone should exceed 0·5 mg a day, an unlikely event, then its hydrocortisone-equivalent must be taken into account (for glucocorticoid effect, 1 mg fludrocortisone is equivalent to 20 mg hydrocortisone). The injectable preparations are obviously valuable for patients liable to vomit. The use of a primarily anti-inflammatory steroid with a larger dose of fludrocortisone is practicable but pointless.*

The dosage of the hormones is determined in the individual by following his general clinical progress and particularly by observing his weight, cardiac size, blood pressure, presence of œdema, serum sodium and potassium concentration and hæmatocrit.

The majority of patients with primary chronic adrenocortical insufficiency on 20 to 40 mg hydrocortisone, plus 0·1 to 0·2 mg fludrocortisone a day orally, have a life expectancy which is equal to that of a normal subject. If any complicating disease arises, such as infection, a need for surgery or other stress, the hydrocortisone dosage should immediately be doubled, see above. If there is vomiting, hormone must be given parenterally without delay.

There are no contra-indications to replacement therapy. The risk lies in withholding rather than in giving it.

Some patients (particularly those with hypopituitarism) when first treated, cannot tolerate full doses of hydrocortisone because they become euphoric or otherwise mentally upset. 10 mg a day may be all they can take. The dose can usually soon be increased if it is done slowly. Patients with peptic ulcer may be unable to exceed 20 mg of hydrocortisone a day.

* Adrenalectomised patients (for Cushing's syndrome) may become œdematous on an otherwise optimal dose of hydrocortisone; for these, a proportion of the hydrocortisone may be replaced by a glucocorticoid (prednisolone).

If diabetes is present the full dose is used and the diabetes controlled with insulin. Diabetics should take some of their daily hydrocortisone requirement late at night.

Chronic secondary adrenocortical insufficiency

This occurs in hypopituitarism. In theory the best treatment is corticotrophin, but the disadvantages of frequent injection are such that hydrocortisone is preferred. Usually less hydrocortisone is needed than in primary insufficiency. Special sodium-retaining hormone is seldom required, for the pituitary has little control over aldosterone production, so that this hormone is still secreted by the adrenal cortex. Thyroxine is given too and sometimes sex hormones. The general conduct of therapy does not differ significantly from that in primary adrenal insufficiency.

Iatrogenic adrenocortical insufficiency

This occurs in patients who have received prolonged high dose steroid therapy, which inhibits pituitary production of corticotrophin and so results in secondary adrenal failure. To avoid an acute crisis on stopping, steroid therapy must be withdrawn gradually to allow both the pituitary and the adrenal to regain normal function. Also, when a patient taking a steroid has an infection or surgical operation he should be treated as for primary insufficiency.

After the use of large doses of hormone to suppress inflammation or allergy, sudden withdrawal may not only lead to an adrenal insufficiency crisis but to relapse of the disease which has only been suppressed, not cured. Such relapse can be extremely severe.

Withdrawal of steroid therapy may be accomplished thus:

If rapid withdrawal is desired a 50% reduction in dose may be made each day, but if, as is more likely with long-term therapy, there is also risk of a flare-up of the disease, then withdrawal should be done very slowly, e.g. by reducing the daily dose by the equivalent of 1 mg prednisolone at weekly intervals.

There is no advantage in giving corticotrophin to revive the suppressed adrenal cortex during withdrawal, for the delay in restoration of normal function rests chiefly with the anterior pituitary. Complete recovery of normal pituitary-adrenal function sufficient to cope with severe intercurrent illnesses may take up to 2 years.

There have been many reports of collapse, even coma, occurring within a few hours of omission of steroid therapy, e.g. due to patients' ignorance of the risk to which their physicians are exposing them or failing to have their tablets with them and other trivial causes; but it is not invariable. Patients *must* be instructed on the hazards of omitting therapy and, during intercurrent disease i.m. preparations should be freely used. Anæsthesia and surgery in adrenocortical insufficiency is discussed above.

Adrenal steroids in severe illness. There has been considerable dispute on the place of adrenal steroids in severe illness, chiefly infections,

where there is no evidence of actual adrenal cortical destruction, but merely a supposition of failure of the pituitary-adrenal system to respond adequately to the stress. There is reason to expect that adrenal steroids might both help and harm such patients. Steroids have been shown experimentally to protect against bacterial endotoxins (especially on the vascular system); any excessive and harmful inflammatory response would be suppressed, and they reduce fever (not necessarily beneficial). They also relieve many symptoms, and patients have seemed so much better that physicians have thought it reasonable to act on the presumption that patients may not be producing enough hydrocortisone for themselves.

On the other hand there are obvious dangers, the suppression of useful inflammation and of antibody formation.

Application of existing knowledge from the laboratory could not resolve the matter. It had to be put to the test in clinical practice. The only ethical way to do this was by formal experiment, and this was attempted by a group of physicians in five hospitals (*23*). They allotted 194 patients with "life-threatening infections" a standard dosage of hydrocortisone or placebo from numbered kits in random order. The trial was double-blind. Other therapy was "according to the best judgement of the clinician in charge". There was no evidence of any benefit from hydrocortisone. Studies such as this are vital if therapy is to advance. Casual use of adrenal steroids by individuals can never answer questions of this sort.

The authors of this study do not state whether the patients or their relatives were informed of the nature of the experiment and their permission sought. Almost certainly they were not, for such discussion could only lead to distress and put the patients or their relatives in an intolerable position. It would have been unkind to have revealed what was being done. This is an example of a highly ethical experiment in which patients and relatives should not be told. Of course, there are many occasions when the opposite is true and it is unethical to experiment without the informed consent of the subjects.

This experiment has not finally resolved the matter and more work is needed, but it is plain that there is no place for *routine* use of a steroid in severe infections. It should only be given if there is a particular reason to do so, and this includes the situation where all seems to be lost, and where it is thought that an inflammatory response is so great as to be more dangerous to the host than to the pathogen. Even here a steroid may do more harm than good.*

Adrenogenital syndrome and adrenal virilism

An attempt may be made to suppress excess adrenal androgen secretion by inhibiting pituitary corticotrophin production by means of prednisolone or dexamethasone. Suppression of androgen production is effective if there is adrenal hyperplasia, but not if an adrenal tumour is present. Hairiness, which women specially dislike, is often unaffected even though

* Bøe, J., *et al.* (1965). *Brit. med. J.*, **1**, 1094.

good suppression is achieved, and menstruation recommences. Interference with adrenal steroid synthesis by o,p′ DDD (see below) can be tried if other treatment fails.

Adrenal steroids in inflammation and immunosuppression

Adrenal steroids have been used in virtually every hitherto untreatable or obscure disease, e.g. collagen diseases, nephrotic syndrome, sarcoidosis, with very variable results. Only a brief survey can be given here.

Drugs with primarily glucocorticoid effects (e.g. prednisolone) are chosen, so that dosage is not limited by the mineralocorticoid effects that are inevitable with hydrocortisone. But it remains essential to use only the minimum dose that will achieve the desired effect, and sometimes therapeutic effect must be partly sacrificed to avoid adverse effects, for it has not yet proved possible to separate the glucocorticoid effects from each other; indeed it is not known if it is possible to eliminate catabolic effects and at the same time retain anti-inflammatory action. In any case, in some conditions (e.g. nephrotic syndrome) the clinician cannot specify exactly what action he wants the drug developer to provide.

The following list comprises diseases in which adrenal steroids may be useful. The decision to give a steroid commonly depends on knowledge of the likelihood and amount of benefit, on the severity of the disease and on whether the patient has failed to respond usefully to other treatment. It often requires expertise that can only be imparted by those with wide experience of the disease concerned.

Adrenal steroids are used in all or nearly all cases of:

Exfoliative dermatitis and pemphigus, if severe.

Systemic lupus erythematosus, if severe. If mild, salicylate and chloroquine may suffice.

Status asthmaticus that has not responded to other drugs (see index).

Acute lymphatic leukæmia (see index).

Acquired hæmolytic anæmia.

Severe allergic reactions of all kinds, e.g. serum sickness; angioneurotic œdema; trichiniasis. They will not control an acute anaphylactic reaction as they do not act quickly enough.

Organ transplant rejection.

Aspiration pneumonitis and pulmonary œdema from near drowning: give prednisolone i.v., up to 50 mg., 4-hrly for 72 hrs.

Adrenal steroids are used in some cases of:

The following collagen diseases: rheumatic fever (which see), chronic discoid lupus erythematosus, polyarteritis nodosa, scleroderma, polymyositis, dermatomyositis, giant-cell arteritis. If, in the latter disease, vision has been at all affected, steroid administration is urgent.

Rheumatoid arthritis (which see).

Ankylosing spondylitis (which see).

Ulcerative colitis and proctitis (which see).

Regional ileitis.

Bronchial asthma and hay fever (*allergic rhinitis*).

Sarcoidosis. If there is hypercalcæmia steroid administration is urgent. Pulmonary fibrosis may be delayed and central nervous system manifestations may improve. Oxyphenbutazone may be as effective.

Blood diseases due to circulating antibodies, e.g. hæmolytic anæmias: thrombocytopenic purpura (there may also be a decrease in capillary fragility with lessening of purpura even though thrombocytes remain few); agranulocytosis.

Eye diseases. Allergic diseases and non-granulomatous inflammation of the uveal tract. Bacterial and virus infections may be made worse and use of steroids to suppress inflammation of infection is generally undesirable, is best left to ophthalmologists and must be accompanied by chemotherapy. Application is generally as hydrocortisone or prednisolone drops or subconjunctival injection.

Nephrotic syndrome. Patients with "minimal change" lesions respond well. With 60 mg/day total of prednisolone 90% of those who will lose their proteinuria will have done so within 4 weeks. Slow withdrawal of the steroid may leave the patient well, but relapses are common (50%) and it is then necessary to find a minimum dose of steroid that will keep the patient well.

Other immunosuppressives (e.g. azathioprine) are also used.

The prognosis of other forms of glomerulonephritis is not improved by drugs.

A variety of skin diseases, such as eczema. Severe cases may be treated by occlusive dressings if a systemic effect is not wanted—though absorption can be substantial.

Post-hepatitic cirrhosis with fever, in which benefit may be due to suppression of immunological mechanisms. Prednisone should not be used as the liver may fail to transform it into the active prednisolone.

Acute gout resistant to other drugs (which see).

Hypercalcæmia of myelomatosis and other malignant diseases, of sarcoidosis and of vit. D intoxication, responds to cortisone 150 mg daily (or its equivalent of other steroid) for 10 days. Hyperparathyroid hypercalcæmia does not respond.

Raised intracranial pressure, e.g. in cerebral tumour: probably an anti-inflammatory effect: acts in about 4 hrs: e.g. dexamethasone 4 to 10 mg i.m. or i.v. (or equivalent) initially and then oral daily total dose 4 to 10 mg (or equivalent).

Miscellaneous diseases. In these, other lines of treatment should be tried first where they exist: steatorrhœa: severe nasal allergy (topical application): "aphthous" ulcers in the mouth (suck a 2·5 mg hydrocortisone tablet (Corlan) four times daily): Bell's palsy: acute polyneuritis: toxic and virus encephalitis: post-irradiation fibrosis: Hunner's

ulcer of the bladder: myasthenia gravis: myotonia: heart-block (which see): severe myocardial infarction.

Inhibition of synthesis of adrenal steroids

Metyrapone, o,p′ DDD and aminoglutethimide (*28–31*)

The discovery that the insecticide dicophane (DDT) interfered with adrenal steroid synthesis was of special interest and began a search for a non-toxic substance with similar effect.

In 1961 metyrapone, chemically related to dicophane, was introduced. It interferes with the enzyme, steroid 11-β-hydroxylase, that converts 11-deoxy precursors into hydrocortisone, corticosterone and aldosterone. When this happens the fall in plasma hydrocortisone stimulates the anterior pituitary to release corticotrophin and this may explain the failure of such inhibitors to control adrenal cortical hypersecretion effectively (neoplasm and hyperplasia), since biologically active precursors accumulate. Inhibitors acting at earlier stages of steroid synthesis offer better prospects of avoiding this, e.g. o,p′ DDD (ortho-para-prime DDD) and aminoglutethimide.

In diagnosis metyrapone can be used to test the ability of the anterior pituitary to produce corticotrophin. A normal response demonstrates both pituitary and adrenal integrity, but a failure of response does not prove pituitary failure, it could also be due to inability of the adrenal cortex to respond to endogenously produced corticotrophin. Therefore, to localise the failure to the pituitary it is necessary to demonstrate adrenal cortical responsiveness to injected corticotrophin on another occasion. It is also useful in distinguishing Cushing's syndrome due to adrenal adenoma from the commoner form due to hyperplasia (in adenoma the pituitary is suppressed, in hyperplasia it is active).

Competitive antagonism of adrenal steroids. Spironolactone (Aldactone) (see index) antagonises the sodium-retaining effect of aldosterone and other mineralocorticoids. There are no competitive antagonists to glucocorticoid effects.

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Chapter 10

SLEEP, HYPNOTICS, SEDATIVES, ANTIEPILEPTICS

Drugs which Depress the Central Nervous System

THE following terms are commonly used:

Narcotic: any drug which depresses the central nervous system. The term is often used to include only general anæsthetics, hypnotics and opiates, or loosely to mean all dependence-producing drugs and therefore to include some convulsants (cocaine). This is a pity, as it tends to cause confusion.

Hypnotic: a drug that induces sleep.

General anæsthetic: a drug that induces controllable and reversible unconsciousness.

Sedative: a drug used to quieten a patient without sending him to sleep; although it may make him feel sleepy. A small dose of a hypnotic or tranquilliser often suffices for this.

Tranquilliser: a drug that will quieten a patient without notably impairing consciousness. The ideal tranquilliser would allay pathological anxiety and nervous tension without altering any other cerebral functions; especially it would not cause sleepiness; in fact there is no clear distinction between tranquillisers and sedatives. It would also suppress mania and psychotic overactivity. The term *ataractic* is sometimes used. It is derived from a Greek word meaning peace of mind: an alternative is **neuroleptic**.

Analgesic: a drug that relieves pain.

Anticonvulsant: a drug that prevents and suppresses convulsions.

It is clear from the above vague definitions that the groups overlap. None is more indefinite than the tranquillisers, which are a heterogeneous group of substances, arbitrarily considered to include only the more recently introduced substances and to exclude the barbiturates and other hypnotics, although these are useful as tranquillisers in practice. There is some justification for this because tranquillisers such as chlorpromazine do not, even at high doses, induce the relatively harmless and readily reversible unconsciousness characteristic of hypnotics.

Sleep and Hypnotics

Normal sleep is of two kinds (*1*).

1. **NREM** (non-rapid eye movement), orthodox, forebrain or slow-wave EEG sleep; awakened subjects state they were "thinking": heart rate, blood pressure and respiration are steady and muscles are relaxed.
2. **REM** (rapid eye movement), paradoxical, hindbrain or fast-wave

EEG sleep; awakened subjects state they were "dreaming": heart rate, blood pressure and respiration are fluctuant, cerebral blood flow increases, the penis is erect (unless there is dream anxiety), skeletal muscles are profoundly relaxed though body movements are more pronounced.

It should be noted that this characterisation of sleep by eye movements is based rather on what can be easily measured, than on what is known to be important; what can be easily measured may, happily, be found to be an indication of what is important, but it is not yet known if this is so.

A normal night begins with about 1 hr of NREM sleep. This is followed by about 20 mins REM sleep, after which cycles of NREM sleep (lasting about 90 mins abruptly alternate with REM sleep (lasting about 20 mins) for the rest of the night. Both kinds of sleep seem to be necessary for health. Hypnotics in full doses can disrupt the normal sleep pattern, suppressing REM sleep, though tolerance may develop. Benzodiazepines (e.g. nitrazepam) and chloral do this least. No hypnotic can be said to induce natural sleep.

On withdrawal of a drug that has suppressed REM sleep there is a rebound increase in this kind of sleep, as though the body requires to recover what has been lost; nightmares occur with severe rebound; abnormal sleep patterns may persist for weeks after withdrawal.

It has not been conclusively shown that the kind of abnormality induced by hypnotics is harmful. But there is some evidence that deprivation of REM sleep may be responsible for emotional disorder so that hypnotics should not be used without good reason. That hypnotics are extensively prescribed, and indeed overprescribed, is well known. In one study (*11*) of 7,500 patients registered in an industrial general practice 97 (1·3%) were receiving repeat prescriptions for hypnotics. They tended to be over 60 years with a preponderance of widows. The original indications were: (1) *medical* (48 patients): the prescribing began for some general medical or surgical disorder, particularly musculoskeletal pain; (2) *psychiatric* (30 patients): depressive-anxiety reactions, e.g. bereavement; (3) *onset insomnia* (19 patients): difficulty in getting to sleep; this was associated with neurotic personality disorder. Twenty per cent of patients started taking hypnotics in hospital. Only 6 of the 97 patients agreed to immediate withdrawal of the hypnotic. The others were dependent to varying degrees, chiefly mild, in that they considered adequate sleep would not be possible without drugs and that they would develop anxiety if withdrawal were attempted. The authors suggest that many of those patients may be merely placebo reactors and that a more critical attitude to hypnotic prescribing is required.

Oswald (*1*) concludes that a prescription for a hypnotic is fully justified for a few nights or weeks to combat insomnia due to anxiety *provided* there is good reason to expect the cause to be removed either by changes in environment or by treatment (e.g. antidepressant drug or electric

convulsions). But where there is chronic insomnia or a long-standing personality disorder he does not consider prescription justified because: (1) tolerance develops; (2) dependence is likely; (3) sleep is not natural.

"At a very rough reckoning about one night's sleep in every ten in this country is hypnotic induced. . . . People seem to want to turn consciousness on and off like a tap. . . . While it is time-consuming to take a careful clinical history, to conduct a full clinical examination and to give wise advice, it takes only a moment to write a prescription and this does please and often satisfies the patient. . . . We do not always draw a clear distinction between the patients' *wants* and what we think are his *needs*, and it is regrettable how much we accede to the patients' demands in order to placate him and to save ourselves time and trouble."*

Other drugs and sleep. A range of other drugs have effects *on eye movement pattern* similar to hypnotics, when given in sufficient dose, e.g. heroin, morphine, alcohol, and curiously, tricyclic and MAOI antidepressants, amphetamine and other appetite suppressants (though not, it seems fenfluramine). But effects on onset and duration of sleep differ.

Measurement of hypnotic effect in man can be best done in the sleep laboratory using EEG and other physiological techniques (see above); alternative cruder but useful studies can be done in which an observer assesses the presence or absence of sleep (preferably not by shining a torch in the patient's face in order to wake him up to ask if he was asleep) and by interviews and questionnaires the next morning.

Hangover. The effects of hypnotics, including ordinary doses of benzodiazepines (e.g. nitrazepam) taken at ordinary bedtime carry over into the afternoon of the following day. Often the patient is aware of drowsiness, but even where he is not, impaired performance in tests measuring functions such as reaction time or tapping speed occurs. This is not surprising since the half-life of nitrazepam is 6 to 10 hrs.

Hypnotics are best taken on going to bed or a *few* minutes before. The practice of trying to get to sleep and taking a hypnotic an hour or two later if still awake will lead to greater impairment of performance the next day. But a person who has been awake all night will also be a bad performer next day.

HYPNOTICS AND SEDATIVES: GENERAL

The effects of barbiturates have been studied most and the following account is based on them. Other hypnotics have substantially similar clinical effects. Principal differences are mentioned in relevant places.

Behaviour. Results of experiments vary with drug and dose, but in general barbiturates impair intellectual functions less than sensory-motor functions. In doses of 100 to 300 mg they impair learned behaviour; both sustained attention and distractability are reduced, and so are some conditioned responses. Amnesia, e.g. for contents of lectures, purchases made, may occur with the benzodiazepines.

* DUNLOP, D. (1970). *Brit. med. Bull.*, **26**, 236.

Simulated motor driving becomes less efficient (quinalbarbitone 100 mg) and judgement is distorted (swimmers thought they had done unusually well when they had really performed badly).

Elation and decreased motor activity may occur (quinalbarbitone 50 mg). Visual perception is reduced and the duration of auditory stimuli is underestimated—time seems to be "flying" (quinalbarbitone 200 mg).

Hypnotic and sedative effects. There are few detailed controlled investigations, perhaps partly because, ideally, dosage needs to be adjusted for each person so that trial design is complicated in relation to the value of the information gained, as differences are probably not great. Also, the patient's mode of life may have considerable bearing on the results which may differ, for example, according to whether he is in hospital or at home.

Analgesia. Hypnotics do not affect pain selectively, but they probably interfere with its perception; patients are less concerned about their pain. By reducing the anxiety associated with pain and its anticipation they can be useful in management provided an analgesic is given too. Unless this is done a full hypnotic dose may cause restlessness and mental confusion.

There is also evidence that barbiturates can antagonise analgesics and this may be borne in mind when they are used in patients with pain.

Respiration. A hypnotic dose of a barbiturate in a patient with marked respiratory insufficiency, e.g. severe pulmonary emphysema or asthma, will depress respiratory minute volume and arterial oxygen saturation. Benzodiazepines, paraldehyde and chloral are less objectionable in this respect.

Cardiovascular function. Barbiturates lower blood pressure at hypnotic and anæsthetic doses by reducing cardiac output, probably by reducing venous return to the heart due to peripheral venous pooling (*21*). Compensatory vascular reflexes are depressed.

Toxic doses may depress the myocardium and also reduce the peripheral resistance by blocking the sympathetic nerves.

Alimentary tract. Prolonged barbiturate sedation constipates.

Tolerance. When eighteen former addicts were given 0·4 g pentobarbitone or quinalbarbitone daily for 90 days tolerance began to develop within 14 days. They showed significant decrease in hours of sleep, in signs of clinical intoxication and in performance in psychomotor tests. Tolerance probably occurs to all hypnotics, but it is less marked than with opiates. With barbiturates and meprobamate the tolerance is at least partly due to **enzyme induction,** and this can enhance adrenal steroid metabolism enough to reduce efficiency of steroid therapy.

Emotional and physical dependence occur with regular dosage of 0·4 g/day, or more, of barbiturate. If the dose exceeds 0·6 g/day the subject generally shows clinical signs of intoxication—impairment of mental ability, regression, confusion, emotional instability, nystagmus, dysarthria, ataxia and depressed somatic reflexes.

The withdrawal syndrome begins in 8 to 36 hrs and passes off over 8 to 14 days. It comprises, in approximate order of appearance, anxiety, twitching, intention tremor, weakness, dizziness, distorted vision, nausea,

vomiting, insomnia and orthostatic hypotension. Convulsions, delirium and death can occur.

It should be assumed that all sedative-hypnotics can induce dependence similar to that of barbiturates. There is clinical evidence of this in most cases.

Dependence on this type of drug is becoming a grave social problem. Withdrawal of a hypnotic after even brief use can be difficult due to disturbed sleep. A single overdose may be followed by disturbed sleep for weeks (in unhabituated subjects).

Withdrawal of hypnotics from dependent patients should be done slowly, over weeks, reducing both dose and frequency; it is wise to warn the patient of possible sleep disturbance, including nightmares. Where withdrawal is impracticable in patients taking REM sleep suppressing drugs, then a drug with minimal suppressive activity on REM sleep should be substituted (chloral derivative, benzodiazepine).

Principal Uses of Hypnotics and Sedatives

These drugs may be used in small doses to reduce anxiety and distress throughout the day, and/or in larger doses to induce sleep at night.

They are most often needed:

1. To help a patient through a sudden distressing situation, e.g. bereavement.
2. In states of chronic distress, whether induced by disease or by environment. The objective is to restore the sleep habit by brief use of a drug.

It is here that the danger of undue reliance on the drugs specially arises and emotional and physical dependence may occur. It is important to limit their use wherever possible and not to allow prescription of sedatives and hypnotics to become a means of evading the patient's real problem. "Unfortunately, some patients use the sedative hypnotics as a crutch to help them in the struggle against the everyday pressure of living."*

Sedatives and hypnotics are also used in many other situations, in hypertension, with analgesics, before surgery and for a variety of psychiatric purposes such as prolonged narcosis.

Insomnia deserves a special discussion, and its successful management involves much more than merely prescribing drugs, which should be regarded as temporary expedients only (see also *sleep and hypnotics*, above).

Kales (*19*) usefully defines insomnia as either, (1) failure to fall asleep within 45 mins, (2) difficulty in staying asleep (six or more awakenings per night, or less than 6 hrs sleep): either of these at least four nights a week.

*Types of insomnia include:**

1. Tense people who lie awake in bed for hours unable to relax, and then sleep well.

* FRIEND, D. G. (1960). *Clin. Pharmacol. Therap.*, **1**, 5.

2. Exhausted people who, because they sleep early in the evening wake early in the morning. They probably need no drug, but a midday rest.
3. People who wake repeatedly throughout the night, for no obvious reason.
4. People who wake repeatedly from physical discomfort or pain and who need treatment of that condition plus a hypnotic.
5. Depression, in which sleep is shorter, less sound, interrupted and restless.

Alcohol should, obviously, be advised with caution, but in the elderly it can be useful as well as acceptable.

Patients should not take a hypnotic more than 20 mins before getting into bed, for obvious reasons.

Choice of hypnotic. The *benzodiazepines* (nitrazepam, diazepam, etc.) are the *first choice* because (1) they alter sleep pattern less, (2) they are safer than other drugs in overdose, (3) they are poor enzyme inducers. Chloral derivatives probably come second.

Speed of onset, duration of effect and incidence of hangover depend more on the dose and on the patient than on the choice of drug.

The old may become confused with hypnotics, particularly perhaps with barbiturates, and an occasional patient becomes excited or has nightmares on a particular drug.

Irritant drugs (chloral hydrate, paraldehyde) are obviously unsuitable for peptic ulcer patients. In cases where it is especially desired to avoid any respiratory depression, e.g. in severe asthmatics or in head injury, benzodiazepines, chloral derivatives and paraldehyde are preferable to the barbiturates, but they too can impair ventilation.

Children: a benzodiazepine, chloral hydrate or promethazine are used.

Food as an aid to sleep (*51*). A *small* meal of milk and cereal promotes less restless sleep and there is experimental support for the popular belief that milk-cereal drinks do the same. The effect persists into the later night, suggesting that the cause is not only psychological expectation resulting from folklore and advertising, though these doubtless assist.

Since broken sleep increases with age it may be worth recommending the adoption of a pre-bed snack or drink before prescribing hypnotics to older patients with mild insomnia.

Choice of sedative. Benzodiazepines (e.g. diazepam) are drugs of first choice. Many other drugs can be used. The relative safety of benzodiazepines in overdose is particularly important if acts of self-poisoning are anticipated, or roving children may get at a parent's drug (see also ch. 14).

Interactions: see ch. 6. Most are enzyme inducers, but benzodiazepines have minimal effect.

Descriptions of the principal hypnotics and sedatives follow. Opiates are described under analgesics, though some are effective hypnotics.

Non-barbiturates

Benzodiazepines are also used as tranquillisers, and i.v. for minor operations, e.g. endoscopy, dental extractions. Their pharmacology is discussed in ch. 14. Their advantages are mentioned under *choice of hypnotic*, above. Overdose, even as much as 80 tablets of nitrazepam results in sleepiness from which patients can be aroused. But since i.v. diazepam can depress respiration, heavy oral overdose must be taken seriously, especially if combined with other drugs. Benzodiazepines can raise phenytoin plasma concentrations, perhaps sufficiently to induce toxicity.

Doses. Nitrazepam (Mogadon) (5 mg) 5 to 10 mg orally at night: diazepam (Valium) (2, 5, 10 mg) 5 to 10 mg orally at night: other members of the series are oxazepam (Serenid-D), medazepam (Nobrium), flurazepam (Dalmane), chlordiazepoxide (Librium), clorazepate (Tranxene).

Chloral hydrate (1869) was the first synthetic hypnotic to be introduced and was a welcome alternative to opium and alcohol. Chloral hydrate is a solid and is usually given orally in solution because it is so irritant to the stomach, and because the solid evaporates. It tastes horrible.

Chloral is readily absorbed from the intestine and induces sleep in about half an hour, lasting 6 to 8 hrs with little hangover. It is rapidly metabolised in the erythrocytes, liver and kidney by alcohol dehydrogenase into the active hypnotic trichloroethanol that is responsible for the prolonged effect. This is conjugated with glucuronic acid to an inert form.

The ultimate metabolites are excreted in the urine and give a positive result in urine tests for reducing substances, but not, of course, for glucose oxidase (enzyme) tests. Chloral is dangerous in serious hepatic or renal failure, and may be bad for peptic ulcer. It is especially widely employed at the extremes of life, in the elderly because barbiturates are inclined to cause confusion, and in children because there is a disinclination to use barbiturates owing to the ease with which poisoning occurs.

The hypnotic dose of chloral hydrate is 0·5 to 2 g.

Interaction with ethanol (*16*) is to be expected since chloral shares the same metabolic path (alcohol dehydrogenase).

Trichloroethanol (active metabolite of chloral) is a competitive inhibitor of the conversion of ethanol to acetaldehyde so that plasma ethanol concentration is higher than it would otherwise be; thus ethanol is potentiated by chloral.

Ethanol delays conjugation of trichloroethanol (active) with glucuronic acid to an inert form, and it also induces the enzyme alcohol dehydrogenase that converts chloral to trichloroethanol; thus chloral is potentiated by ethanol.

If chloral has been taken for several days, ingestion of alcohol may induce vasodilatation, hypotension and tachycardia that cannot be explained by a simple potentiation. There is also potentiation of CNS effects.

Interaction with anticoagulants: see *drug interactions*.

Triclofos (Tricloryl) (500 mg) is a stable ester of trichloroethanol, see above. The oral dose is 1 to 2 g.

Dichloralphenazone (Welldorm) (650 mg) does not evaporate and is less irritant. The oral dose is 650 mg to 1·3 g. Phenazone is an analgesic, obsolete because of adverse reactions, but this complex has proved satisfactory. The phenazone renders the complex a potent enzyme inducer.

Chloral glycerolate (Somnos) and chlorhexadol (Medodorm) are alternatives.

The above chloral derivatives are available as stable tablets and so are thus often preferred to chloral hydrate.

Chlorbutol is related to chloral hydrate; it often appears in proprietary medicines and has no particular merit.

Paraldehyde (**1882**) is an offensive, irritant, inflammable, but not explosive liquid. It is a safe and therefore useful hypnotic but has a great disadvantage in addition to those mentioned above. A proportion (10 to 30%) is excreted unchanged in the breath, so that after taking it a patient may smell and indeed make a large room smell for 24 hrs, though unconscious of it himself. When swallowed it acts in about 15 mins and lasts 4 to 8 hrs. Hangover is usually trivial. Most of a dose of paraldehyde is metabolised in the liver and action may be prolonged in liver disease. Paraldehyde is chiefly employed as an occasional hypnotic, especially in alcoholics, e.g. in delirium tremens, who tend to be tolerant of it unless they have hepatic cirrhosis. Dependence occurs. It has also been used as a basal narcotic for surgery and as an anticonvulsant, but it is obsolescent. The dose is 5 to 10 ml by oral, i.m. (it dissolves polystyrene syringes) or rectal administration although this can often be safely exceeded. When a large dose is given i.m. it is advisable to divide it between two sites to reduce the liability to chemical abscess formation. When given rectally it should be diluted to 10 times the volume of the dose with 0·9% sodium chloride solution. Paraldehyde is sometimes said to be self-sterile, but it is not. It *decomposes*, especially when subject to light and heat, when as much as 70% may become acetic acid. Deaths due to corrosive poisoning have occurred with old paraldehyde, so any stored for over 6 months should be discarded, or at least tested for acidity before use.

Bromide (**1857**) is obsolete except in rare cases of epilepsy that are not controlled by other drugs. It is never necessary for sedation. Bromide is notoriously cumulative for reasons given below, and cases of chronic intoxication are still sometimes seen, and this is the only reason for retaining the following account. The main difficulty in diagnosis is failure to think of it, and the diagnosis is confirmed by measuring the blood bromide level.

Bromide is readily absorbed from the alimentary tract and is distributed throughout the body, almost entirely in the extracellular fluid. It is treated by the body just like chloride and so, if the intake of bromide is high and that

of chloride low, bromide will replace chloride in steadily increasing amount until toxic levels are reached. Since a blood bromide level high enough to sedate can only be achieved by replacing chloride, many grams would be needed to achieve this with a single dose, so it is evident that administration of two or three grams occasionally is irrational, as it cannot have any effect at all other than as a placebo.

Sodium or potassium bromide are used, and toxicity may appear at a blood level of 100 mg/100 ml (12·5 mEq/litre). If no steps are taken to hasten bromide excretion and the sodium chloride intake is average the blood level falls by about 50% in 4 weeks, so that a patient may be left with toxic effects for some weeks after leaving off the drug. Excretion may be hastened by a high daily intake of fluid (4 litres) and chloride (5 to 10 g sodium chloride above what is in the diet). Diuretics are also valuable. Forced diuresis (as in barbiturate poisoning) or hæmodialysis may be needed in severe cases; they are very effective as bromide is not bound to plasma proteins and behaves like chloride.

Bromide intoxication (bromism) declares itself with psychotic states of all kinds, but chiefly depression and irritability, although excitement may occur. It is dangerous to use more sedative for this excitement, although it may have to be done. Tremors and incoordination with depressed reflexes occur. Rashes, commonly acneiform, on the face and upper half of body are usual. Increased mucus secretion from mouth, nose and eyes causes the patient to appear to have a "cold". Headache, anorexia, foul breath, indigestion and constipation occur.

Bromism commonly occurs insidiously and the symptoms may be attributed to the disease for which the sedative is given, sometimes with the result that the dose has been increased. Prescriptions for bromide can be renewed indefinitely by the patient, who can also obtain bromide in a variety of futile proprietary medicines.

Other non-barbiturate hypnotics

Promethazine is a useful long-acting hypnotic, especially in children. It is described under antihistamines. It potentiates barbiturates as do most other phenothiazine compounds. Trimeprazine (Vallergan) is similar.

Mandrax is a mixture of methaqualone (hypnotic) and diphenhydramine (sedative antihistamine): it is rapidly effective and potent, which may account for its popularity. It is dangerous in overdose.

Chlormethiazole (Heminevrin) has hypnotic and anticonvulsant effects. It is chemically related to vitamin B_1 (thiamine) though this seems to be irrelevant to its particular use in controlling alcohol withdrawal syndromes. It is probably no better for this purpose than other drugs. Dependence can occur.

Sulphonal and its derivatives are toxic to the liver, kidney and blood and so are obsolete.

Apronal (Sedormid) is a urea derivative that is famous for causing thrombocytopenic purpura, the mechanism of which is known (see *drug allergy*). It is deservedly obsolete.

Other drugs of no particular merit include: methylpentynol (Oblivon): glutethimide (Doriden): methyprylone (Noludar): carbromal (Carbrital is carbromal plus pentobarbitone), it can cause bromism: meprobamate

(Miltown, Equanil): ethchlorvynol (Arvynol): methaqualone (Melsed): doxylamine (Decapryn).

Barbiturates (1903)

The development of organic chemistry in the late 19th century led to the testing on animals of many compounds in the search for an ideal hypnotic drug.

Because urethane was known to be a hypnotic, although weak and unreliable, other urea derivatives were investigated. Derivatives of barbituric acid* (malonyl urea) were found to be effective and in 1903 barbitone was introduced. Since then a huge number of barbiturates have been tested and many are used to provide depression of the central nervous system ranging from mild sedation to surgical anæsthesia. For use as hypnotics and sedatives depressant barbiturates have qualitatively similar actions; but they differ in the rate and method of disposal in the body, which has a bearing on their clinical use, and phenobarbitone and methylphenobarbitone have a greater anticonvulsant effect relative to the hypnotic effect. Barbiturates which are convulsants have also been made but have not found clinical use.

There is now enough evidence that the traditional **classification** of barbiturates as long, medium and short acting, derived from experiments on animal anæsthesia, does not apply to their clinical use as hypnotics, and so it should be abandoned. However, for overdose, rates of metabolism and excretion do have some relevance (see below). Duration of hypnotic effect is similar for drugs previously classified into each group, being about 8 hrs. Incidence of hangover is similar, and it is common after a placebo, being more closely related to the patient than to the drug. However, there is evidence that there are differences of intensity of hypnotic effect, and quinalbarbitone and pentobarbitone may be best (*20*). Phenobarbitone in daily doses is cumulative and its effect will eventually extend into the day if used on many successive nights. It is therefore more suitable for continuous sedation than as a hypnotic.

Pharmacokinetics. Absorption after oral administration is rapid: plasma protein binding is variable, those with longer half-lives being less protein bound than those with shorter half-lives (surprisingly). **Plasma half-lives** are the result of renal excretion and of metabolism in those used as hypnotics and sedatives. For those used as i.v. anæsthetics (which see), redistribution is a major factor in plasma half-life of initial doses.

Examples: $t_{\frac{1}{2}}$: 49–90 hrs: phenobarbitone, barbitone, allobarbitone.
30–40 hrs: pentobarbitone, quinalbarbitone, amylobarbitone, butobarbitone, cyclobarbitone.
less than 8 hrs: i.v. anæsthetics (initial doses).

* Reputedly named by the original synthesiser after "a charming lady named Barbara". Miller, L. C. (1961). *J. Amer. med. Ass.*, **177**, 27.

Distribution is throughout the body with rather more in the C.N.S. than elsewhere.

Metabolism and excretion. For most barbiturates metabolism is chiefly hepatic with a little urinary excretion and, from the point of view of safety, the more rapidly metabolised barbiturates may be preferred. Those most rapidly metabolised are quinalbarbitone, pentobarbitone and cyclobarbitone, followed by amylobarbitone and butobarbitone. The most persistent are phenobarbitone (about 25% excreted unchanged by the kidney) and barbitone, the only member wholly excreted unchanged by the kidney.

The reason why there is little renal excretion of most barbiturates is not that they do not appear in the glomerular filtrate, but because barbiturate that appears in the glomerular filtrate, if unionised, diffuses back into the circulation through the renal tubule. This diffusion will be less if the drug is ionised, and, being weak organic acids, ionisation will be maximal at a high (alkaline) pH.

Renal excretion of barbiturate can therefore be enhanced both by making the urine alkaline to pH 8 with a sodium bicarbonate or lactate* infusion, and by hastening the passage of glomerular filtrate through the tubule by inducing a diuresis. This has been used successfully in the treatment of poisoning.

Forced *alkaline* diuresis is useful only in the case of phenobarbitone (see pH, pKa); for other barbiturates nothing useful is achieved by doing more than ensuring profuse urine volume. The alkaline diuresis treatment is not itself life-saving and so is never essential. Its benefit consists in reduction of duration of coma by up to two-thirds; therefore the complications of prolonged unconsciousness are less; but it needs skilful handling and it should not be begun until the clinical condition (respiration, circulation) is under control. The same remarks apply to dialysis.

Indications for forced alkaline diuresis (*F.A.D*) *in phenobarbitone poisoning*†: patient unrousable, hypoventilating and hypotensive, plasma concentration above 10 mg/100 ml of phenobarbitone itself (excluding metabolites).

Technique: "Before beginning F.A.D. the state of hydration and of the renal, respiratory and cardiac function of the patient must be assessed and, if possible, improved. A catheter to measure central venous pressure and a bladder catheter should be inserted. Baseline readings of plasma electrolytes, urea, pH, pCO_2, bicarbonate and urine osmolality levels should be made. The plasma level of the drug should be measured. It is not necessary to await the results. In the first hour 500 ml of 1·2% sodium bicarbonate (or M/6 sodium lactate), plus 20 mg frusemide ('*Lasix*') and 1 litre of 5%

* In the past sodium lactate has been preferred to sodium bicarbonate (lactate is metabolised, and the sodium is freed to take up bicarbonate ion made available by dissociation of H_2CO_3) because of difficulty in sterilising bicarbonate by heat without chemical change. But this has been overcome and sterile sodium bicarbonate solution is now generally available.

† Boulton-Jones, J. M. (1971). *Prescr. J.* **11**, 146. By permission of the author and the editor.

dextrose, plus 20 mg frusemide, should be given intravenously. The urine flow should be above 3 ml per minute at the end of the hour and it is then safe to continue; if not, renal function should be investigated more fully. The exact composition and amount of the fluid given intravenously depends on the continuous monitoring of the patient's state. Volume requirements depend on changes in the central venous pressure and in the urine volume.

A diuretic must be used in order to achieve a urine volume of 500 ml/hr. The type of diuretic to be preferred for this purpose is still controversial. Mannitol, the osmotic diuretic most commonly used should not be given in doses of more than 20 g/hr; but such doses may not produce the necessary urinary volume and in larger doses mannitol causes an undesirable expansion of the extra-cellular volume and an intracellular shift of sodium. If a more powerful diuretic is required, frusemide should be used. It is often effective alone and can be used in large doses (up to 500 mg i.v. per 24 hrs) over a few days.

The amount of sodium given should depend on the urinary loss. Both serum and urinary electrolytes should be measured 6-hrly. To start with it is safe to assume that 40–60 mEq of sodium will be passed in the urine per litre. Therefore, every third bottle used for intravenous infusion should contain sodium in a concentration of 154 mEq/litre.

The aim is to render the urine alkaline, and so the urinary pH should be measured hourly, preferably by means of a pH meter (litmus paper should never be used). Sodium lactate or sodium bicarbonate should be given in such concentration as will keep the urinary pH between 7·5 and 8·5. Care should be taken to check the plasma pH 3-hrly and to ensure that it never rises above 7·5.

Lastly, almost all patients who undergo F.A.D. become hypokalæmic, even when large potassium replacements are given intravenously. It has been calculated that in salicylate poisoning 20 mEq of potassium per litre of infused fluid will be required, and in barbiturate poisoning 10 mEq/litre. Continuous E.C.G. monitoring may help to indicate over-zealous or inadequate replacement.

Contraindications and complications. Shock, or cardiac failure, or renal impairment are absolute contra-indications to forced diuresis.

The dangers are (a) hypokalæmia, and (b) overloading the circulation to a degree which may cause either pulmonary œdema or cerebral œdema and convulsions. With care these dangers can be minimised, but this requires the co-operation of laboratory, nursing and medical staff. Resources needed for F.A.D. to be safe are best co-ordinated in an intensive care unit."*

When the patient regains consciousness, and this may not be for 2 or 3 days, the diuretic is stopped and the i.v. fluid continued for about 8 hrs to prevent dehydration.

See also *dialysis* in *treatment of poisoning.*

Contra-indications. In severe pulmonary insufficiency, e.g. emphysema, even hypnotic doses of barbiturates depress respiration (see general account above).

* Boulton-Jones, J. M. (1971). *Prescr. J.*, **11**, 146. By permission of the author and the editor.

Hepatic failure potentiates barbiturates (except barbitone, which is not metabolised).

Attacks of porphyria (which see) are induced in predisposed people.

Dosage. The principal barbiturates are listed below with proprietary name, tablet size in mg. and the oral hypnotic dose:

phenobarbitone (Luminal) (15, 30, 60) (30–120 mg)
pentobarbitone sodium (Nembutal) (30, 50, 100) (100–200 mg)
quinalbarbitone sodium (Seconal) (50, 100) (100–200 mg)

Other orally active barbiturates include: butobarbitone sodium (Soneryl): amylobarbitone (Amytal): cyclobarbitone (Phanodorm): barbitone: nealbarbitone (Censedal): heptabarbitone (Medomin).

Barbiturates for i.v. anæsthesia (which see).

Uses. For their use as hypnotics and sedatives see above. The choice of drugs in convulsive states is discussed below. For intravenous anæsthesia no drug has been shown to be superior to thiopentone. For oral use the barbiturate or its more soluble sodium salt can be used, it matters little; but for parenteral administration a sodium salt is required. Soluble barbiturates may be injected i.m. or s.c., when the dose is similar to that given orally. For i.v. injection the drug is given slowly and the dose judged by results. It is dangerous to give the more slowly metabolised and excreted drugs i.v.

Unwanted effects of barbiturates are almost entirely those of overdose: coma and respiratory and circulatory failure, leading to renal failure. Allergic reactions occur occasionally, particularly with phenobarbitone, rashes being the most common (bullæ in acute poisoning can be of diagnostic use), but severe fatal reactions have rarely been recorded. See also *contra-indications* and *interactions*, above.

Dependence is now recognised as a serious problem: see under *hypnotics and sedatives: general*, above.

Poisoning by Hypnotic Drugs

(see also ch. 33)

This problem will be discussed as barbiturate poisoning, but most remarks apply to other hypnotics except the benzodiazepines which are substantially less dangerous. Some cases of barbiturate poisoning result from a patient taking a large dose, going to sleep and then waking after a short time in a confused or amnesic state and taking a second dose. It is not known how often this occurs, but the sequence is sometimes proposed at coroners' inquests.

When confronted with poisoning it is especially necessary to have a clear notion of what can be achieved and of what should be done.

The usefulness of techniques for removing the drug from stomach or bowels is a general topic, and is discussed in ch. 31.

However, in hypnotic poisoning identification of the drug is important and this is itself a valid reason for attempting gastric aspiration in the

unconscious and aspiration or emesis in the conscious, if this is the only way of finding out what the drug is.

"At present the choice of treatment is apt to be tinged with respect for the beliefs of the local coroner or with aversion for too much masterly inactivity."*

To this may be added the remark that these techniques of removing the drug from the body benefit the patient by shortening the period of unconsciousness and so of exposure to the risks mentioned below. Their use requires skill and attention, and the outcome will depend on this at least as much as on choice of treatment. They are not required if unconsciousness is shallow and if there is reason to expect it to be brief. On the other hand, a heavy dose of phenobarbitone, butobarbitone or barbitone can cause coma lasting many days and the energetic method of removing the drug from the body, if used, should be begun early and not left until complications have occurred.

Forced diuresis should be used in all who are drowsy or unconscious on admission to hospital, provided the cardiovascular system is in good condition (systolic blood pressure above 70 mm Hg and no clinical evidence of cardiac disease). Dialysis should be considered with plasma concentration above 3 mg/100 ml of shorter and 10 mg/100 ml of longer acting barbiturate. They are discussed elsewhere, see index.

The common life-endangering complications are respiratory, circulatory and renal failure, fluid and electrolyte upset and pneumonia. Treatment is directed at preventing and reversing these potentially fatal effects and encouraging elimination of the drug.

Respiratory failure. There is a marked tendency to overtreat patients with barbiturate poisoning; the temptation to interfere unnecessarily must be consciously resisted. If a pharyngeal reflex is present and respiration is adequate for oxygenation then no specific action need be taken. When respiratory failure occurs a decision must be made to use either artificial respiration or an analeptic drug. If the facilities are available, the results of intermittent positive pressure respiration cannot be surpassed. Generally analeptics are only used to keep the patient breathing until he can be attached to a respirator. If it is decided to use drugs, then it should be remembered that the state to aim for is adequate respiration with a present pharyngeal reflex. There is no indication for attempting to wake the patient up, for all analeptics can cause convulsions and the aim is to keep the patient alive until the drug has been eliminated rather than to satisfy curiosity by obtaining from him an early answer to the question how and why he took the overdose, which, interesting though it is, can very well wait for a few days.

"The temptation to give a respiratory stimulant is strong, but the evidence that it will benefit the patient is weak"†. The following account is included for emergency use where assisted respiration facilities are unavailable.

* Editorial (1962). Barbiturate antagonists. *Brit. med. J.*, **2**, 462.
† Editorial (1962). *Brit. med. J.*, **2**, 462.

Though bemegride (50 mg i.v. every 5 to 10 mins) is popular there is no convincing evidence that it is superior to others, or, indeed, that it is useful; also it interferes with the estimation of barbiturate in the blood.

Other analeptics include leptazol (5 ml of 10% solution slowly i.v. about every 20 to 30 mins). Amphetamine acts for longer (10 to 20 mg i.m. or i.v.) and may be useful if the blood pressure is unduly low. Leptazol and amphetamine may be used together. Excess of amphetamine, i.e. more than 300 mg in 24 hrs, may cause a fatal cardiac arrhythmia. Nikethamide (2 to 10 ml i.v. of the usual 25% solution every 20 to 30 mins) can be used. Picrotoxin was for long regarded with special favour in barbiturate poisoning; it may have a delayed onset of action and 6 mg i.v. are given at intervals of not less than 30 mins. All patients given analeptics should be watched carefully for early signs of overdose, twitching of the face or extremities, which can occur before any improvement in respiration, when administration should stop. The above intervals are only a general guide to therapy, the drugs are "titrated" against respiratory depression as clinical judgement counsels.

Caffeine, as a retention enema of coffee, is a traditional emergency remedy.

The response of the respiratory centre to CO_2 is depressed by barbiturate and, where there is serious hypoventilation, it is unlikely to respond usefully to inhalations of CO_2 which will just increase the respiratory acidosis.

A clear airway and adequate oxygenation are obviously essential and in severe cases there should be no hesitation about making a tracheostomy. An endotracheal tube is an alternative if it is expected that recovery will occur in 48 hrs, but it will damage the larynx and trachea if left in place for much longer. If bronchial secretions are excessive a tube or tracheostomy will also facilitate their removal by *gentle* suction: vigorous suction can strip off the tracheobronchial lining.

Circulatory failure. Barbiturates reduce sympathetic tone, causing dilatation of arterioles (resistance vessels) and of veins (capacitance vessels) so that the capacity of the vascular system is increased. The arterial pressure falls both because of the decreased total peripheral resistance and because the lowered central venous filling of the heart reduces cardiac output.

Cardiac output can be raised by tilting the patient head down and this will ordinarily suffice to maintain adequate blood flow, albeit with a low blood pressure, to the brain, kidney and myocardium. A sympathomimetic drug may be used if hypotension remains extreme after tilting. An alternative is to increase venous filling pressure and so raise cardiac output by expanding the intravascular volume, but this can be dangerous in patients with normal blood volume, if not skilfully handled. Of course, if intravascular volume is low due to fluid loss or deprivation, replacement is essential.

Anoxia contributes to myocardial depression and cardiac arrest may occur.

Dixogin may be needed for cardiac failure.

Renal failure with oliguria or anuria may occur secondary to circula-

tory failure, which must be treated, see above. Hæmodialysis should be considered.

Pneumonia is common in unconscious patients. Its prevention is discussed elsewhere (see index).

Evaluation. Unfortunately no definitive scientific comparisons of different regimens has been possible, and this is not surprising. Attempts to decide the merits of a treatment are frequently made by comparing published mortality rates. So intrinsically variable a condition is poisoning, especially suicidal poisoning, and so low is its mortality (about 2%), that it is important to be wary of any such claims. That figures based on less than several hundred cases are useless is made clear by the fact that in one hospital there were 134 consecutive recoveries amongst patients comatose on admission to hospital and then three deaths in the next five cases.*

A genuinely selective barbiturate antagonist, that is a drug acting by substrate competition, is much needed, and development of such a substance should not be a very difficult matter for modern medicinal chemists.

Late effects. After recovery of consciousness, restlessness, even delirium may occur days later. Sleep pattern may be abnormal for weeks, even in unhabituated subjects.

ANTIEPILEPTICS

Bromide (1857) was the first effective antiepileptic drug, but is now virtually obsolete. When phenobarbitone was introduced in 1912 it was found to control patients resistant to bromides and to be far superior to barbitone which had been available since 1903. It became clear that minor differences in molecular structure were significant and that, in the barbiturate series, there was prospect of separating hypnotic from anticonvulsant effects. But these possibilities could not be exploited without suitable animal experimental techniques. Many ingenious techniques have now been developed. The first success was the discovery of phenytoin, which is structurally related to the barbiturates, in 1938. Since then many drugs have been discovered, but phenobarbitone and phenytoin remain the most useful drugs in the treatment of major epilepsy.

Epilepsy

Epilepsy has never been more accurately defined than by Hughlings Jackson a long time ago when he said it was a sudden, excessive and rapid discharge in grey matter of the brain. Moreover, he early recognised that most (if not all) forms of epilepsy have a focal origin, the form of the seizures depending on the site of the focus in the brain, the regions to which the discharge spreads, and the effects of post-ictal paralysis of these regions. Although the exact relationship of the abnormal and

* LOCKET, S. (1956). *Proc. roy. Soc. Med.*, **49**, 585.

excessive excitation to normal neuronal activity is not yet understood, it has long been known that any general depressant of nervous activity (e.g. a general anæsthetic) will diminish or abolish epileptic activity.

Antiepileptics are drugs which inhibit discharge with minimal general depressing or hypnotic effect. Animal experiments suggest that they act chiefly by *preventing the spread of the discharge*, but that phenobarbitone may also *suppress the focus*. Phenobarbitone and phenytoin make a good combination in practice.

Drug treatment of epilepsy

As more effective anticonvulsants become available the possibility of dramatic advances naturally becomes less, so that it is important to be able to detect even small improvements in therapeutic effect. This means that therapeutic trials have to be designed and conducted more carefully and accurately than before.

Measurement of therapeutic effect includes careful recording of fits (by patient or other), measures to ensure that patients who do not take the drug as instructed are detected (measurement of plasma concentrations is best), avoidance or control of environmental interfering factors (e.g. stress, alcohol), knowledge of pharmacokinetics of drugs under test. For ethical reasons initial trials are generally on patients taking orthodox therapy who are not well controlled, which adds to the problems of measuring comparative efficacy. Also trials must be prolonged for months to allow for spontaneous variations in seizure frequency.

Principles in the general treatment of epilepsy:

1. Treatment of causative factors, e.g. cerebral neoplasm.
2. Avoidance of precipitating factors, e.g. alcohol, stress.
3. Anticipation of natural variations, e.g. fits may occur only at night or shortly after waking.
4. Antiepileptic drugs.

Throughout this book little is included about therapy other than drugs, but this does not mean that drugs are necessarily the most important feature of the treatment of any disease. The **principles of drug therapy of epilepsy** are simple, have been well stated by Putnam,* and illustrate many of the principles of drug therapy in general:

1. *Relatively well-known and non-toxic drugs* should be preferred to dangerous or untried ones, which should only be added if the former have failed.

2. *The maximum tolerated dose* should, if necessary, be found for each drug, i.e. the dose should be increased until symptoms of overdose are produced and then it should be reduced slightly. The best therapeutic effect is usually only obtained near the toxic dose.

* PUTNAM, T. J. *Drugs of Choice*, 1962–63. Ed. Modell, W. St. Louis: Mosby.

3. Unless a drug under trial is obviously useless *it should not be stopped* until the next drug to be tried is being given in reasonable dose. Sudden withdrawal of an effective drug may result in status epilepticus. If sudden withdrawal of an effective drug is necessary because of toxicity, a substantial dose of another drug should be given at once.

4. This trial of drug after drug should be continued *until the epilepsy is controlled*, or until there are no more drugs to try. Up to 3 months may be needed to try a drug thoroughly in an individual patient.

5. In cases where fits are liable to occur at a particular time of day, dosage should be adjusted to achieve *maximal drug effect at that time.*

Amphetamine may be used to counteract drowsiness due to the drugs without making the fits worse, but it should be avoided if possible, for it is not a good principle to oppose one drug with another. Drug effects seldom exactly cancel each other out. It is naïve to imagine that amphetamine versus phenobarbitone equals normality.

It is doubtful whether any epileptic is ever the better for taking more than three anticonvulsant drugs at a time, and he is seldom the better for more than two.

Dosage. In general, dosage is increased weekly, because maximum therapeutic effect takes time to develop and to allow a steady state of drug concentration to be established. Knowledge of plasma concentrations allows improved control. Plainly, where fits are infrequent, dosage adjustment is difficult. Occurrence of enzyme induction also makes knowledge of plasma concentrations desirable, as does patient "disobedience", a common cause of drug failure.

Results of drug treatment of epilepsy may be summed up thus. Up to half the patients are completely relieved of fits, one in five of whom may be able to give up drugs after 3 years, without recurrence. About a third are partially relieved and the remainder are not benefited at all. Patients must be persuaded of the importance of continuous medication.

Choice of drugs in epilepsy. The doses and toxic effects of the principal drugs used in epilepsy are in the table. The molecular structures of the three main groups, barbiturates, hydantoins and oxazolidinediones are related.

Phenytoin (diphenylhydantoin, Epanutin, Dilantin) well absorbed orally, but bioavailability varies markedly with the nature of the diluent in the capsule (see index). The plasma half-life is variable, it is influenced by whether the tissues are saturated (the drug is bound in the tissues), by the dose, by duration of administration (amount of enzyme induction) and by race (it is longer in Caucasians than in Negroes) (*44*). It is generally 20 to 30 hrs.

Phenytoin displaces iodine from its carrier protein so that the measured protein-bound iodine may be in the range characteristic of hypothyroidism. In uræmia the free (unbound) fraction of phenytoin in the plasma is higher than in normals and lower doses are needed.

About half the dose of phenytoin is hydroxylated to an inert form.

THE PRINCIPAL ANTIEPILEPTIC DRUGS

Chemical group and non-proprietary name (Proprietary name)	*Approx. total daily oral dose given in 2–4 doses (Tablet sizes in mg)*	*Type of epilepsy against which drug is useful*	*Remarks and commoner unwanted effects*
Barbiturates and primidone			
phenobarbitone (Luminal)	100–300 mg (15, 30, 60)	grand mal	A drug of 1st choice. Sleepiness, occasional rashes. Can make petit mal worse.
primidone (Mysoline)	250–2000 mg (250)	grand mal psychomotor	Sleepiness, nausea, ataxia, which often disappear after first few doses. Closely related to phenobarbitone: 20% converted to phenobarbitone in body.
Hydantoins			
phenytoin sodium (Epanutin, Dilantin)	300–600 mg (50, 100)	grand mal psychomotor	A drug of 1st choice. Hyperplasia of gums, specially in children. Ataxia, headache, tremors, rashes and blood disorders. Hirsutes. Lymphoma-like syndrome.
Oxazolidinediones			
troxidone (Tridione)	600–1200 mg (300)	petit mal	A drug of 1st choice. May make grand mal worse and should be combined with phenytoin in cases with both petit and grand mal. Photophobia, day blindness and dazzle; nephrotic syndrome, hiccough, blood disorders, rashes.
Succinimides			
ethosuximide (Zarontin)	0·5–1·5 g (250)	petit mal psychomotor	Sleepiness, dizziness, vomiting, leucopenia.

There is a rare genetically determined failure of hydroxylation, and such patients are, of course, intolerant of the drug.

Phenobarbitone has a plasma half-life of about 80 hrs and is therefore also cumulative. For a general account of barbiturates, see above.

Enzyme induction occurs with both drugs and with prolonged therapy can cause rickets (children) or osteomalacia (adults) due to enhanced metabolism of calciferol (*39*). It perhaps also causes the folate deficiency that is common with long-term anticonvulsant therapy and that sometimes progresses to megaloblastic anæmia. The mechanism suggested is that the enzyme induction results in increased hydroxylation and that since folate is a cofactor in these hydroxylations the demand for folate is increased. The effect may be reversed by administering folate, but, simultaneously there will be an increase in hydroxylation

which was previously limited by lack of folate. This will result in greater capacity to hydroxylate phenytoin, the plasma concentration of phenytoin falls, and fits may return.

It is not, at present, thought desirable to give folic acid routinely to epileptics, partly because the clinical problem is not large and perhaps also because of the risk of neurological complications in any epileptic who developed pernicious anæmia.

Deterioration of mental function in epileptics has been attributed to folate and cyanocobalamin deficiency, due to antiepileptic drugs, but this is not conclusively established.

Alternative antiepileptics include:

Barbiturates: methylphenobarbitone (mephobarbital, phemitone, Prominal); metharbitone (Gemonil). They are converted into phenobarbitone in the body.

Hydantoins: methoin (Mesontoin); ethotoin (Peganone).

Oxazolidinediones: e.g. paramethadione (Paradione).

Succinimides: methsuximide (Celontin); phensuximide (Milontin).

Phenylacetylureas: drugs of second choice; may be specially useful in psychomotor epilepsy e.g. pheneturide (Benuride).

Others: beclamide (benzchlorpropamide, Nydrane); sulthiame (Ospolot); bromide; carbamazepine (Tegretol).

Benzodiazepines: diazepam: tolerance develops with chronic use: see *status epilepticus.*

All the above drugs may sometimes be found, by a process of trial and error, to suit an individual patient best.

Grand mal. Phenobarbitone and phenytoin are the drugs of choice. A patient may begin treatment with 30 mg phenobarbitone orally, two or three times a day. If he tends to have his fits at any particular time of day then medication should naturally be heaviest then. Patients who have fits soon after rising in the morning may be advised to take a dose on waking and to stay in bed for at least a further 15 mins. The phenobarbitone may be increased to a total of about 200 mg in a day, at which dose sleepiness will probably be marked.

If control is incomplete then phenytoin may be added, 100 mg three times a day, and increased up to a total of about 600 mg a day. If control becomes complete it may be possible to reduce the dose of phenobarbitone or even to withdraw it.

When a second drug is added, it is obviously desirable to choose one that belongs to a different chemical group from the first, e.g. do not add primidone to phenobarbitone.

If control is still incomplete, primidone and then other drugs can be tried in a similar fashion. If a drug is useless it can be withdrawn suddenly, if not, withdrawal *must* be gradual.

In patients who are not relieved by any combination of drugs tried

in the usual way, intensive anticonvulsant therapy in hospital with phenytoin (4 g total per day for 4 days) can be tried (*36*). The patient may be too sleepy to eat or drink on this dose and may need fluid and glucose by vein. Very careful supervision is vital, and the treatment is not to be lightly undertaken. After the course the patient may respond to ordinary anticonvulsant dosage. Dehydration, by withholding fluids, sometimes helps in resistant cases.

Pregnancy. There is evidence that antiepileptic drugs in clinical dosage increase the incidence of fetal malformations, especially cleft lip and palate; but the risk of stopping treatment is greater than the risk of continuing.

Although pregnancy may make epilepsy worse it often does not, and it is unnecessary to increase anticonvulsants unless previous experience recommends it; nor is it necessary to increase medication before surgery.

Petit mal (and physiologically related seizures such as generalised myoclonus). Troxidone or ethosuximide are used. If there is no response to the maximum dose in 3 weeks, there will be none.

Phenobarbitone can make petit mal worse. Amphetamine may help.

Focal epilepsy (Jacksonian, psychomotor, temporal lobe) is treated like grand mal: carbamazepine can be useful.

Myoclonic epilepsy is ordinarily very resistant to treatment but diazepam, ethosuximide, meprobamate and chlorpromazine are worth trying.

Duration of anti-epileptic drug therapy. It is essential that full drug therapy be continued for at least 2 years after the last fit. Those who are by nature cautious would put it at 3 years, after which time the drugs can be withdrawn gradually over a period of months. If another fit occurs then a further 2- to 3-year period is necessary before another attempt is made to withdraw therapy. Sudden withdrawal of drugs may result in status epilepticus.

It is not generally thought necessary to begin such prolonged therapy after a solitary fit.

Status epilepticus: a treatment of choice is diazepam i.v. slowly (up to 10 mg/min). The dose needed is likely to be in the range 0·25 to 0·75 mg/kg. It can be repeated as necessary, i.v. or i.m. Hypotension and respiratory depression (particularly if other antiepileptics have been used) may occur. Alternatives are:

Sodium phenytoin i.m. or i.v. (250–500 mg/50 mg/min).

Sodium phenobarbitone (200 mg i.m.), repeated as necessary; paraldehyde (5 to 10 ml i.m. or even i.v. very slowly); thiopentone or methohexitone by slow i.v. infusion; phenytoin (100 mg i.m. or i.v.); lignocaine i.v. Inhalation anæsthetics can be used in emergency to gain time to arrange less drastic therapy. Neuromuscular block (with artificial respiration) stops the convulsions but does not affect the brain. Chlormethiazole can be effective.

Behaviour disorders with epilepsy may respond to chlordiazepoxide (Librium), which has some anticonvulsant effect, or to chlorpromazine or other phenothiazine which may make the fits worse and so should only be used with effective anticonvulsant control.

Fits in children are treated as in adults, but children may respond differently to the drugs and become irritable, especially with phenobarbitone. If febrile convulsions have occurred, phenobarbitone (or phenytoin) should be given whenever the child subsequently becomes febrile. This is important between the ages of 1½ and 3 years. Sometimes convulsions occur at the onset of fever and so cannot be forestalled. Continuous medication can then be given if they are at all frequent, but opinions vary on just when to embark on continuous medication in children who are dubiously epileptic.

TETANUS (*45–50*)

Whilst only the pharmacology of the convulsions can be strictly considered appropriate to this book, the practical immunological aspects of tetanus are also discussed as they form a perennial clinical problem.

Active immunisation provides the best and safest protection against tetanus. If all wounded patients were known to be actively immune there would be no need for passive protection. Since this ideal situation does not exist in Britain many wounded patients need *passive protection.* This is best provided by the use of human tetanus immunoglobulin (Humotet).

In the past, horse antitoxin has been widely used, but in recent years the seriousness of allergic reactions to it and the knowledge that it may fail to protect patients who have had it before, has led some doctors to substitute antibiotics for antitoxin in the treatment of the non-immune wounded patient, and more recently to use human immunoglobulin.

It is known that both antitoxin and antibiotics can fail,* but since serious adverse reactions are believed to be less likely after antibiotics, they have gained popularity. However, until a valid comparison of the relative merits of horse antitoxin and of antibiotics has been made, it is necessary to adopt a compromise scheme for prophylaxis.

Prevention of tetanus in the wounded

Toxoid

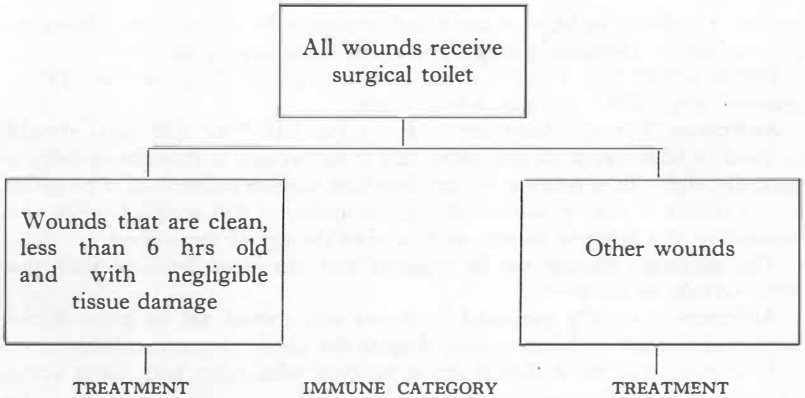
Adsorbed tetanus toxoid, that is, toxoid containing an aluminium adjuvant, such as Tet/Vac/PTAP (B.P.), 0·5 ml, i.m. (all ages) is recommended.

A complete course comprises three doses of toxoid with about 6 weeks between the first and second, and 6 to 12 months between the second and third.

Additional prophylaxis

Additional prophylaxis is provided by an antibiotic with or without antitoxin.

* People who have had horse serum once may eliminate any subsequent dose in a few hours even in the absence of an overt allergic reaction. It is not known how often this occurs.



TREATMENT	IMMUNE CATEGORY	TREATMENT
Nothing more required	A	Nothing more required
Toxoid 1 dose	B	Toxoid 1 dose
Toxoid 1 dose	C	Toxoid 1 dose plus additional prophylaxis
Toxoid complete course	D	Toxoid complete course plus additional prophylaxis

Adrenaline Injection (B.P.) should be available during prophylactic procedures. For anaphylactic shock in adults 0·5 to 1 ml, i.m.

IMMUNE CATEGORIES

A. Has had a complete course of toxoid or a booster dose within the past year.

B. Has had a complete course of toxoid or a booster dose more than one and less than 10 years ago.

C. Has had a complete course of toxoid or a booster dose more than 10 years ago.

D. Has not had a complete course of toxoid or immune status is unknown.

The preceding recommendations represent reasonable practice at present.*

Antibiotics. An antibiotic should be given for 4 days; if the wound then appears clean, is healing well and there is no suspicion of retained foreign matter the antibiotic may be stopped. Otherwise, the antibiotic should be continued until the wound is healed or for at least 10 days in Immune Category C, and 4 weeks in Immune Category D.

Penicillin is preferred and on general principles a choice may be made between:

1. *Oral*—Phenoxymethylpenicillin Capsules (B.P.), 250 mg, 6-hrly.
2. *Intramuscular, daily*—Fortified Procaine Penicillin Inj. (B.P.), 2 ml.
3. *Intramuscular, one dose treatment*—A mixture of benzathine penicillin 0·9 g: procaine penicillin 600 mg: benzylpenicillin 380 mg, e.g. "Penidural All-Purpose". This is a substitute for daily penicillin to be used if the

* By LAURENCE, D. R., EVANS, D. G. and SMITH, J. W. G. (1966). *Brit. med. J.*, **1**, 33. Reproduced by permission of the authors and the editor.

patient is unlikely to be seen again and/or cannot be relied on to adhere to daily schedule. It should provide protection for at least 4 days.

Tetracycline may be used if the patient is allergic to penicillin: Tetracycline Tabs. (B.P.), 250 mg, 6-hrly, orally.

Antitoxin. Tetanus Antitoxin (B.P.), 1,500 I.U.,* s.c. (all ages) should be used in addition to an antibiotic only if the wound is thought to carry a specially high risk of tetanus. In deciding this, consideration should be given to the extent of contamination, the practicability of full surgical toilet, the possibility of a retained foreign body and to the age of the wound.

The antitoxin should *not* be injected into the same limb or with the same syringe as the toxoid.

Antitoxin is usually prepared in horses and should *not* be given if the patient is allergic to horse serum, despite the above recommendation.

It should also be withheld from patients who have had horse serum before if it is at all reasonable to do so.

A test for allergy should always be made (see page 10.26) if heterologous antitoxin is used. If a general or a local reaction occurs the full dose of antitoxin should be withheld.

In patients with a history of any allergy the above test should be preceded by a similar test using a 1 : 10 dilution of the antitoxin.

Comments

The emphasis of this scheme is placed on the desirability of establishing and maintaining active immunity and on restricting the use of heterologous serum. In addition, it is important for the doctor who treats wounded patients to explain the significance of active immunisation to each patient, so that an increasing proportion of the population will come to realise the importance of being immunised and of knowing their immune status.

Surgical toilet is of prime prophylactic importance since removal of foreign bodies and of tissues that are dead or likely to die renders the wound unsuitable for the growth of *Cl. tetani*.

Immune Categories

Immune Category A: The patient is in a state of adequate active immunity and no additional prophylaxis is needed.

Immune Category B: The toxoid acts as a booster which suffices for immediate prophylaxis and no additional prophylaxis is needed.

Immune Category C: The toxoid recalls the active immunity, but this may not suffice for immediate prophylaxis and additional prophylaxis may be needed.

Immune Category D: The toxoid is the first dose of a complete course of active immunisation and additional prophylaxis may be needed.

Toxoid. Adsorbed toxoid (such as Tet/Vac/PTAP) is recommended rather than plain toxoid in simple solution (Tet/Vac/FT), since there is evidence that it stimulates a more rapid, higher and longer-lasting antitoxin response. In addition, adsorbed toxoid is effective when given concurrently with antitoxin.

Although there is some evidence that plain toxoid, when used for

* **Human Tetanus Immunoglobulin** is increasingly available, though expensive. It is obviously preferable since it does not carry the hazards of heterologous protein, and testing for allergy is unnecessary. The prophylactic dose is 250 I.U., i.m.; but the *therapeutic* dose should be the same as for horse antitoxin.

booster injections, gives a faster response, we consider this evidence is not strong enough to justify the inconvenience of using two kinds of toxoid in a prophylactic scheme.

Antibiotics. When additional prophylaxis is required in Immune Categories C and D this should be provided by an antibiotic wherever it may reasonably be expected to give protection. There is support for this use of antibiotics from clinical experience and from animal experiments.

Although there is no direct evidence from man regarding the duration of antibiotic prophylaxis, animal experiments suggest that 4 days is an acceptable minimum. Since antibiotics may fail to eliminate *Cl. tetani* from the wound it is important that they be continued until there is no likelihood of anaerobic areas remaining, or until active immunity is established. It is probable that in the majority of patients, immunity can be produced within 10 days of a toxoid injection in the case of Immune Category C and within 4 weeks in Immune Category D.

Penicillin is the drug of choice, although resistant strains have been reported.

Tetracycline should be used if the patient is allergic to penicillin.

Antitoxin prepared in *animals* is advised only in Immune Categories C and D where the wound carries a high risk of tetanus. This is the case where the wound is such that an adequate concentration of antibiotic may not reach the site of infection, and also where it is possible that a tetanus infection has been active long enough to produce a dangerous amount of toxin. Thus, we suggest that where wounds have remained untreated for 6 hrs the use of antitoxin in addition to an antibiotic should be considered. This period is suggested because experiments indicate that in animals a lethal dose of toxin may be produced within 4 hrs. Plainly, in this situation antibiotics can be of no value; neutralisation of toxin is also needed. It is recognised that the animal experiments do not truly represent the clinical situation, and it would be possible to argue in favour of any period from 4 to 24 hrs. We suggest 6 hrs as the dividing line. The majority of wounds liable to cause tetanus are, in Britain, seen by a doctor within that time.

The recommendations on the use of antitoxin in patients who are allergic to horse serum or who have had horse serum previously, may not apply in the treatment of clinical tetanus. **But see footnote p. 10.24.**

Treatment of clinical tetanus: there are five principal aims:

1. To neutralise with antitoxin any bacterial toxin that has not yet become attached irreversibly to the central nervous system.
2. To kill the tetanus bacteria by chemotherapy.
3. To control the convulsions.
4. To prevent intercurrent infection (usually pulmonary).
5. To prevent electrolyte disturbances and to maintain nutrition.

10,000 I.U. of horse *antitoxin** are almost certainly enough (*48*). This dose will provide high blood levels which outlast the disease unless the patient has had horse serum before or is allergic to it, when the dose should be doubled to ensure that there is enough to deal with the patient's antibodies to horse serum as well as the tetanus toxin. Since large amounts of toxin

* Or the same dose of human teta. immunoglob. for immediate neutralization.

may be present in the tissues surrounding the wound, local infiltration with 3 to 4,000 I.U. antitoxin is advisable. There is evidence from animals that antitoxin given i.v. has greater protective value than when given i.m., but it is also more likely to cause anaphylaxis. A test for allergy should be made by pricking through a drop of antitoxin on the skin (with saline control), and read in 15 min. See also footnote p. 10.24. If there has been no reaction, 10,000 I.U. may be given i.v.

If there is a reaction to the test dose, treatment will depend on its kind and severity (see *drug allergy*). However, it is still necessary to proceed, under antihistamine (say, diphenhydramine 50 mg orally or 25 mg i.m.) and hydrocortisone (100 mg i.v.) cover, to give 20,000 I.U. antitoxin.* Unfortunately there are no reliable data to guide the technique.

Drugs for treating severe reactions should be ready in syringes at the bedside (see *anaphylactic shock*).

A recurrence of anaphylaxis within a few hours of an attack is unlikely.

In the unlikely event of an actively immunised person getting tetanus an injection of toxoid may be given but the large therapeutic dose of antitoxin may interfere with it.

Chemotherapy with penicillin or tetracycline will stop further production of toxin. It is often continued as prophylaxis against pneumonia, but there is no certainty whether it is better to do this and risk pneumonia from antibiotic-resistant organisms or to stop the antibiotic after the wound has healed and start it again if infection occurs. In any case a severe wound may require prolonged chemotherapy, so that this problem does not always arise.

Convulsions may be controlled by diazepam, barbiturates or paraldehyde. All have the disadvantage that adequate dosage may lead to loss of consciousness for long periods and so promote respiratory failure and pneumonia, though this is least with diazepam, which is probably the drug of first choice, though it may not control severe cases. Chlorpromazine and mephenesin control convulsions without causing loss of consciousness, but may fail in the most severe cases. An excess of chlorpromazine may make the convulsions worse, probably by stimulating the brain stem reticular formation. Morphine and pethidine have no useful anticonvulsant effect. Both may stimulate the spinal cord.

The dosage and route of administration can only be decided when confronted with the patient. A regimen which should control convulsions of any severity would be chlorpromazine, up to 100 mg i.m. or i.v. 4 to 6-hrly with sodium amylobarbitone i.m. or s.c. or i.v. in addition as required. It may be impossible to avoid abolishing consciousness at times.

An alternative is to paralyse the patient with tubocurarine or gallamine (on theoretical grounds these are preferable to depolarising agents) and provide artificial respiration and enough sedation to impair awareness and memory. This requires skill and much equipment, with facilities for measuring blood pH, electrolytes and gases as well as ability to understand the meaning of the results. Unfortunately this limits its applicability, particularly in the countries where tetanus is common, so that it is especially

* If there is an immunological reaction against the foreign serum, a higher dose should be used, as less will be available for neutralising toxin. The same may apply to any patient who has had foreign serum before (see above). Antitoxin prepared in man is always preferable, wherever available; see footnote p. 10.24.

difficult to know whether results are superior to the more conservative anticonvulsant regimens. This treatment reduces the mortality in severe cases of tetanus neonatorum, though not in those cases classified as mild or moderate (*46*), but results in adults remain equivocal, though a similar effect is likely. Treatment by paralysis need only be considered at present in very severe cases, and these are a minority. Unfortunately it is not easy to know which cases are going to become severe. Paralysis and artificial respiration should be seriously considered in all cases with laryngospasm, respiratory failure, severe chest infection and spasms so severe that they can only be controlled by making the patient unconscious.

Anticonvulsant therapy may be needed for 2 weeks or more and so attention to nutrition and body electrolytes is vital right from the start. Nursing care, in avoiding convulsions and pneumonia, is at least as important as drug therapy.

An attack of tetanus does not confer immunity and if the patient has had horse serum it is particularly important that he be actively immunised.

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Chapter 11

GENERAL ANÆSTHETICS, NEUROMUSCULAR BLOCKING AGENTS, LOCAL ANÆSTHETICS

ANÆSTHESIA

UNTIL the mid-19th century such relief of pain as was possible during surgery was achieved with natural substances such as alcohol, opium, hyoscine, cannabis indica and occasionally by concussion or suffocation. The problem of inducing quick, safe and easily reversible unconsciousness for any desired length of time in man only began to be solved in the 1840's when the long-known substances nitrous oxide, ether and chloroform were introduced in rapid succession.

The details surrounding the first use of surgical anæsthesia make unedifying reading at times for there were bitter disputes on priority of discovery following an attempt to take out a patent for ether.

Sir James Simpson, who popularised chloroform in man, heard of the initial trials of ether in 1846 and wrote,* "It is a glorious thought, I can think of naught else." Just before his death in 1870 he summarised the chief events of the introduction of anæsthesia in the U.S.A. "It appears to me that we might correctly state the whole matter as follows:

"(1) That on the 11th December, 1844, Dr. Wells had, at Hartford, by his own desire and suggestion, one of his upper molar teeth extracted without any pain, in consequence of his having deeply breathed nitrous oxide gas for the purpose, as suggested nearly half a century before by Sir Humphrey Davy.

"(2) That having with others proved, in a limited series of cases, the anæsthetic powers of nitrous oxide gas, Dr. Wells proceeded to Boston to lay his discovery before the Medical School and Hospital there, but was unsuccessful in the single attempt which he made, in consequence of the gas-bag being removed too soon, and that he was hooted away by his audience, as if the whole matter were an imposition, and was totally discouraged.

"(3) That Dr. Wells' former pupil and partner, Dr. Morton of Boston, was present with Dr. Wells when he made his experiments there.

"(4) That on the 30th September, 1846, Dr. Morton extracted a tooth without any pain, whilst the patient was breathing sulphuric ether, this fact and discovery of itself making a NEW ERA in anæsthetics and in surgery."

(5) & (6) That ether was soon used in general surgery and midwifery.

* COMRIE, J. D. (1932). *History of Scottish Medicine*, 2nd ed. London: Baillière, Tindall and Cox, for Wellcome Hist. Med. Museum.

"(7) That on the 15th November, 1847, the anæsthetic effects of chloroform were discovered in Edinburgh. . . ."*

Simpson undertook screening experiments, of a kind that would now only be done on animals, on himself and his colleagues. He tested a variety of substances. "Late one evening" in 1847 "on returning home after a weary day's labour, Dr. Simpson, with his two friends and assistants, Drs. Keith and Matthews Duncan, set down to their somewhat hazardous work in Dr. Simpson's dining-room. Having inhaled several substances, but without much effect, it occurred to Dr. Simpson to try a ponderous material, which he had formerly set aside on a lumber-table, and which, on account of its great weight, he had hitherto regarded as of no likelihood whatever. That happened to be a small bottle of chloroform. It was searched for, and recovered from beneath a heap of waste paper. And, with each tumbler newly charged, the inhalers resumed their vocation. Immediately an unwonted hilarity seized the party; they became bright-eyed, very happy and very loquacious—expatiating on the delicious aroma of the new fluid. The conversation was of unusual intelligence, and quite charmed the listeners—some ladies of the family. . . ." There was a crash. "On awaking, Dr. Simpson's first perception was mental—'This is far stronger and better than ether' said he to himself. His second was to note that he was prostrate on the floor and that among the friends about him there was both confusion and alarm." Dr. Duncan was unconscious beneath a chair and Dr. Keith was struggling.

It was not technical difficulties alone that had to be overcome before surgical anæsthesia could become acceptable.

"Dr. Simpson refers, in his pamphlet on the religious objections which have been urged to chloroform, to the first operation ever performed—namely the extraction of the rib of Adam, as having been executed while our primogenitor was in a state of sopor, which the professor learnedly argues was similar to the anæsthesia of chloroform. He further draws a justification of his own proceedings from this history of the creation of man. Putting aside the impiety of making Jehovah an operating surgeon, and the absurdity of suggesting that anæsthesia would be necessary in His hands, Dr. Simpson surely forgets that the deep sleep of Adam took place before the introduction of pain into the world during his state of innocence."†

It is significant that the first two effective general anæsthetics, nitrous oxide and ether, are still, when used together, after more than 100 years, the safest choice for an unpractised doctor who finds himself obliged by circumstances to administer a prolonged anæsthetic.

The next important developments in anæsthesia were in the 20th century when the introduction of new drugs and new apparatus increased the range of anæsthesia and as a result, the range of the surgeon.

* Its effects had, however, been discovered by a 17-year-old medical student and used in surgery in London some months earlier (SYKES, W. S. (1961). *Essays on the first hundred years of anæsthesia.* Edinburgh: Livingstone.)

† *Lancet* (1848), **1**, 292.

Stages of Anæsthesia (Fig. 7)

Anæsthesia is conventionally divided into four stages, and the third stage again subdivided into four planes; obviously each merges with the next.

The procession of stages derives from descriptions of open ether anæsthesia in unpremedicated patients, a slow, unpleasant process. With modern techniques of i.v. anæsthesia and of premedicated inhalation, stages 1 and 2 may hardly be noticed by patient or anæsthetist. They are retained here because they assist understanding.

Stage 1. Analgesia. Analgesia is partial until stage 2 is about to be reached. Consciousness and sense of touch are retained and sense of hearing is increased.

Stage 2. Delirium. The patient is unconscious, but automatic movements may occur. He may shout coherently or incoherently, become violent or leap up and run about. The prevention of these unpleasant manifestations lies in a skilful, smooth and quick induction in quiet surroundings. Sudden death, probably due to vagal inhibition of the heart or to sensitisation of the heart to adrenaline by the anæsthetic agent, may occur in a violent second stage.

Stage 3. Surgical anæsthesia. This is divided into four planes and the required depth differs according to the kind of operation to be performed. Depth is determined by noting characteristic changes in respiration, pupils, spontaneous eyeball movements, reflexes and muscle tone.

Stage 4. Medullary paralysis. Arrival at this stage constitutes an anæsthetic accident.

General Points About Anæsthesia

The practice of the anæsthetist has three main parts:

1. *Before surgery*, the preparation of the patient for surgery by premedication as well as assessment of his physical condition, which may very well affect the choice of drugs in 2.
2. *During surgery*, the production of:
   (a) *hypnosis.*
   (b) *analgesia.*
   (c) *muscular relaxation.*

Whilst all three can be produced by a single drug, e.g. ether, thiopentone, this carries disadvantages of heavy dosage (cardiac and respiratory depression, slow recovery) and it is usual to use a drug for each purpose from the wide range available.

3. *After surgery*, the relief of pain and other aspects of postoperative care.

These three components are interdependent, the choice of drugs to be used at any one point affecting the choice of drugs both before and after;

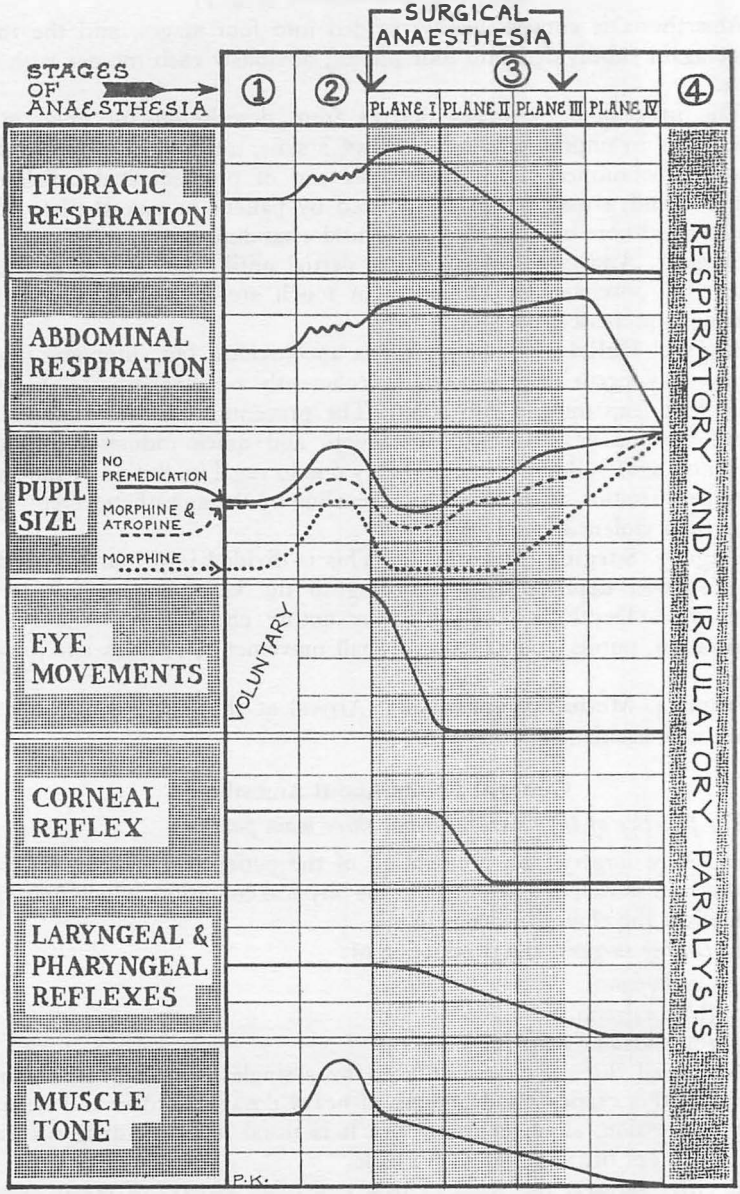

FIG. 7. The stages of anæsthesia related to various physiological changes.

for instance drugs used in premedication may reduce both the amount of general anæsthetic and the postoperative medication required. Safety and comfort for the patient and good operating conditions for the surgeon are all desirable, but the provision of one may compromise the others. The problem may be approached in many different ways, using different combinations of the wide array of drugs which are available.

Simplicity leads to safety, for it is much easier to reach a clear diagnosis when few drugs have been given than when many drugs have, inevitably, confused the picture. With drugs, safety does not lie in numbers.

The anæsthetist's job is nowadays complicated by the fact that he is often presented with patients already taking potent drugs affecting the central nervous and cardiovascular systems.

The techniques of administration of anæsthetic drugs and physical control of respiration are of great importance, but are outside the scope of this book. Premedication is treated relatively extensively as the non-anæsthetist is more likely to find himself concerned with it than with surgical anæsthesia.

Before surgery (premedication) (*10, 15, 16, 34*). The principal aims are to provide:

1. **Sedation and amnesia.** A patient who is going to have a surgical operation is naturally apprehensive, and it is kind to attempt to reduce this by explanation, reassurance and drugs. In one study a reassuring talk with the anæsthetist was found to have a greater calming effect than a barbiturate (*34*). But it cannot be assumed that all anæsthetists will be so successful. Preoperative preparation (which may commence on arrival in hospital for planned surgery, e.g. tranquillisers, and not merely 1 hr before operation) is not solely humanitarian, for the discharge of adrenaline from the suprarenal medulla and the increased metabolic rate, which are concomitants of anxiety, render the patient both more difficult to anæsthetise and more liable to cardiac arrhythmias with some anæsthetics (cyclopropane, halothane, trichloroethylene, chloroform).

Every hypnotic, sedative and tranquillising drug has been applied to this purpose and claimed to have special utility, but morphine, morphine derivatives, hyoscine and barbiturates can still fill most needs.

2. **Analgesia,** if there is existing pain, or as a supplement to a weak anæsthetic agent, such as nitrous oxide, later on. Analgesia is not required if there is no existing pain and a potent agent such as ether is to be used. However, if postoperative pain is expected an analgesic may be given at the end of the operation without waiting for the patient to complain of pain. This helps to avoid the postoperative restlessness that occurs if only sedatives were used preoperatively. Subanæsthetic doses of barbiturates actually have an anti-analgesic effect.

3. **Inhibition of the parasympathetic nerve supply** to:

(a) *the lungs* to reduce bronchial secretions, which are liable to be profuse if an irritating drug such as ether is used, and to reduce any tendency to bronchospasm.

(b) *the salivary glands*, to reduce secretion, for saliva may enter the larynx and cause laryngospasm.

(c) *the heart* (vagus) to reduce the likelihood of cardiac arrhythmias.

Atropine or hyoscine are generally used, s.c. or i.v.

The advent of new sedative and analgesic drugs has naturally led to much experimentation with premedication. In addition, with the increasing knowledge of the physiology and pharmacology of anæsthesia and the development of new anæsthetics the disadvantages of the classic morphine and atropine routine, which has been in use for over 80 years, have become more obvious.

There is a tendency nowadays to lighten premedication and to adjust it to the expected needs of the patient and of the procedure to be undertaken. Anæsthetists are no longer content to accept that tranquillity before induction can only be obtained at the cost of slow recovery with vomiting.

The desirability of interfering with parasympathetic responses with atropine has also been questioned. Now that non-irritant gases are available (halothane, cyclopropane), there is no need to block salivary and bronchial secretion unless an irritant inhalation (ether) is to be used. In addition, too dry a mucous membrane in the respiratory tract is disadvantageous in that ciliary activity is diminished, and viscous mucus is more likely to obstruct small bronchi. Vagal block is only needed if an anæsthetic that stimulates the vagus (halothane, cyclopropane) is used, and then atropine is probably best given i.v. at the time of induction (remembering that it transiently stimulates the vagus before blocking it). Cardiac arrhythmias due to sympathetic stimulation may be enhanced in the presence of vagal block, and the claim that atropine antagonises morphine induced respiratory depression is now contested (*10*). The usefulness of atropine and hyoscine as antiemetics, though also disputed, probably remains, especially if morphine has been used in premedication. In one study it was found that when morphine (10 mg) alone was used in premedication 67% of patients vomited after operation. After the addition of atropine (0·6 mg) to the premedication, only 35% of patients vomited although the incidence of nausea and retching remained high (*25*).

Thus, premedication should be chosen in the light of knowledge of the patient's temperament and of the way he reacts to the approaching ordeal, of his disease, of the nature and likely duration of surgery, of his age and medical history and of the anæsthetic agents that it is intended to use.

Though it is usual to give premedication 1 hr before anæsthetic induction, anxious patients (the majority) will be grateful for sedation from the start of the day of surgery; diazepam is useful for this.

Routes of administration. Traditionally, drugs are given s.c., but this is not always essential, and oral premedication can give good results, as well as wasting less of the nurses' time and being pleasanter for the patients, especially children. It is important to restrict the substances taken thus to the minimum amount or the dangers of regurgitation are increased. (N.B. the stomach is never empty and a tablet or two and a

mouthful of water 2 hrs before surgery are not likely to make a significant addition to the volume of gastric juice already there). Caution is needed in the case of children who may demand, and receive from too-kindly nurses, jam, sweets and biscuits as the price of co-operation.

Children provide a special opportunity for the anæsthetist to demonstrate his skill; whether he and the nurses conspire to keep them happy and fearless without premedication, and painlessly inject a barbiturate (and perhaps atropine) i.v. in the anæsthetic room, or whether sedation or narcosis* (oral, s.c., i.m.) is used. Rectal administration is unreliable, for obvious reasons.

The following suggested courses have the sanction of long usage and should only be generally abandoned for the newer techniques at present under trial when these too have been proved by time. The inexperienced and the inept should not readily adopt unfamiliar practices in this, or, indeed, in any other complex situation.

Typical combinations used in premedication include:

morphine		*hyoscine*
or		or
papaveretum	plus	*atropine*
or		or
pethidine		*promethazine*

They are usually administered s.c. 1 hr before the operation (but see above) (for dosages see under individual drugs).

Morphine and its derivatives cause dangerous respiratory depression in cases of raised intracranial pressure, respiratory obstruction or pulmonary insufficiency. In asthmatics, pethidine is preferable to morphine.

Hyoscine can cause confusion in the old.

In a patient who is merely anxious and who is not going to a painful operation, a benzodiazepine (e.g. diazepam) or a barbiturate may be used instead of the above analgesics.

Many drugs used in anæsthetic premedication, for instance morphine and atropine, alter the pupil size and this will affect the utility of the pupils as a gauge of anæsthetic depth. A single dose of less than 1 mg atropine will not precipitate glaucoma.

During surgery. The modern trend is to induce sleep, analgesia and muscular relaxation with separate drugs. This triad can be produced with a single drug in large doses but the consequences of the resulting deep anæsthesia are unpleasant and may be dangerous.

A typical anæsthetic consists of:

1. *Induction:* thiopentone, i.v. (with suxamethonium if intubation is intended).

2. *Maintenance:* (a) with nitrous oxide plus halothane or ether if the patient is to breathe spontaneously.

* Narcosis prior to going to the anæsthetic room is demanding of staff as unconscious patients may not be left alone.

(b) with nitrous oxide plus i.v. analgesic (pethidine) plus tubocurarine if muscle relaxation is needed for abdominal surgery (with tubocurarine, respiration will necessarily have to be provided by the anæsthetist).

If a neuromuscular blocking drug is not used, muscle relaxation can be provided by deep anæsthesia with an inhalation agent or by nerve block with a local anæsthetic, according to circumstances.

In addition, special techniques such as the production of hypotension or hypothermia may be required.

After surgery the anæsthetist ensures that the effects of neuromuscular blocking agents and opiate-induced respiratory depression have either worn off adequately or have been reversed by antagonists; the patient must never be left alone until he is conscious, with protective reflexes present, and his circulation is stable.

"After operation the patient, who has already been submitted to preoperative medication and anæsthesia, may receive antibiotics; analgesics, sedatives and tranquillisers; purgatives and enemas; hypotensive or hypertensive agents; anticoagulants; cardiac stimulants or depressants; steroids, diuretics, and bronchodilators; and parenteral blood-volume expanders. To eliminate unnecessary drugs and reduce the use of others would be an act of clemency besides a welcome economy."*

Relief of pain after surgery presents many problems. Morphine and its derivatives are commonly used, but since they constipate, may cause vomiting, and depress cough and respiration, it will be appreciated that they have disadvantages, for instance after operations on the bowel and chest. Pethidine neither constipates nor suppresses spontaneous cough significantly, although it can be useful, given i.v., to reduce cough from an endotracheal tube. In a substantial study of 14 preparations, the following were found best: levorphanol (2 mg), pethidine (100 mg), oxycodone (10 mg), pentazocine (20 mg), morphine (10, 15 mg) plus cyclizine (50 mg) (Cyclimorph) (*22*). Inhalation of nitrous oxide/oxygen mixture (Entonox) is also effective (see nitrous oxide) (*22*, *25*, *32*, *39*, *45*).

Postoperative **vomiting** is largely preventable by skilled technique in avoiding very deep anæsthesia and prolonged use of agents specially liable to cause it (ether, cyclopropane). Anti-emetics (which see) can be effective.

PHARMACOLOGY OF ANÆSTHETIC DRUGS

All the successful general anæsthetics are given by inhalation or i.v. because these routes allow closest control over blood levels and so of brain levels.

Mode of action

How general anæsthetics produce complete, controllable, reversible loss of consciousness and sensation is unknown. There are no known

* Editorial (1961). *Lancet*, **2**, 589.

properties which are common to every agent and so it is possible that there are several modes of action.

Many are very **fat-soluble** and there is some correlation between this and anæsthetic potency; the more fat-soluble tend to be the more potent anæsthetics, but such a correlation is not invariable. Some anæsthetic agents are not fat-soluble and many fat-soluble substances are not anæsthetic agents. Studies on cell membranes have shown that some anæsthetics protect cells from osmotic effects and increase the area of the cell membrane, probably by electrostatic action. This has been related to the fact that high atmospheric pressures can reverse anæsthesia.

It is likely that effects on cation movement (Na, K), colloids, cell oxidative processes and utilisation of energy derived from oxidation are concerned in producing anæsthesia and it is unlikely that, when eventually explained, anæsthetic action will be found simple.

Similar remarks apply to the sites of action of general anæsthetics in the brain.

Pharmacokinetics of inhalation anæsthetics (*4–9*) (volatile liquids: gases)

The level of anæsthesia is correlated with the amount of anæsthetic drug in the brain and this is dependent on the development of a series of tension gradients from the high partial pressure delivered to the alveoli and decreasing through the blood to the brain and other tissues. These gradients are dependent on the physical properties of the anæsthetic and the tissues, as well as on physiological functions (ventilation, blood flow).

"Clinical anæsthetists have administered millions of anæsthetics during more than a century with little precise information of the uptake, distribution and elimination of inhalational and non-volatile anæsthetic agents. Considering how serious is the handicap of not knowing these fundamental and essential facts about the drugs they have used so often, the record of success and safety in clinical anæsthesia is an extraordinary accomplishment indeed. It can in some measure be attributed to the accumulated experience and successful teaching of a highly developed sense of intuition from generation to generation of anæsthetists. It can often be attributed in part to the ability to learn by error after observing patients come uncomfortably close to injury and even to death" (*7*).

It is not appropriate to discuss the detailed pharmacokinetics of anæsthetics here as they are chiefly important to professional anæsthetists, but a few points of general interest are mentioned below.

An anæsthetic that is highly soluble in blood (ether, methoxyflurane) will, if given at a steady concentration, provide a slow induction. This is because the blood acts as a reservoir for the drug and it does not enter the brain rapidly until the blood has become saturated. A rapid induction can be obtained by increasing the concentration of drug inhaled initially and by hyperventilating the patient. This is difficult to do with ether

because it is so irritant, and dangerous to do with halothane because it depresses the cardiovascular system.

Agents that are less soluble in blood (nitrous oxide, cyclopropane) provide a rapid induction because the blood is quickly saturated, and equilibrates with the inspired concentration, and so is available to pass into the brain sooner.

Solubility of halothane is intermediate between nitrous oxide and ether, and so halothane can be used for induction.

During induction of anæsthesia the blood is taking up anæsthetic gas selectively and the loss of volume in the alveoli leads to a flow of gas into the lungs which is independent of respiratory activity. When the anæsthetic is withdrawn the reverse occurs and there is a rapid diffusion of gas from the blood into the alveoli which, in the case of nitrous oxide, can account for as much as 10% of the expired volume and so can significantly lower the alveolar partial pressure of oxygen. Thus mild clinical anoxia occurs, and it may last for as long as 10 mins, and, though harmless to most, it may be a factor in cardiac arrest in patients with reduced pulmonary and cardiac reserve. Oxygen should therefore be given to such patients in the early postanæsthetic period.

This phenomenon, *diffusion anoxia*, occurs with all gaseous anæsthetics, but is most prominent with gases that are relatively insoluble in blood, for they will diffuse out most rapidly when the drug is no longer inhaled. A combination of nitrous oxide and cyclopropane is therefore specially potent in this respect. Highly blood-soluble agents will diffuse out more slowly, so that recovery will be slower just as induction is slower, and with them diffusion anoxia is insignificant.

Pharmacokinetics of intravenous anæsthetics (*13*)

While intravenous anæsthetics allow an extremely rapid induction because the blood concentration can be raised rapidly, recovery is slower than with inhalation anæsthetics because there is no channel of elimination that can compete with the lungs for speed. The metabolic breakdown of drugs does not occur fast enough for really quick recovery, and reliance for rapid recovery on redistribution of the drug within the body (thiopentone) is only satisfactory for brief operations. With prolonged anæsthesia recovery must be slower, for the body is storing more of the drug, and it will depend on the mass of the storage tissues, the blood flow through them and the rate of metabolism and excretion of the drug.

Therefore substances absorbed and excreted through the lungs offer the best prospect of accurate control, even in the presence of pulmonary disease, except perhaps severe emphysema. Elimination of inhaled anæsthetics can be hastened by inducing hyperventilation. There is no quick method of eliminating drugs whose action is normally terminated by metabolism or by redistribution. For the present it is usual to attempt

to approach the ideal by using a combination of drugs in such a way that the disadvantages of each are less prominent.

The requirements of the "ideal" anæsthetic gas* are strict and it is not surprising that they have not yet been met by any of the drugs described below.

The patient wants a fast and pleasant induction with a non-irritant gas with no unpleasant smell. He wants to recover comfortably too, without serious delayed after-effects, e.g. liver damage.

The surgeon's requirements are that the gas should be non-explosive so that he can use diathermy, should not increase capillary bleeding and should induce complete muscular relaxation for abdominal surgery.

The anæsthetist wants a gas that can be administered with simple apparatus and that has a wide safety margin (so does the patient), to alter normal physiology as little as possible and to be potent enough to allow adequate concentrations of oxygen to be administered with it. It should be absorbed and excreted unchanged and rapidly to provide accurate control of induction, depth of anæsthesia and recovery.

The manufacturer would be pleased if the gas could be made and purified easily and cheaply and if it was unaffected by conditions and duration of storage. If he also had a monopoly and complete freedom to fix the price he would be jubilant.

Comparisons of anæsthetics under routine clinical conditions are difficult to arrange, but they can be done (*11*, *12*).

Testing a new general anæsthetic on man presents a specially difficult problem. Now that existing techniques of anæsthesia are so safe it is hard to expect a patient undergoing the anxiety of approaching surgery to consent to an experimental trial of a new drug, and, to administer the drug, in however cautious a fashion, without the patient's informed assent is certainly immoral and assuredly illegal. In at least one country (U.S.A.) the problem has been solved by paying volunteers to undergo careful administration of graduated doses in a laboratory, with extensive monitoring of cardiovascular, respiratory and central nervous functions.

Comparison of the potency of inhalation drugs may be done by measuring the minimum alveolar concentration (MAC) necessary to prevent response to a surgical skin incision. Various other techniques employing electroencephalography can be used. Results, correlated with measures of cardiovascular and respiratory function help in the overall evaluation of the drug (*17*).

INHALATION AGENTS

Ethyl ether (1842) is relatively non-toxic and is justly reputed to be a safe drug even in relatively unskilled hands. This is because the blood level which stops respiration is less than that which stops the heart, so that there is greater opportunity to retrieve the situation. It is easier to provide artificial respiration than it is to start an arrested heart.

* SEEVERS, M. H., and WATERS, R. M. (1938). *Physiol. Rev.*, 18, 447.

"Unfortunately, with the advance of modern methods, ether has come to be regarded as 'old-fashioned', and an anæsthetist administering it as 'out-of-date'. As a result, too many anæsthetists have for too long tried to avoid its use for reasons entirely unconnected with the merits and demerits of the drug. . . . Experience has shown that, in the long run, the simplest methods are the best."*

However, ether has disadvantages. The pungent smell is objectionable and induction of anæsthesia with it alone is slow and therefore unpleasant for the patient. Irritation of the respiratory tract leads to coughing, laryngeal spasm and increased mucus secretion. Ether also causes vasodilatation which, in the third plane of the third stage, may be great enough to cause severe fall in blood pressure. It increases capillary bleeding.

A vigorous sympathetic autonomic response normally occurs during ether anæsthesia and counteracts the circulatory effects. If this response fails then circulatory collapse may occur, obviously especially in patients taking a β-adrenoceptor blocker. The hyperglycæmia that occurs is chiefly due to release of adrenaline. Ether interferes with the homeostatic mechanisms in peripheral circulatory failure more than does cyclopropane.

If ether anæsthesia is deep and prolonged, recovery is slow and post-operative vomiting occurs, largely due to swallowing saliva containing ether. Beside these disadvantages must be placed the very practical advantage that, for a given degree of competence, anæsthetic deaths with simple techniques using ether are less common than with more complicated techniques employing other drugs.

Liquid ether boils at 35°C and so may prove inconvenient in hot climates. The vapour is explosive, and as it is heavier than air a dangerous layer may accumulate near the floor of the operating theatre.

When open drop administration is used it is important to avoid getting ether into the eyes or on to the skin because it is irritant. The same applies to chloroform.

A rare complication of ether anæsthesia is "ether convulsions". They are thought to be the result of a combination of circumstances, and are most common in children. They are promoted by deep anæsthesia, sepsis, atropine premedication, fever or overheating, and carbon dioxide retention. They are dangerous and can be largely avoided. Treatment is by cooling and i.v. barbiturate for the convulsions; oxygen and artificial respiration by positive pressure may be needed after giving the barbiturate because convulsions are followed by respiratory depression, which is increased by the treatment.

Ether decomposes, forming toxic aldehydes and peroxides, unless protected from light and heat. Addition of carbon dioxide and copper delay decomposition. Very old ether should be suspected and discarded if possible.

Vinyl ether (1930) (Vinesthene) **and ethyl chloride** (1844) are potent, short acting and can be used for quick induction. Ethyl chloride boils at 12°C and so has to be kept under pressure if it is to be liquid at room temperature; it is somewhat explosive. Because of its extreme volatility it may be used for local anæsthesia, for which purpose it is sprayed on the skin, and, in vaporising, removes heat, thus paralysing sensory nerve endings by cooling.

* GOULD, R. B. (1954). In *Modern Practice in Anæsthesia.* Ed. F. T. Evans. London: Butterworth.

Nitrous oxide (1844) (*4*) is an entirely safe* anæsthetic gas *provided that it is used correctly*. Untoward effects are due to anoxia resulting from improper use. It is comparatively impotent and cannot alone maintain full surgical anæsthesia. For this reason it is commonly used with analgesics or as a vehicle for other inhalants such as ether. It is used alone for very brief operations (e.g. dental). Induction and recovery are rapid. It is not explosive, but supports combustion.

Nitrous oxide, inhaled as a 50% mixture with oxygen, is used as a self-administered analgesic, chiefly in obstetrics, but also in postoperative pain and myocardial infarction; it is also useful to take to the site of accidents (44). Premixed cylinders (Entonox) are cheaper to produce than are machines that mix the gases from separate cylinders, but they can give trouble in one respect; if cooled to −8°C the gases liquefy and partially separate so that at first a high concentration of oxygen is delivered, and pain is not relieved; this is followed by delivery of a dangerously low concentration of oxygen. Apart from avoiding cooling, this can be minimised by keeping and using cylinders on their side, not upright; by inverting the cylinder three times before use; by warming it, and by avoiding needlessly high gas delivery rates.

Chloroform (1847) was the only non-explosive potent anæsthetic until the introduction of trichloroethylene in 1934. But owing to cardiac depression and hepatic toxicity, which may be delayed for several days after anæsthesia, it is now little used. However, like so many drugs labelled as dangerous, its undesirable properties can be minimised by skill and familiarity, so that it can compare favourably with a "safer" drug handled badly. In domiciliary practice the safer inhalation substitutes for chloroform are at a disadvantage for they either require complicated apparatus or are less potent and more unpleasant. Chloroform is easy to administer, very potent and not extraordinarily unpleasant to inhale, so that for use in out-of-the-way places it is convenient. It boils at 61°C and is not explosive.

Chloroform sensitises the heart to adrenaline so that if there is a violent second stage of anæsthesia the accompanying endogenous secretion of adrenaline may cause fatal ventricular fibrillation. Chloroform vapour is heavier than air, more so than ether, and when given by dropping on an open mask there should be no padding between the mask and face, as too high a concentration of vapour may occur in a mask thus sealed.

Chloroform decomposes if exposed to light, air and alkalis, and any liquid remaining in an anæsthetic machine after a session should be discarded.

Cyclopropane (1929) is a potent, explosive, non-irritant gas. It is preferable to halothane where a quick induction is desired and it is particularly desired to avoid hypotension. It sensitises the heart to adrenaline and this, together with the carbon dioxide retention which results from respiratory depression, promotes cardiac arrhythmias. It tends to cause laryngospasm. When cyclopropane is withdrawn there is sometimes a sudden drop in blood pressure, "cyclopropane shock", which is said to be due to the rapid fall in carbon dioxide in the blood.

Trichloroethylene (1934) is similar to chloroform but less toxic. It is not used for deep anæsthesia because it is liable to cause tachypnœa and

* Bone marrow depression occurs if it is given for very many hours or for days but such use is never necessary, though it has been tried in leukæmia.

respiratory irregularity or arrest. Though it can be used to supplement nitrous oxide in surgery, it is now almost confined to obstetrics where, in special vaporisers that prevent overdose, it can be self-administered.

Trichloroethylene should not be used in carbon dioxide absorption systems for it decomposes in contact with soda lime to form toxic products which may be the cause of cranial nerve damage (especially 5th nerve). It also decomposes if exposed to light and air. It is non-inflammable and is non-irritant in anæsthetic concentrations.

Halothane (Fluothane, 1956) is a liquid, boiling at 50°C. It is an extremely convenient anæsthetic, being potent, and non-irritant. Induction is reasonably quick, but less so than with cyclopropane. It is non-explosive. However, it has three important disadvantages; it causes hypotension, respiratory depression (rapid, shallow breathing) and cardiac arrhythmias. Despite these and its expense, the good qualities of halothane have gained it a large place in routine anæsthetic practice. Halothane, especially when administered repeatedly over short periods, has been incriminated as a cause of allergic postoperative jaundice, e.g. cystoscopy followed by surgery.

The present majority opinion appears to be that multiple halothane anæsthetics should not be given within a short period without careful study of previous postoperative course, especially for unexplained fever lasting longer than 5 days. The controversy provides a useful intellectual exercise in evaluation of evidence and opinion; it can be followed from refs (*36–38*), also correspondence columns following the articles. The difficulty is that, lacking any clear diagnostic feature, it is impossible to be certain in any one case that the jaundice is not due to another factor, e.g. pre-existing disease, virus infection.

Up to 25% of halothane is metabolised in the liver and it induces hepatic microsomal enzymes; indeed anæsthetists using it may be in a state of partial enzyme induction.

Methoxyflurane (Penthrane, 1959) is a liquid, boiling at 104°C. It is potent, non-irritant and non-explosive. It is more highly lipid soluble than halothane so that induction and recovery are slower than with halothane. Otherwise it is somewhat similar. As well as its use as a general anæsthetic it is used for self-administration analgesia in obstetrics. It can damage the kidney.

INTRAVENOUS ANÆSTHETICS

Thiopentone sodium is the most widely used intravenous anæsthetic It is potent and quick acting and is especially suited to providing a pleasant induction. Anæsthesia may be induced in a healthy adult by injecting i.v. 6 to 10 ml of a 2·5% solution (i.e. 150 to 250 mg) in 30 sec (a 5% solution is prone to cause venous thrombosis) and waiting at least 1 min before injecting more. In those with a slow circulation time (the old, the diseased) injection should be slower. Laryngospasm is comparatively frequent. The great rapidity with which a patient may pass through the stages of anæsthesia means that the first obvious sign of overdose may be apnœa. Great care is therefore necessary when using thiopentone. Anæsthesia may be continued by nitrous oxide, supplemented if necessary by pethidine i.v. or by another inhalation agent, e.g. ether, for thiopentone does not prevent reflex response to painful stimuli and it is therefore unsatisfactory by itself for painful

operations, struggling and laryngospasm resulting from any attempt to use it thus. Other disadvantages are respiratory depression which is relatively greater for a given degree of muscular relaxation than is the case with inhalants, and regurgitation of gastric contents, which may be silent and so unnoticed. It is dangerous in oligæmic patients because it abolishes compensatory vasoconstriction (see barbiturate poisoning) and it may cause dangerous hypotension in the elderly or the arteriosclerotic.

Thiopentone is **metabolised** slowly by the liver and other body tissues. It quickly enters the brain from the blood. The comparatively rapid recovery from a single dose is due to **redistribution** of the drug into the well perfused viscera and lean tissues of the body. Fat is not as important an element in this redistribution as was previously supposed, for, though thiopentone is highly fat soluble, fat has a low blood flow compared with the other tissues (*13*). Thus rapid recovery may follow several repeated doses of thiopentone until the time comes when the tissues can store no more drug. A further dose then produces prolonged anæsthesia, as recovery now depends on destruction of the drug and not on redistribution. It is inadvisable to exceed a total of 1·0 g thiopentone in any operation.

Injection other than into the vein is dangerous. If it is given subcutaneously the skin may slough. Given into or around a nerve (usually the median), permanent palsy may follow. To dilute the irritant solution, and to induce local hyperæmia to hasten absorption, 0·5% procaine (without adrenaline) may be injected into the site. In the case of nerve injury it may be desirable to incise the area and try to wash out the drug. If thiopentone is accidentally injected into an artery, thrombosis occurs and amputation may even become necessary. Treatment of this mishap is to heparinise the patient immediately and perhaps to block the sympathetic supply to the limb, e.g. stellate ganglion block. Vasodilator drugs are probably not helpful. The arm should be kept cold to reduce oxygen requirements. Surgical removal of the clot may be tried after about 6 hrs if there is no improvement in the physical signs. Heparin may be continued, or oral anticoagulant therapy begun, with allowance for surgery, until it is sure that all is well, which will probably mean about a week. Serious consequences from these mishaps are unlikely if 2·5% solution rather than 5% solution is used, and damage to arteries or nerves is less likely if the lateral border of the forearm and the back of the hand are chosen for injection and the vessel is palpated (without a tourniquet on the arm) before inserting the needle.

Methohexitone is similar, but provides specially quick recovery and so is suited for use in outpatient departments.

There are numerous other i.v. agents. None has been proved superior to thiopentone. They include: hexobarbitone sodium, thialbarbitone, thiamylal, buthalitone, alphaxolone plus alphadolone (Althesin) (steroid) and propanidid (Epontol) a non-barbiturate that can be used in porphyria.

Some special techniques for:

1. *Single-handed operator/anæsthetist:* this situation should be avoided wherever possible for general anæsthesia; but it is sometimes unavoidable.
2. *Repeated small procedures*, e.g. burns dressings.

3. "*Minor*" *procedures*, e.g. cardiac catheterisation, neuroradiology, endoscopy, cardioversion (*19*).

These situations require analgesia of varying degrees and sedation, without depression of respiration, so that the operator is not distracted by the need to guard the patient's airway.

Available techniques include:

(a) **Ketamine** (Ketalar) (*21*) is related to phencyclidine (a hallucinogen); it induces what is sometimes called "dissociative anæsthesia", i.e. profound analgesia with light sleep (the eyes may remain open). There is increased muscle tone; the blood pressure commonly rises; respiratory depression can occur. Given i.v. ketamine anæsthetises in about 30 secs and i.m. in about 3 mins. Anaesthesia lasts about 5 to 20 mins. Unpleasant dreams are characteristic and recovery is slow and may be accompanied by "emergence delirium". Both these unpleasantnesses can be reduced or eliminated by proper premedication and management.

(b) **Combinations of a neuroleptic** (an antipsychotic drug which also increases muscle tone) **with a potent narcotic analgesic** are used to induce "neuroleptanalgesia" during which the patient may remain cooperative. Injected slowly i.v. they induce sedation and analgesia in a few minutes. Respiratory depression occurs. Combinations include Thalamonal (droperidol, a butyrophenone, plus fentanyl, related to pethidine); phenoperidine is an alternative to fentanyl.

(c) **Diazepam,** i.v. used in conjunction with a local anæsthetic, e.g. for removal of impacted wisdom teeth, or without local anæsthetic where severe pain is not expected. Amnesia is characteristic; respiratory depression is not usually important. The patient remains cooperative. Dose: by slow i.v. injection 10–40 mg.

(d) Rectal thiopentone, bromethol or paraldehyde.

None of the above is completely safe and respiratory depression and apnœa can occur. Laryngeal reflexes are not spared and inhalation of oral secretions or dental debris can occur.

NEUROMUSCULAR BLOCKING DRUGS (*24*)

These substances first attracted scientific notice because of their use as arrow poisons by the natives of South America, who use the most famous of all, curare. Specimens of crude curare had been reaching Europe before 1811 when Sir Benjamin Brodie smeared "woorara paste" on wounds of guinea-pigs and noted that death could be delayed by inflating the lungs through a tube introduced into the trachea. He did not attempt to avoid death altogether, but did suggest that the drug might be of use in tetanus. A year later the traveller Charles Waterton visited South America to seek "the deadly wourali poison".* He

* WATERTON, C. *Wanderings in South America.* Revised edition 1828. Reprinted by Hutchinson, London, 1906. Numerous other editions.

obtained a specimen and tried it on a sloth, "from the time the poison began to operate, you would have conjectured that sleep was overpowering it and you would have exclaimed, 'Pressitque jacentem, dulcis et alta quies, placidæque simillima morti'." He also used it on an ox "whose flesh was very sweet and savoury at dinner". Having noted that "it totally destroys all tension in the muscles" Waterton turned to experiment with reputed antidotes on a fowl. He held the bird up to its mouth in water, poured sugar-cane juice and rum down its throat and filled its mouth with salt, but despite, or perhaps because of, this treatment, the bird died. He discussed the most promising antidote but did not then try it: "It is supposed by some, that wind introduced into the lungs by means of a small pair of bellows, would revive the poisoned patient, provided the operation be continued for a sufficient length of time. It may be so; but this is a difficult and a tedious mode of cure."

On his return to England he experimented on a donkey which "died apparently" in 10 mins. He incised the windpipe and inflated the lungs with bellows for 2 hrs which "saved the ass from final dissolution". She recovered, was named Wouralia, and lived in idleness at the expense of a sentimental peer for a further 25 years as reparation.

Despite attempts to use curare for a variety of diseases including epilepsy, chorea and rabies, the lack of pure and accurately standardised preparations as well as the absence of convenient routine techniques of artificial respiration if overdose occurred, prevented it from gaining any firm place in medical practice until 1942, when these difficulties were removed.

Drugs acting at the myoneural junction produce complete paralysis of all voluntary muscle so that movement is impossible and artificial respiration is needed. Attempts to achieve selective relaxation, sparing respiration, in the treatment of convulsions and disorders of muscle tone, have met with little success as the dose level is critical in the few patients in whom this can be achieved.

The necessity for artificial respiration no longer deters anæsthetists who are now quite accustomed to taking over respiration from the patient as a routine. It is less easy to decide whether a patient is unconscious if he is paralysed (*46*).

Neuromuscular transmission and its modification by drugs

When an impulse passes down a motor nerve to voluntary muscle it causes release of acetylcholine at the nerve endings. This modifies the condition of the membrane of the motor end-place, a specialised area on the muscle fibre. In its resting state the inside of the membrane has a negative and the outside a positive electrical charge and is said to be polarised. The acetylcholine causes an increase in the permeability of this membrane to some ions so that depolarisation occurs, and this triggers the action potential which is associated with contraction of the muscle.

Neuromuscular blocking agents used in clinical practice interfere with

the process described above. They do not affect either muscle or nerve, nor do they interfere with acetylcholine release.

However, substances which prevent the release of acetylcholine at nerve endings exist (procaine in large doses, botulinus toxin and some analogues of choline).

There are two principal mechanisms by which drugs used clinically interfere with neuromuscular transmission:

By competition (tubocurarine, gallamine, pancuronium). It would appear that these drugs can combine with, and block, the receptors on the motor end-plate which are the normal site of action of acetylcholine. Tubocurarine and gallamine "compete" with acetylcholine for these receptors. They do not cause depolarisation themselves but they protect the end-plate from depolarisation by acetylcholine. The result is a flaccid paralysis.

Reversal of this type of neuromuscular block can be achieved with anticholinesterase drugs, such as neostigmine, which prevent the destruction of acetylcholine released at nerve endings and so allow the concentration to build up, thus reducing the competitive effect of a given concentration of blocking agent.

By depolarisation (suxamethonium). Such drugs imitate the action of acetylcholine at the motor end-place and at their first application voluntary muscle contracts, but, as they are not destroyed immediately like acetylcholine, the depolarisation persists. It might be expected that this prolonged depolarisation would result in muscles remaining contracted, but this is not so (except in chickens), probably because the drug also causes a decrease in excitability of the area around the end-plate; although a standing depolarisation of the end-plate exists, it is not strong enough to send the muscle into contraction. The cause of neuromuscular block by these drugs may therefore be the reduction in excitability of the muscle rather than the depolarisation, although these two effects may be interdependent.

Anticholinesterase drugs in huge doses can produce neuromuscular block by depolarisation, but cannot be used clinically for this purpose because of their effect on the central and autonomic nervous systems. Anticholinesterases are thus not only useless as antidotes to depolarising drugs but may even increase the paralysis. However, with prolonged administration a depolarisation block changes to a competitive block (dual block). Because of the uncertainty of this situation a competitive blocking agent is preferred for anything other than very short procedures.

Neuromuscular blocking agents acting by competition

Tubocurarine* is an alkaloid which produces neuromuscular block by competition with acetylcholine. The peripheral site of action of curare was demonstrated by Claude Bernard in 1850 in a famous series of simple

* Curare is the crude plant preparation. The word is often used loosely when one of the pure alkaloids is, in fact, intended.

experiments on frogs. Its chief use is to provide muscle relaxation during surgery without incurring the disadvantages of deep anæsthesia. Its introduction into surgery made it desirable to decide once and for all whether the drug altered consciousness. Doubts were resolved in a single experiment.* A normal subject was slowly curarised after arranging a detailed and complicated system of communication. Twelve minutes after beginning the slow infusion of curare, the subject, having artificial respiration, could move only his head. He indicated that the experience was not unpleasant, that he was mentally clear and did not want an endotracheal tube inserted. After 22 mins, communication was possible only by slight movement of the left eyebrow and after 35 mins paralysis was complete and direct communication lost. An airway was inserted. The subject's eyelids were then lifted for him and the resulting inhibition of alpha rhythm of the electroencephalogram suggested that vision and consciousness were normal. After recovery, aided by neostigmine, the subject reported that he had been mentally "clear as a bell" throughout, and confirmed this by recalling what he had heard and seen. The insertion of the endotracheal airway had caused only minor discomfort, perhaps because of the prevention of reflex muscle spasm. During artificial respiration he had "felt that (he) would give anything to be able to take one deep breath" despite adequate oxygenation. In another study curare was excluded from one arm by an inflated cuff so that the subject could make finger signals.‡

It is therefore essential to ensure that paralysed patients do not regain consciousness unnoticed during surgery (*46*). That this is not merely a theoretical risk is shown by the occasion when an anæsthetist, visiting his patient the day after the operation, was horrified when she sympathetically remarked, "I had no idea you doctors were so badly paid". He had discussed the inadequacy of his salary with a colleague during the operation. The patient had felt her bowels being manipulated but no pain. However, pain can occur on such occasions, and both anæsthetists and patients will wish to avoid them. Consciousness is most likely when nitrous oxide and oxygen are being used with neuromuscular block, and suggestive signs include bronchospasm, sweating and response of the pupil to light, as well as movement.

In addition to its neuromuscular blocking effect tubocurarine blocks autonomic ganglia and causes tissue histamine to be released. Both these effects may cause a transient drop in blood pressure and the latter may induce bronchospasm.

Curare is **insignificantly absorbed from the alimentary tract,** a fact known to the South American Indians who use it to procure food, as well as in war.

After an intravenous injection the action is maximal in 4 mins and lasts about 30 mins.

* SMITH, S. M., *et al.* (1947). *Anesthesiology*, **8**, 1.
† CAMPBELL, E. J. M., *et al.* (1969). *Clin. Sci.*, **36**, 323.

Tubocurarine is partly **excreted** unchanged in the urine and partly metabolised. But the brief action of single doses is partly due to redistribution of the drug in the body rather than to its elimination. It follows therefore that repeated use over a few days may result in prolongation of action of the later doses.

Tubocurarine is well tolerated at all ages, except perhaps in neonates, though there is enough individual variation for some anæsthesists to advise a small initial test dose routinely.

Potentiation occurs with ether and with chlorpromazine.

Some **antibiotics** (neomycin, streptomycin, polymyxin) can cause neuromuscular block and synergise with competitive blocking agents. But this is only clinically important if they are used in situations where overdose is easy, e.g. when they are tipped into the pleural or peritoneal cavities at operation.

Apart from occasional prolongation of action for unknown reasons, after-effects of tubocurarine are slight, although diplopia may rarely persist for a few days.

The action of tubocurarine is **antagonised** by anticholinesterase drugs. Neostigmine (1·0 to 2·5 mg of the methylsulphate) is usually given intravenously, preceded if possible by atropine sulphate (1 mg) to prevent the parasympathetic autonomic effects of the neostigmine. If the pulse rate slows unduly after the neostigmine more atropine may be given. The patient may relapse into paralysis again and so must be carefully watched. Too much neostigmine can cause neuromuscular block by depolarisation, which can cause confusion unless there have been some signs of recovery before neostigmine is given.

It is theoretically undesirable to give atropine and neostigmine in full doses i.v. simultaneously, for atropine, before blocking the vagus nerve, causes, by a central action, transient vagal stimulation (except in negroes). If this is added to the effect of neostigmine, undue cardiac slowing may result. Atropine is therefore best given a few minutes before the neostigmine.

The best course is to allow the effect of the tubocurarine to wear off whilst the patient is still supervised by the anæsthetist.

Dose: Tubocurarine chloride, 15 to 20 mg, i.v. (or i.m.).

Whenever tubocurarine is used artificial respiration will be needed; it is provided by inflating the lungs with appropriate gases (intermittent positive-pressure respiration, I.P.P.R.).

Gallamine (Flaxedil) and pancuronium (Pavulon) are synthetic alternatives which release histamine less.

Neuromuscular blocking agents acting by depolarisation

Suxamethonium (succinylcholine, Scoline) paralysis is usually preceded by muscular fasciculation, and this is probably the cause of the muscle pain lasting 1 to 3 days that is a common sequence of its use and which can simulate meningeal irritation. The pain can be largely prevented by preceding the suxamethonium with a small dose of a competitive blocking agent. Suxamethonium acts for less than 5 mins and is particularly useful for brief procedures such as tracheal intubation or electric convulsion therapy. Suxamethonium is destroyed by plasma pseudocholinesterase and so its persistence in the body is increased by neostigmine

which inactivates that enzyme, and in patients with hepatic disease or severe malnutrition whose plasma enzyme levels may be lower than normal. Procaine also is destroyed by plasma pseudo-cholinesterase and so, by competing with suxamethonium for the enzyme, may prolong its action and vice versa. In addition there are individuals (about 1 in 3000 of the population) with hereditary defects in amount or kind of enzyme, who cannot destroy the drug as rapidly as normals.* Paralysis then lasts for hours; there is no effective way of restoring the enzyme or of eliminating the drug. Treatment consists in calmly applying intermittent positive pressure respiration until the patient recovers.

Repeated injections of suxamethonium can cause bradycardia, extrasystoles, other cardiac irregularities and even ventricular arrest. These are probably due to stimulation of cholinoceptors in the heart and are prevented by 1·0 mg atropine i.v. It stimulates the pregnant uterus. The i.v. dose is 10 to 50 mg of the chloride. Continuous i.v. infusions (2 to 3 mg/min) or intermittent doses can be used for more prolonged and readily variable relaxation, but dual block (see above) may occur.

Uses of Neuromuscular Blocking Agents

Drugs acting by competition may antagonise those acting by depolarisation and it would seem better not to use them simultaneously. A dose of suxamethonium for tracheal intubation followed by tubocurarine some minutes later, after its action has worn off, would not, of course, be objectionable.

Neuromuscular blocking agents should only be employed by those who have received special training in their use:

In surgery they are used to provide muscular relaxation.

In convulsions (e.g. electric convulsion therapy) they are used to prevent injury due to the violence of the fit. In status epilepticus or convulsant drug poisoning, neuromuscular blocking agents with artificial respiration have been used. They are also used in tetanus (which see).

In diagnosis of myasthenia gravis the characteristically increased sensitivity to curare and the decreased sensitivity to suxamethonium have been used as indicators. It is a dangerous technique only to be employed in otherwise undiagnosable cases with apparatus for artificial respiration at hand.

Centrally-acting Muscle Relaxants

Mephenesin (Myanesin) was accidentally found to paralyse voluntary movements in animals, without depressing respiration. Plainly such a drug might be useful for relaxation in surgery and it was tried but found ineffective. Now that the technical difficulties of neuromuscular block with controlled respiration have been largely overcome, the attractions of preserving spontaneous respiration are not so great as they were.

* When cases are discovered the family should be investigated and abnormal individuals warned.

Also, any drug that, by a central action, induces full surgical relaxation is unlikely to be without any depressant effect on respiration, and controlled respiration is preferable to depressed spontaneous respiration.

But there is a need for drugs that reduce spasm of the voluntary muscles without impairing voluntary movement. Such drugs would be useful in *rheumatism* and *neurological spastic states.*

Unfortunately all the drugs produced are either ineffective or have too powerful a sedative effect when used in adequate dose. Indeed all sedative-hypnotics, including barbiturates, can be classed as centrally-acting muscle relaxants.

Available drugs depress all synapses on motor paths in the spinal cord, thus, by addition, depressing polysynaptic more than monosynaptic paths; spasticity is mediated by polysynaptic paths.

The drugs most likely to be useful are orphenadrine (Disipal), and diazepam (Valium); also in this class are carisoprodol (Carisoma), chlormezanone (Trancopal), chlorzoxazone (Paraflex), methocarbamol (Robaxin), styramate (Sinaxar). Chlorpromazine, though useful in tetanus, does not share this polysynaptic effect.

The realisation that muscle tone depends on both gamma and alpha motor nerve activity and that drugs may preferentially depress either system, opens the possibility that more selective muscle relaxant drugs may be produced, e.g. baclofen (Lioresal) a derivative of gamma-aminobutyric acid, an inhibitory transmitter in the CNS.

LOCAL ANÆSTHETICS (*33, 35, 47*)

Cocaine was the first local anæsthetic discovered. It was isolated in 1860 and suggested as a local anæsthetic for clinical use in 1879. Nothing however was done until 1884 when Dr. Sigmund Freud in Vienna was reinvestigating the alkaloid, and invited Dr. Carl Koller to join him. The latter had long been interested in the problem of local anæsthesia in the eye, for general anæsthesia has disadvantages in ophthalmology. On observing the numbness of the mouth caused by taking cocaine orally he realised that this was a local anæsthetic effect. He tried cocaine on animals' eyes and introduced it into clinical ophthalmological practice,* whilst Freud was on holiday. Freud had already thought of this use and discussed it, but, appreciating that sex was of greater importance than surgery, he had gone off to see his fiancée. The use of cocaine spread rapidly and it was seen being used to block nerve trunks. Chemists then began to search for less toxic substitutes, with the result that procaine was introduced in 1905.

Desired properties. Innumerable compounds have local anæsthetic properties, but comparatively few are suitable for clinical use. Suitable substances must be water-soluble, sterilizable by heat, non-irritant, have a rapid onset of effect, a duration of action suitable for the operation to be performed, be non-toxic when absorbed into the circulation, and leave no local after-effects.

* KOLLER, C. (1928). *J. Amer. med. Ass.*, **90**, 1742.

Mode of action. Local anæsthetics act on all nervous tissue to prevent the nerve impulse from arising and from passing. They do this by preventing the sodium influx through the cell membrane, which is necessary for generation of the action potential. The mechanism achieving this may be an interference with calcium binding on the membrane. They paralyse afferent nerve endings, sensory and motor nerve trunks and the central nervous system, although they may stimulate the latter first.

The fibres in nerve trunks are affected in order of size, the smallest (sympathetic, sensory) first, probably because they have a proportionately high surface area, and then the larger (motor) fibres.

Absorption from mucous membranes varies according to the compound. Those which are well absorbed are used as surface anæsthetics (cocaine, lignocaine, prilocaine, etc.). Procaine is not significantly absorbed and is useless for this purpose. Absorption of topically applied local anæsthetic can be extremely rapid and give plasma concentrations comparable to those obtained by injection. This has led to deaths from overdosage, especially via the urethra.

Prolongation of action by vasoconstrictors. The effect of a local anæsthetic is terminated by its removal from the site of application. Thus anything that delays its absorption into the circulation will prolong its local action and can reduce its systemic toxicity (where large volumes are used). Adrenaline (1 : 250,000) is commonly used (dentists use 1 : 80,000) and doubles the duration (e.g. from 1 to 2 hrs); noradrenaline is less effective locally. A vasoconstrictor should not be used for nerve block of an extremity (finger, toe, nose, penis). For obvious anatomical reasons, the whole blood supply may be cut off by intense vasoconstriction so that the organ may be damaged or even lost.

Enough adrenaline can be absorbed to affect the heart and circulation and, whilst this does not matter in the healthy, it can be dangerous in cardiovascular disease and with general anæsthetics that sensitise the heart to catecholamines (chloroform, halothane, cyclopropane). An alternative vasoconstrictor is felypressin (synthetic vasopressin) which, *in the concentrations used*, does not affect the heart rate or blood pressure and may be preferable in patients with cardiovascular disease. There is no significant added hazard to the use of adrenaline in patients taking an MAOI, except perhaps where there is cardiovascular disease, but tricyclics can potentiate adrenaline dangerously.

Fate. Most of these drugs are destroyed by enzymes in the blood and liver. The plasma half-life of procaine is about 0·7 min in normals, 1·5 mins in newborn and 2·3 mins in liver disease.

Administration. Most local anæsthetics are used in the form of the acid salts, as these are stable. The acid salt must dissociate in the tissue to liberate the free base to produce anæsthesia. This dissociation is delayed in abnormally acid, e.g. inflamed, tissues. The risk of spreading infection also makes local anæsthesia undesirable in infected areas.

Local anæsthetics are usually effective within 5 mins of application

for 1 to 2 hrs. Their duration may be doubled by adding a vasoconstrictor.

Antagonists. Procaine and amethocaine, which are derivatives of p-aminobenzoic acid, inhibit sulphonamide antibacterial activity. This probably has no significant effect in antagonising sulphonamides throughout the body, but with wounds, or when local anæsthesia is being used for lumbar puncture or other exploration in sulphonamide-treated patients, local sulphonamide antagonism followed by infection is a theoretical risk. Lignocaine and prilocaine do not antagonise sulphonamides.

Other effects. Local anæsthetics also have the following clinically important effects in varying degree:

1. Stimulation of the central nervous system, which may show itself by anxiety, restlessness, tremors and even convulsions which are followed by depression.
2. Quinidine-like actions on the heart.

Uses. Local anæsthesia is generally used for trivial operations, when loss of consciousness is neither necessary nor desirable and also as an adjunct to major surgery to avoid deep general anæsthesia. It is seldom used alone for major surgery, not because it is impracticable, but because patients prefer unconsciousness. It is invaluable when the surgeon must be his own anæsthetist. Local anæsthetics can also be used topically for short periods to give relief from local pain or itching (but skin allergy is common).

For any but the most trivial operation premedication with barbiturates is theoretically desirable both to counteract the central stimulant action of local anæsthetics and, in the case of cocaine, to counteract its potentiation of the effect of adrenaline on the central nervous system; but the doses used may in fact provide little or no protection.

Local anæsthetics may be used in several ways to provide:

1. *Surface anæsthesia;* as solution, jelly or lozenge. Chronic use is liable to cause allergy.

2. *Infiltration anæsthesia*, to paralyse the sensory nerve endings and small cutaneous nerves.

3. *Regional anæsthesia.*

(a) *Intravenous;* a cuff is applied to a limb, inflated above arterial pressure after elevating the limb to drain the venous system, and the veins filled with local anæsthetic (e.g. 0·5% lignocaine) *without* adrenaline. This technique is useful in, for example, a drunk with a full stomach who has fallen and fractured his wrist, in whom a general anæsthetic would be dangerous.

(b) *Nerve block*, to anæsthetise a region, which may be small or large, by injecting the drug around, not into, the appropriate nerves, usually either a peripheral nerve or a plexus. Nerve block provides its own muscular relaxation as motor fibres are blocked as well as sensory fibres, although with care differential block can be achieved. Areas of selective

sensory, but not motor nerve block, are found at the edges of some regional nerve blocks. Even when motor fibres are intact, provided there is sensory block, muscular relaxation will occur if the patient's consciousness is blunted with a hypnotic drug. There are various specialised forms: paravertebral, epidural and caudal block. Sympathetic nerve blocks may be used in vascular disease to induce vasodilatation.

(c) *Spinal block*, in which the drug is put into the subarachnoid space. By using a solution of appropriate specific gravity and tilting the patient the drug can be kept at an appropriate level. Hypotension due to block of the sympathetic nervous system outflow occurs if the drug is at the right anatomical level. Serious local neurological complications have occurred both from the drug and from accidentally introduced bacteria. For these reasons spinal block is no longer popular, but may be useful in single-handed emergency.

Regional anæsthesia requires considerable knowledge of anatomy and attention to detail for both success and safety.

Toxicity. Excessive absorption results in nervousness, tremors and even convulsions. These latter are very dangerous and are followed by respiratory depression. Diazepam may be used to control the convulsions but may cause respiratory failure so that artificial respiration is needed. Respiratory stimulants are useless and dangerous as the patient has already passed through a phase of overstimulation. Nausea, vomiting and abdominal pain may occur, and also sudden cardiovascular collapse and respiratory failure for which there is no specific treatment other than artificial respiration and cardiac massage as necessary. When systemic toxicity follows injection of a local anæsthetic into an extremity a tourniquet may be used to delay entry of what remains into the general circulation.

Allergic reactions such as rashes, asthma and anaphylactic shock, occur, and the subject may be allergic to more than one drug. Regular users are wise if they take care to keep them off their own skin when filling syringes. Reactions are rarer with lignocaine than with procaine.

Routine tests for allergy or intolerance have been advocated in all cases before injecting local anæsthetics. Their value is doubtful and they are very time-consuming. A ship's cook aged 62 was to have a bronchogram performed because of suspected bronchial carcinoma. "He was given an amethocaine lozenge to suck, to indicate whether or not he was allergic to amethocaine. As he showed no reaction, half an hour later his throat was sprayed with 0·5 to 1 ml of amethocaine solution. During this procedure he suddenly collapsed, had a convulsive fit, and died within three minutes."*

Local inflammatory or necrotic effects may occur, for these drugs can damage all cells.

Cocaine is used solely as a surface anæsthetic, usually as a 4% solution, because toxic effects are both common and dangerous when it is injected.

* *Brit. med. J.* (1955), **1**, 610.

Approximate Data on Some Widely Used Local Anæsthetics

Drug	*Surface anæsthesia*			*Infiltration*		*Nerve block*		*Onset of effect: infilt. and nerve block*	*Duration:* infilt. and nerve block*	*Max dose* for an adult (injected)*
	soln. strength	*effective in (mins)*	*duration*	*soln. strength*	*max. vol.**	*soln. strength*	*max. vol.**			
Procaine	no effect			0·5%	300 ml	1%	125 ml	5–10 min	1–2 hrs	1·5 g
Prilocaine	—	—	—	0·5%	120 ml	1%	40 ml	3–6 min	1½–3 hrs	0·6 g
Lignocaine	2%, 4%	5 min	1–2 hrs	0·5%	100 ml	1%	50 ml	5–10 min	2–4 hrs	0·5 g

* With adrenaline or noradrenaline (but see text); if these are not used to delay absorption the doses in the table are toxic and so *substantially* less should be given. If weaker solutions are used, larger volumes may be injected. Lozenges, lollipops for children, creams, ointments, jellies and suppositories are available for appropriate local use. As anæsthesia develops there is a danger of aspirating a lozenge into the trachea; captive preparations such as the lollipop are safer. All dosage figures apply to the hydrochlorides and are only approximate, larger amounts can often be given safely, but deaths have occurred with smaller amounts, so the minimum amount that will do the job should be used. Widely different solution strengths are used in some cases.

Even as a surface anæsthetic sufficient absorption may take place to cause serious toxicity, anxiety tremors, convulsions, hypertension (treat with anticonvulsant and α and β adrenoceptor blockers).

Cocaine differs from other local anæsthetics in that it blocks re-uptake of released catecholamines and thus causes general sympathetic stimulation; it has a built-in vasoconstrictor effect which is particularly useful in nose and throat surgery to which its use is now largely confined.

By mouth the only use for cocaine is in the relief of nausea and vomiting in patients dying of gastric carcinoma (initial dose 5 to 10 mg cocaine hydrochloride).

Cocaine dependence is widespread amongst South American natives who chew the leaves with lime to release the alkaloid. It is claimed to give relief from fatigue and hunger and to induce a pleasant introverted mental state. Remarkable feats of endurance attributed to chewing cocaine leaves have been reported, but there is no adequate scientific confirmation of them. A United Nations enquiry into coca-leaf chewing reported that there was emotional but not physical dependence. It also reported that its use caused physical exhaustion rather than the reverse, and advocated gradual suppression in the interest of the populations concerned.*

In more "civilised" societies pure cocaine is used intermittently as a "spree" drug to obtain pleasant interludes, and courage, sometimes for the commission of crimes. Continuous use leads rapidly to an acute toxic psychosis. Tolerance does not occur. The drug is taken as a snuff, "snow", by "snowbirds", who often develop nasal ulceration, probably as a result of the accompanying vasoconstriction. It is also taken by self-injection, often intravenous.

Procaine (Novocain) (see table) is not absorbed through mucous membranes and is useless as a surface anæsthetic. It is rapidly hydrolysed in the blood, which is an advantage when toxic doses have been given.

It is rarely used for cardiac arrhythmias now that procainamide is available.

Lignocaine (Xylocaine, lidocaine) (see table) is a successful drug for surface use as well as for injection, combining efficacy with comparative lack of toxicity. It is also useful in cardiac arrhythmias (which see). Overdose of lignocaine, however, can cause convulsions although this is often preceded by somnolence rather than by excitement. Chemically, lignocaine differs from most other local anæsthetics and so is especially suitable for trial in cases of known allergy to other drugs.

Prilocaine (Citanest) (see table). It is used similarly to lignocaine, but it is less toxic. This was shown in a double-blind experiment in which 20 volunteers received each drug i.v. It can cause methæmoglobinæmia at highest doses and this is only clinically important in patients in whom slight decrease of oxygen carrying capacity is harmful, e.g. severe heart failure.

Amethocaine (Anethaine) resembles cocaine more than procaine and is effective on surfaces as well as by injection. It is dangerous, being absorbed fast through mucous membranes so that systemic toxic effects may occur.

Cinchocaine (Nupercaine) resembles amethocaine.

* Report of commission of enquiry on coca leaf (April 1950). United Nations document E/1666.

Bupivicaine (Marcain) is long acting and is used for obstetric epidural block.

Proxymetacaine (Ophthaine) is used in the eye if it is important not to dilate the pupil, e.g. for tonometry.

There are numerous other local anæsthetics (e.g. amylocaine, benzocaine, oxybuprocaine, butacaine, orthocaine), and their omission here is not meant to imply that good results are not obtainable with them.

Choice of local anæsthetic. The many agents available are proof that all have disadvantages and that no agent is unchallengeably the best for all occasions. This is particularly the case for surface anæsthesia, although a claim that lignocaine is safest and best could not easily be dismissed, though prilocaine is a contender where dosage must be heavy. For injection by the occasional user lignocaine or prilocaine are satisfactory. Professional anæsthetists will choose from a wider range.

There have been many deaths due to confusion of the names, all ending in "caine" and to the use of wrong concentrations of unfamiliar drugs.

OBSTETRIC ANALGESIA AND ANÆSTHESIA (*41–43*)

Although this soon ceased to be considered immoral, it has been a technically controversial topic since 1853 when Queen Victoria, having inhaled chloroform during the birth of her eighth child, "expressed herself as grateful for the discovery of this means of alleviating and preventing pain." ". . . the acknowledged skill of the physicians who sanctioned the inhalation of the chloroform" was contested by the *Lancet* which recorded "intense astonishment . . . throughout the profession" at this use of chloroform, "an agent which has unquestionably caused instantaneous death in a considerable number of cases. . . . Probably some officious meddlers about the Court. . . ."*

Pain-free labour sometimes occurs spontaneously but, rightly or wrongly, most women in Western civilisations anticipate pain and demand relief. The reason for lack of general agreement on which drugs are best is that requirements are stringent, and much depends on the skill with which they are used. The ideal drug must relieve pain without making the patient confused or uncooperative. It must not interfere with uterine activity nor must it influence the fetus (respiratory depression is the chief disadvantage and may occur by a direct action of the drug on the fetus, by prolonging labour or by reducing uterine blood supply). It should also be suitable for use by a midwife without supervision.

Innumerable schemes have been proposed and good results can be obtained with many, by those who take the trouble to familiarise themselves with them. Generally, strong analgesic drugs should not be started before uterine contractions are well advanced as they can stop feeble contractions. The following may be taken as a general guide:

Onset of labour, up to three-quarter dilatation of cervix: non-inhalational tranquillisers and analgesics, e.g. pethidine.

* Editorial. (1953) (*sic*). *Brit. med. J.* **1**, 824.

From three-quarter dilatation of cervix till birth: inhalation drugs, e.g. nitrous oxide/oxygen, trichloroethylene, methoxyflurane: this is to avoid respiratory depression of the fetus which occurs with effective doses of narcotic analgesics.

Pethidine is widely used. It seldom causes serious respiratory depression but has been shown to reduce respiratory minute volume in the baby. Morphine depresses fetal respiration more than pethidine, and nalorphine administered to the mother before birth or to the child after birth will reverse the effect. Diazepam can also depress the baby.

Barbiturates combined with pethidine may produce severe fetal respiratory depression and they may reduce the analgesic effect.

In general the baby will be about as depressed as the mother at the time of birth, and respiratory depressant should be withheld if birth is imminent. The intervals between doses are judged on clinical progress.

Sympathomimetic amines and other vasoconstrictors may cause fetal distress by reducing placental blood flow. They do not enter the fetus. Extreme hypotension from any cause also results in fetal anoxia.

Nitrous oxide and oxygen may be administered for each pain from a machine the patient works herself or supervised by a midwife. Nitrous oxide and air mixtures are obsolete because hypoxia is unavoidable at effective concentrations of nitrous oxide.

Trichloroethylene in a special vaporiser for self-administration can be used, but onset of analgesia is slower than with nitrous oxide and the patient is liable to become drowsy and so to be less co-operative. Methoxyflurane is an alternative.

Special techniques, e.g. extra-dural and paracervical nerve block are also used by specialists.

General anæsthesia presents a special problem in that the safety of the fetus must also be considered, and the anæsthetist is more often presented with a patient with a full stomach so that regurgitation is a particular risk. All anæsthetics and analgesics in general use cross the placenta in varying amounts and, apart from respiratory depression, produce no important effects except that deep general anæsthesia interferes with uterine retraction and may be followed by uterine hæmorrhage. All neuromuscular blocking agents can be used safely although gallamine crosses the placenta and suxamethonium stimulates the uterus; none interferes with uterine retraction.

ANÆSTHESIA IN PATIENTS ALREADY TAKING DRUGS (*30*)

The most important groups of drugs that affect anæsthesia are adrenal steroids, tranquillisers, antidepressants and antihypertensives. There is a paucity of useful data.

Adrenal steroids, see ch. 9. *Oestrogen* containing oral contraceptives increase liability to thrombosis and should be withdrawn, if possible, four weeks before surgery.

Tranquillisers. Phenothiazines (chlorpromazine, etc.) potentiate or synergise with opiates, hypnotics and general anæsthetics. Those with antihypertensive properties, chlorpromazine, reserpine, may cause severe hypotension during anæsthesia. In the case of reserpine, which depletes tissues of stored noradrenaline, response to infused sympathomimetics can be altered; also, extreme vagal bradycardia may occur (reserpine alone causes some bradycardia) and atropine should be used in premedication. *β-adrenoceptor blockers* inhibit the sympathetic response to ether and cyclopropane.

Antidepressants. Monoamineoxidase inhibitors can potentiate anæsthetics, opiates (especially pethidine).

Hypotensives. Hypotension may complicate anæsthesia.

Diuretics. If hypokalæmia occurs, this will potentiate neuromuscular blocking agents and perhaps general anæsthetics.

Diabetics, see index

Anticoagulants can cause serious hæmatomas with any needling procedure (lumbar puncture, caudal block, etc.).

Opiate analgesics, hypnotics and alcohol. If enough of these has been habitually taken for tolerance to result, there will be some cross-tolerance with general anæsthetics.

ANÆSTHESIA IN THE DISEASED AND AGED

The normal response to anæsthesia may be greatly modified by disease. The possibilities are vast and only some of the more important aspects will be mentioned here.

Respiratory infections predispose the patient to postanæsthetic pulmonary complications such as collapse or pneumonia.

Pneumonia due to a drug sensitive organism is preferable to pneumonia due to a drug resistant organism. Therefore prophylaxis should be begun immediately before or after operation, not days before, for this would allow colonisation of the lungs by resistant organisms. Routine use of antimicrobials does not prevent postanæsthetic pneumonia in healthy people.

Irritant inhalation anæsthetics and reduction of respiratory excursion by depression of the respiratory centre should obviously be avoided as far as possible, although postoperative chest complications have little relation to the anæsthetic drug used, being chiefly associated with the site of operation and the incidence of pain, i.e. they are due to defective ventilation due to pain and fear of coughing.

Anæsthesia in cardiac disease. The aim is to avoid the circulatory stress which is caused by struggling, coughing, laryngospasm and breath holding. Drugs given i.v. should be injected slowly to avoid hypotension, which may occur with very many substances if they are given too fast.

Patients with fixed cardiac output, e.g. mitral stenosis, constrictive pericarditis, are specially liable to a drop in cardiac output, for which they cannot compensate, with drugs that depress the myocardium and

vasomotor centre. Thiopentone induction is liable to do this and inhalation induction may be preferable. Anoxia is obviously harmful. It will be seen that skilled technique rather than choice of drugs on pharmacological grounds is the important factor. If heart failure or arrhythmias are anticipated from the condition of the patient or the nature of the operation, digitalis or antiarrhythmic drugs may be begun preoperatively.

Anæsthesia in hepatic and renal disease. Very many drugs are metabolised by the liver or excreted by the kidney so that disease of these organs is liable to lead to increased drug effects. This should be taken into account when selecting drugs and their doses. General anæsthetics can also impair hepatic function.

Anæsthesia in diabetes. Ether causes hyperglycæmia by stimulating the sympathetic centre in the brain, it therefore slightly complicates the management of the disease and so is best avoided. Details of preparation of diabetics for surgery are given in ch. 26.

Anæsthesia in thyroid disease. Nowadays patients are not operated on for hyperthyroidism until the metabolic rate has been controlled by drugs. If by some mischance an operation must be done whilst the metabolic rate is high and a thyroid "crisis" follows, it may be treated by methods used in anæsthetic hypothermia; β-adrenoceptor block is used to protect the heart which is sensitive to catecholamines. Hypothyroid patients are liable to be intolerant of anæsthetic drugs. Hypothyroidism may be corrected rapidly with liothyronine.

Anæsthesia in porphyria. Barbiturates should never be used as they may precipitate a severe attack. Chlorpromazine is safe for premedication and propanidid (a non-barbiturate) is safe for induction, but see also *porphyria.*

Anæsthesia in muscle diseases. Patients with myasthenia gravis are very sensitive to competitive but not to depolarising neuromuscular blocking drugs. Those with dystrophia myotonica may recover less rapidly than normal from central respiratory depression and neuromuscular block. All patients with generalised muscular weakness or disease should be treated with caution.

Genetics: (1) *Sickle-cell trait:* anoxia can precipitate a crisis.

(2) *Atypical pseudocholinesterase* (*or deficiency*) delays metabolism of suxamethonium (which see) and of procaine and related local anæsthetics.

(3) *Malignant hyperpyrexia* occurs in cases of a rare inherited muscular defect which may be evident as a clinical myopathy or which may be without clinical manifestations. The principal form is inherited as a dominant characteristic, but other forms occur. The condition is due to increased muscle metabolism (associated with altered calcium penetration of the cell) with or without rigidity, and is usually triggered by suxamethonium and/or halothane. The mortality has hitherto been about 65%. Treatment is to reduce the temperature by vasodilator drugs and cooling, attention to electrolytes and pH, and support of the circulation.

Raised intracranial pressure depresses the respiratory centre and

these patients are liable to respiratory failure with central nervous depressants, especially opiates. Therefore, premedication may consist of atropine alone.

Old age. Old people are liable to become confused by narcotics, especially by hyoscine, and atropine is usually substituted. Apart from this there are no special problems, but mistakes and overdose are less easily retrieved in the old and frail than in the young and healthy. In general, elderly patients require smaller doses than the young. Hypotension should be especially avoided as it may lead to cerebral hypoxia.

Childhood. Here again the problems are more technical, physiological and psychological than pharmacological. Premedication is often by sedatives, e.g. barbiturates, orally or by rectum, rather than by injected morphine or papaveretum with hyoscine, although children in fact tolerate these well. Very little anæsthesia is needed for neonates and they are said to be intolerant of competitive, and tolerant of depolarising, neuromuscular blocking agents.

Atmospheric contamination by anæsthetics may be a cause of a variety of reproductive difficulties in women who work in operating theatres.

Closed-circuit administration, with a CO_2 absorber, is used both for economy of anæsthetic cost and to prevent pollution of the atmosphere of the operating theatre. Indeed, so important is the latter that anæsthetists in the U.S.S.R. are reported to have applied for a 15% salary bonus for working in a hazardous atmosphere.*

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Chapter 12

ANALGESICS, PAIN, RHEUMATISM

PAIN AND ANALGESICS

ONE of the greatest services a doctor can do his patients is to acquire skill in the management of pain.

> . . . For what avails
> Valour or strength, though matchless, quelled with pain,
> Which all subdues, and makes remiss the hands
> Of mightiest? Sense of pleasure we may well
> Spare out of life perhaps, and not repine,
> But live content—which is the calmest life;
> But pain is perfect misery, the worst
> Of evils, and, excessive, overturns
> All patience.*

When the cause of pain cannot be removed, drugs acting on the central nervous system are generally used to relieve it.

For therapeutic purposes, pain may be considered a dual phenomenon, one part being the perception of the sensation and the other the patient's emotional reaction to it.

Drugs give relief in two ways, *first* by reducing the ability of the patient to perceive the sensation, probably by an action on the thalamus, or *second*, by altering the appreciation of the sensation so that it is no longer unpleasant, probably by an action on the cerebral cortex.

All the most potent drugs act in both ways, and although pain may be relieved, the patient cannot be considered to be mentally entirely normal whilst under their influence, for the cortical effects are not completely selective for pain. It has hitherto been thought that all drugs, such as morphine, that alter what Beecher (*1*) has called the "psychic processing" of pain must also induce morphine-type dependence and that complete selectivity is unobtainable, on physiological grounds. Fortunately, this may not be so, for nalorphine, a morphine antagonist that precipitates the withdrawal syndrome in addicts, is about as potent an analgesic as morphine. But, unfortunately, nalorphine induces unpleasant abnormalities of mood (dysphoria) and hallucinations, and so is useless as an analgesic. Other morphine antagonists are being sought (see pentazocine) in the hope of discovering a potent analgesic that does not induce dependence and that is free from disagreeable mental effects.

The pain threshold itself is influenced by the emotional state of the

* JOHN MILTON (1608–1674). *Paradise Lost.* Book 6. 456–464.

subject and by the personal significance that the pain has for him. A substernal pain that the victim believes to be a "heart attack" may cause greater distress than a pain of the same intensity in a leg (*38*), and the relief given by a drug in the former particularly will be greater or less according to the relationship the physician has with his patient.

Anxiety lowers, and relief of anxiety, or anger, raises the pain threshold. "To the wounded soldier who had been under unremitting shell fire for weeks, his wound was a good thing (it meant the end of the war for him) and was associated with far less pain than was the case of the civilians who considered their need for surgery a disaster" (*1*). The desire for analgesics was less amongst victims of battle injuries than amongst comparable civilian injuries (*2*). On the other hand, morphine has been found to be relatively ineffective against various forms of experimental pain in man, probably because it acts chiefly against pain which has emotional significance for the patient and less on other pain. But pain due to intraperitoneal injection of bradykinin in human volunteers, may provide a valid experimental model (*15*) though it is hardly suitable for routine use.

Although barbiturates are not analgesics, they are more effective than dummy tablets in relieving pain and this is probably due to relief of anxiety or to alteration of the "psychic processing" of the sensation. The fact that barbiturates have some "antianalgesic" effect does not necessarily contradict this, for a lot depends on the circumstances in which observations are made. Addition of a tranquilliser or antidepressant to analgesic therapy can be useful. Dummy tablets or injections have long been known to be effective remedies for pain, giving relief usually to about 35% of cases, but with the disadvantage that they rapidly lose effect with repetition.

New analgesics have been successfully developed by **animal testing,** possibly because the emotional response to experimental pain in an animal is akin to the human response to disease or accidental injury. This emotional response does not generally occur in a subject who has volunteered to undergo laboratory experiments which he can stop at any time, and it probably accounts for the fact that a placebo gives relief in only 3% of these cases; also for the fact that experimental pain in man has proved to be virtually useless for assessing the clinical value of potential analgesics which may act on the psychic response to pain, with the possible exception of intraperitoneal bradykinin (see above).

When a drug has been found to raise the threshold of response to the measured application of heat, electric shock or local pressure in animals and is thought to have reasonable prospect of being an improvement on existing analgesics, it must be **evaluated in man** by trial on patients suffering from the pain of disease. This is often done, with drugs of the morphine (narcotic) type on the postoperative pain of abdominal surgery, and with drugs of the aspirin (non-narcotic) type on chronic rheumatic conditions. Unwanted effects are, of course, simultaneously recorded and taken into account when deciding its clinical utility. Since what is being

measured is how the patient *says* he feels, careful precautions must be taken if a reliable result is to be obtained. The trial must be double-blind, or made double-blind as soon as possible. Observers who interrogate the patients for relief (intensity and duration) and unwanted effects must be constant and trained. It has been found, for example, that if asked by a personable young woman, a higher proportion of patients admit to pain relief than if the same question is put by a man.

The necessity for the utmost care in design of drug trials and the interpretation of the results is well shown by the following experiment (7):

One physician, using the double-blind technique, treated patients suffering from joint pain with aspirin and with dummy tablets. The patients filled in report cards after two weeks, analysis of which showed that they could not distinguish between the effect of aspirin and the dummy (or placebo). A second physician performed a similar study, also double-blind, in which the patients were interviewed by an observer at their bedside, who recorded the development of analgesic effect. The analysis of the records of this experiment showed that the patients distinguished between aspirin and the dummy tablets, and that these results were "highly significant statistically", that is, the results were unlikely to be due to chance, which is all that this phrase means. It does not mean that the results *cannot* be due to chance. The question now arises which result should be accepted. The second may be taken as reliable, partly because it accords with general clinical experience over 50 years, although this is by no means infallible, and partly because it is well known that memory for pain is bad, so that recollection of pain that occurred days or weeks ago for comparison with pain felt in the present cannot be, and is not, reliable, whereas comparison of the present with, say, half an hour ago, can give very consistent results. If a trial of the first kind were done on a new analgesic there would be a risk of missing a useful drug. No amount of care in recording results, no expertise by the statistician, can compensate for such a fault in design, responsibility for which lies with the clinician.

The **reliability of clinical methods** of measuring analgesic efficacy has been well shown. When one new analgesic was being tried, it was found that the dose required to produce a given amount of relief increased steadily with the age of the drug sample. Enquiry of the maker's whether the drug was chemically stable was met by an assurance that it was. The clinical experiments were repeated with the same result, and further chemical investigation revealed that the compound was indeed not stable.

Other support for the reliability of these techniques comes from the fact that similar results are obtained with the same drugs in different centres and that workers have identified " unknown" coded samples (1).

Despite all the activity of chemists producing new compounds and of physicians in testing them with increasing accuracy it is of interest that it is the alkaloids of opium and one of the first synthetic analgesics, aspirin, that are still pre-eminent in the treatment of pain.

Choice of Analgesic

In general, pain arising from somatic structures (skin, muscles, bones, joints) responds to analgesics such as aspirin and paracetamol (non-narcotic) which act solely by raising the pain threshold and do not induce serious dependence (addiction). Pain arising from the viscera is most readily reduced by morphine and pethidine (narcotic) which act both on the pain threshold and on the psychic reaction to pain and do induce serious dependence; but pentazocine is safer in this respect. This distinction is not, of course, absolute and drugs of the opium group, which are the most potent, may be needed for severe somatic pain. Mild pain from any source may respond to the non-narcotic analgesics and these should always be tried first. It is generally held that mixtures of these analgesics give better results than higher doses of one drug alone: probably by giving less unwanted effects for equivalent relief of pain. Innumerable combinations are available, perhaps the most widely used being Aspirin, Phenacetin* and Codeine Tabs B.P., a time-hallowed combination. The latter drug, although an opium alkaloid, is a comparatively weak analgesic and is virtually non-addicting; it is commonly used for somatic pain. Caffeine potentiates aspirin and is included in some mixtures. Pentazocine (Fortral) is a non-constipating alternative to codeine.

Pain due to spasm of visceral smooth muscle, when severe, requires large doses of the most potent narcotic analgesics, morphine, pethidine, methadone. These drugs themselves cause spasm of visceral smooth muscle and so have a simultaneous action tending to increase the pain. Papaveretum may be less prone to do this as it contains other opium alkaloids. Pentazocine is somewhat less liable to cause spasm. An anticholinergic drug such as atropine may be given simultaneously to antagonise this effect. Mild pain due to spasm can sometimes be relieved by atropine-like drugs, alone or in combination with a non-narcotic analgesic or pentazocine.

Spasm of striated muscle is often a cause of pain, including some headaches. Treatment is directed at reduction of the spasm in a variety of ways, including psychotherapy, sedation and the use of a centrally-acting muscle relaxant as well as non-narcotic analgesics, e.g. orphenadrine plus paracetamol (Norgesic). Local injections of procaine are sometimes useful, as are alcoholic drinks. Skin cooling (below) may also be useful.

Neuralgias, such as post-herpetic neuralgia, trigeminal neuralgia or causalgia, can present almost insoluble problems. Analgesics may play only a subsidiary part in their management. In severe cases very high doses of non-narcotic analgesics are often reached with little benefit and an almost inevitable demand for narcotic analgesics follows, with the risk of serious dependence. Pentazocine may be preferable.

It has been accidentally discovered that an antiepileptic, *carbamazepine*

* Because of the renal toxicity of phenacetin, paracetamol is sometimes substituted, though it is not certainly less toxic.

(Tegretol) (200 mg), chemically related to imipramine, is effective in trigeminal neuralgia, probably by reducing excitability of the trigeminal nucleus. It supplants other drug therapy. A start should be made with a low dose which should be adjusted to suit each patient, who generally soon learns to alter it himself during remissions and exacerbations. The daily dose is 200 to 1,600 mg orally, in divided doses. It is sometimes possible to withdraw the drug gradually over several months without relapse. Unwanted effects include dizziness, sleepiness, nausea, vomiting, dry mouth, rashes and blood disorders.

In this and in other forms of neuralgia, drugs worth trying in resistant cases include *phenytoin* (it raises the threshold of nerve cells to electrical stimulation), and tranquillisers, which may potentiate analgesics and also have an independent effect on the patient's anxiety about his pain.

Phenytoin may sometimes help tabetic pain.

Local skin cooling, by spraying with ethyl chloride or a mixture of chlorofluoromethanes (Skefron) may provide relatively long-lasting relief where other measures fail.*

Sedation during the acute stage of herpes zoster in patients over 55 years may perhaps help to prevent post-herpetic neuralgia. Posterior pituitary extracts and cyanocobalamin injections have been advocated for the pain of herpes zoster. Evidence in their favour is exceedingly weak.

Thalamic pain commonly fails to respond to analgesics. Chlorpromazine may be worth trying, and perhaps carbamazepine.

The pain of inflammation commonly responds to non-narcotic anti-inflammatory analgesics (aspirin, phenylbutazone) which may interfere with release or effect of pharmacologically active substances released by inflammation (bradykinin, prostaglandins, etc.), and various combinations of non-narcotic analgesics, e.g. dextropropoxyphene plus paracetamol (Distalgesic). Alcohol, by causing vasodilatation, may make it worse.

The pain of wounds usually needs narcotic analgesics but the "suffering" of wounds and shock is often relieved by a barbiturate (*8*).

The pain of peripheral vascular insufficiency should be treated with non-narcotic analgesics. Narcotic analgesics may be needed eventually. Vasodilator drugs (which see) may help but also may be quite ineffective.

Arthritis, see later.

The pain of malignant disease may require combination of narcotic analgesics with tranquillisers.

Headache (*6*) originating inside the skull may be due to traction on, or distension of, arteries arising from the circle of Willis, or to traction on the dura mater. Headache originating outside the skull may be due to muscle spasm† or to arterial distension. It may also be a referred pain from, for example, the teeth, neck or nasal sinuses. Treatment by drugs is directed to relieving the muscle spasm, producing vasoconstriction

* Ellis, M. (1961). *Brit. med. J.*, **1**, 250.

† As in tension headache or frontal headache from eyestrain.

or simply administering analgesics, beginning, of course, with the non-narcotics. Combinations of analgesics, with each other and with caffeine are more effective than the ingredients given alone.

Migraine (*20–22*). The cause is uncertain, but there is evidence that vasoactive amines in the diet (tyramine in foods, see *MAOI interactions*) or released in the tissues (5-HT) play a part, both by inducing vasodilatation of extracerebral arteries and by lowering the pain threshold of the periarterial nerve endings. Treatment consists in:

1. **Prophylaxis:** attention to precipitating factors, e.g. stress, diet, and the use of drugs in severe cases. *Clonidine* (Dixarit) (0·025 mg) is worth trying though benefit may be slight. It probably acts by altering the responsiveness of the vessels to vasoactive substances. It is taken continually (orally, 0.025 to 0.075 mg twice a day) in doses that do not lower the blood pressure; larger doses are used in hypertension: *dosage* for these two diseases *must not be confused:* indeed the drug is marketed under a different proprietary name (Catapres) for hypertension in the hope of avoiding such confusion. If a migrainous hypertensive is being treated with Catapres, it is plainly futile to add Dixarit. Unwanted effects include depression, drowsiness and dry mouth.

Methysergide (Deseril), a 5-HT antagonist related to ergotamine, is an effective prophylactic, but it has a grave, rare and unpredictable adverse effect, inflammatory fibrosis that can involve the ureters retroperitoneally (obstructive renal disease), the heart, pleura and lung. It is thus a drug of last resort. Courses should be intermittent. It may also be useful in carcinoid syndromes.

2. **The acute attack,** if mild, is treated with non-narcotic analgesics (aspirin, paracetamol) or codeine or pentazocine. Severer attacks may require ergotamine for its vasoconstrictor effect, though its anti-5-HT effect and interference with catecholamine metabolism may play a part. Full doses may cause such unpleasant malaise, nausea and vomiting that some patients may prefer the disease to the treatment. A full account of ergot is given elsewhere.

The earlier in the attack that drug therapy begins the more effective it is likely to be. Ergotamine tartrate 0·25 to 0·5 mg s.c. or i.m., is best. It can be repeated as necessary, with a maximum of 1 mg in 24 hrs. If given i.v. the maximum 24-hr dose should be 0·5 mg. When ergotamine is highly effective it is sometimes worth teaching a patient to give himself injections.

Oral administration is less effective due to slow and erratic absorption, and tablets should be well crushed before swallowing, or retained in the mouth for buccal absorption. Caffeine has been found to improve ergotamine absorption from the intestine and may also help by its vasoconstrictor effect. Both the disease and ergotamine cause vomiting and an antiemetic may rationally be given too. Preparations include: Ergotamine Tartrate Tabs. B.P. (1 mg), 1 to 2 mg repeated every 30 min until relief, or 8 mg has been taken: maximum dose in 1 week 12 mg. Higher doses (5 mg at

once with up to 10 mg in one day) are used by some but risk of overdose (see below) is greater though therapeutic effects may be better.

Alternative preparations are Cafergot (ergotamine 1 mg, caffeine 100 mg) and Migril (ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg); see also antiemetics. Special rapidly dispersing tablets for buccal absorption are available (Lingraine, Cafergot-Q).

Suppositories are more effective than oral administration, though less effective than injection, but they are unpopular with all except a perverse minority (maximum dose in 24 hrs, 8 mg ergotamine).

In an attempt to avoid the inconvenience of injections and suppositories and the relative inefficacy, due to slow absorption, of oral ergotamine, a device for giving it by inhalation has been developed (Medihaler ergotamine). This delivers 0·36 mg ergotamine per dose, repeated every 10 mins until relief, or six inhalations have been taken. Used correctly, it is convenient and nearly as effective as injection. It is not known to cause pulmonary damage.

If ergotamine is used frequently headache may recur on withdrawal, and persist, which can lead to overdosage. It sometimes seems to increase the frequency of attacks. It is unsuitable for continuous use as a suppressant.

Overdose can cause headache and gangrene of the extremities. The drug should be avoided in pregnancy and used cautiously, if at all, in obliterative vascular disease and in renal or hepatic insufficiency.

Ergometrine and dihydroergotamine are sometimes effective in migraine; they are less powerful vasoconstrictors and can be tried in patients with obliterative vascular disease. Other vasoconstrictor agents, ephedrine and caffeine are sometimes useful. Midrid is a mixture of a sympathomimetic vasoconstrictor with paracetamol and dichloralphenazone. Occasional therapeutic success has been claimed with a variety of hormones. Carbon dioxide inhalation can sometimes stop an attack. The most convenient technique is to rebreathe into a bag until dyspnœa occurs.

Attention to detail in the treatment of migraine is well repaid. General aspects of treatment are often more important than are drugs, e.g. psychotherapy, modification of way of living. Premenstrual migraine may respond to a diuretic.

Periodic migrainous neuralgia (cluster headaches) may be treated as for migraine, but use of ergotamine by injection may need to be more prolonged.

Chronic tension headache due to muscle spasm may be helped by benzodiazepine tranquillisers or by tricyclic antidepressants.

Dysmenorrhœa, see index.

Antidepressants may help chronic pain in patients in whom there is no recognisable depression and a **tranquilliser**, e.g. diazepam is worth using, especially at night, if the patient is tense or anxious.

Miscellaneous. Inhalation of trichloroethylene or nitrous oxide and oxygen as in obstetrics, may be used temporarily for severe intermittent pain when other drugs fail, in, for instance urinary lithiasis, trigeminal neuralgia and during postoperative chest physiotherapy.

The general principle that the best treatment of a symptom is the

removal of its cause is well exemplified in the routine treatment of the pain of peptic ulcer, for which analgesics are not used.

NARCOTIC OR OPIATE ANALGESICS (*23–42*)

"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." Thomas Sydenham, 1680.

It is not known when opium was first procured and used as a drug, but it was certainly in prehistoric times, and medical practice always has leaned and still does lean heavily on its alkaloids, using them as analgesic, tranquilliser, antitussive and in diarrhœa. Opium is obtained by incising the seed heads of the opium poppy, allowing the exuded juice to dry for 24 hrs and then collecting it. A good yield of opium requires greater sunshine than is usual in Britain, although the plant will grow here.

Crude opium alone was used in medicine until 1803, when the principal active ingredient was isolated by Friedrich Sertürner who tested the separate fractions he extracted from it on animals and proceeded to try pure morphine on himself and three young men. He observed that the drug caused cerebral depression and spasms of the extremities and that it relieved toothache. He named it after Morpheus the god of sleep.

Opium is still occasionally used, as a pill or as an alcoholic solution (tincture) for arresting diarrhœa (Chalk and Opium Mixture, B.P.C.) and as Dover's powder, which is nowadays made as a tablet (Ipecacuanha and Opium Tablet, B.P.C.) to promote sweating and sleep in trivial fevers, but pure substances are preferable as they are more reliable.

The originator of Dover's powder, Captain Thomas Dover, devised it when he retired into medical practice from a career as licensed pirate, during which, in 1709, he rescued Alexander Selkirk (Robinson Crusoe) from his island. Dr. Dover combined the two ingredients so that an overdose of opium would be accompanied by an emetic dose of ipecacuanha. This type of built-in safety device has recently been revived in other connections and hailed as a new idea. Dr. Dover's notion of how his powder should be used has been modified greatly, and the formula slightly. He administered 2 to 4 g in a "white wine Posset" of which he advised the patient to drink a further 2 to 4 pints. Nowadays 0·3 to 0·6 g is considered sufficient, and no Posset.

Opium contains many alkaloids, but the only important ones are morphine and codeine, although two others, noscapine (narcotine) and papaverine, are occasionally used. In general, morphine is used now where opium was used in the past; its effects differ little from those of opium. However, purified preparations of mixtures of opium alkaloids (e.g. papaveretum, Omnopon) are available.

Morphine will be described in some detail and other opiate analgesics in so far as they differ from it.

The principal actions of morphine may be summarised:

On the Central Nervous System:

Depression, leading to: analgesia
respiratory depression
depression of cough reflex
sleep

Stimulation, leading to: vomiting
miosis
hyperactive spinal cord reflexes, some only
convulsions (very rare)

Changes of mood, euphoria or dysphoria

Dependence (addiction); affects other systems too.

Smooth Muscle Stimulation:

Gastro-intestinal muscle spasm (delayed passage of contents with constipation)

Biliary tract spasm

Renal tract spasm: dubious, see below

Morphine on the central nervous system. Morphine is the most generally useful narcotic analgesic, relieving pain in the ways described earlier. It both stimulates and depresses the central nervous system. It induces a state of relaxation, tranquillity and happiness (euphoria), or occasionally of malaise (dysphoria), and causes sleepiness, inability to concentrate and lethargy, always supposing that this pleasant state is not destroyed or prevented by nausea and vomiting, more common if the patient is ambulant. Excitement can occur but is unusual; it is said that women are more prone to it than men, though there is now evidence against this, and it seems to be "another of those interesting myths that textbook writers are fond of repeating without evidence down through the years" (*38*). However, there is no doubt that morphine excites cats and horses, though it is illegal to put this to practical use in horse racing; cats don't race, though they could. Generally, morphine has a useful hypnotic effect.

Morphine **depresses respiration** principally by reducing sensitivity of the respiratory centre to rises in blood carbon dioxide tension. With therapeutic doses there is a reduced minute volume due to diminished rate and tidal volume. With higher doses carbon dioxide narcosis may develop.

Morphine is dangerous in all patients with respiratory insufficiency. In asthmatics, in addition to the effect on the respiratory centre, it may cause thickening of bronchial secretions, which, with depression of cough and bronchospasm (see below) will increase airway resistance.

In postoperative patients morphine may promote pulmonary atelectasis by discouraging deep breathing.

Morphine is useful in the control of paroxysmal nocturnal dyspnœa,

relieving mental distress by its tranquillising action and respiratory distress by rendering the centre insensitive to the afferent stimuli from the lungs and CO_2 which reduces muscular work. Morphine also suppresses **cough** by a central action. It stimulates the third nerve nucleus causing **miosis** (pin-point pupils are characteristic of poisoning, acute or chronic; at therapeutic doses the pupil is merely smaller.)

The chemoreceptor trigger zone of the **vomiting centre** is stimulated, causing nausea (40%) and vomiting (15%), a side-effect which, in addition to being unpleasant, can be dangerous in patients who have had gastric operations, a cataract removed, or myocardial infarction. A preparation of morphine plus an antiemetic, e.g. cyclizine (Cyclimorph) reduces this liability. Some spinal cord reflexes are also stimulated and so morphine is unsuitable for use in tetanus and convulsant poisoning; indeed, morphine can itself cause convulsions.

Morphine causes **antidiuresis** by releasing antidiuretic hormone, and this can be clinically important.

Morphine on smooth muscle. *Alimentary tract.* Morphine acts directly on the smooth muscle of both large and small bowel, causing it to contract. Peristalsis is reduced and segmentation increased. Thus, although morphine "stimulates" smooth muscle, constipation occurs, with the intestine in a state of tonic contraction. The central action of the drug probably also leads to neglect of the urge to defæcate. Delay in the passage of the intestinal contents results in greater absorption of water, which contributes to the constipation.

Morphine causes high intra-sigmoid pressures which, in diverticulitis, may result in the diverticula blowing up and becoming obstructed and failing to drain into the colon. Pethidine neither produces these high pressures, nor prevents drainage, and so is preferable for the pain of diverticulitis if it should be severe enough to demand a narcotic analgesic. Morphine is probably also unsuitable after anastomoses of the colon, and it should not be given in intestinal obstruction.

Intrabiliary pressure may rise substantially after morphine, due to spasm of the sphincter of Oddi. It has been measured in man by attaching a manometer to biliary fistulæ in patients who have undergone surgery (*41*). Sometimes biliary colic is made worse by morphine, presumably in a patient in whom the dose happens to be adequate to increase intrabiliary pressure, but insufficient to produce more than slight analgesia.

In patients who have had a cholecystectomy this can produce a syndrome sufficiently like a myocardial infarction to cause diagnostic confusion. The electrocardiograph may be abnormal and the serum glutamic oxaloacetic transaminase may rise. Nalorphine gives dramatic symptomatic relief. Another result of this action of morphine is to hold back the pancreatic juice and so to cause a rise in the serum amylase concentration. Morphine and allied drugs are therefore best avoided in pancreatitis.

Ureters. It has long been believed that ureters contract under influence of morphine and relax under atropine and propantheline. The truth

is probably that none of these drugs has any important effect. Micturition may be delayed due to spasm of the bladder sphincter.

Bronchial muscle is constricted, partly due to histamine release, but so slightly as to be of no importance, except in asthmatics in whom morphine is best avoided anyway because of its respiratory depressant effect.

When morphine is used and the smooth muscle effects are objectionable, atropine may be given simultaneously to antagonise spasm. Unfortunately it does not effectively oppose the rise of pressure induced in the biliary system, nor does it restore bowel peristalsis.

Cardiovascular system. Morphine impairs sympathetic vascular reflexes and stimulates the vagal centre. This is ordinarily unimportant, but hypotension and bradycardia may occur in those taking antihypertensive drugs and in myocardial infarction.

Other effects include increased sweating, pruritus and piloerection.

Morphine tends to prolong childbirth.

Pharmacokinetics. Morphine is poorly absorbed from the gut, but readily absorbed after s.c. injection. Its analgesic half-life is about 80 mins and duration of useful analgesia is 4 to 6 hrs. It is conjugated in the liver (glucuronide) and excreted by the kidney.

Dosage. It may be given s.c., i.m. or i.v. 10 mg is usually adequate. With 15 mg unwanted effects increase relatively more than does analgesia.

The important uses of morphine and its allies are:

1. to relieve pain
2. to relieve anxiety in serious and frightening disease, e.g. shock, hæmatemesis or heart failure
3. to control diarrhœa
4. as premedication for surgery
5. to control cough
6. for dyspnœa in acute left ventricular failure (paroxysmal nocturnal dyspnœa)
7. to control restlessness, rarely
8. to produce euphoria in the dying

Any of the desirable effects may be interfered with by morphine-induced vomiting or dysphoria.

Morphine and disease. Morphine is a standard tranquilliser for shocked patients, but there may be such intense peripheral vasoconstriction that s.c. absorption is delayed for hrs. A second or even third dose may therefore be injected before the patient has absorbed the first and so lead to poisoning when the vasoconstriction passes off. In such cases morphine should be given i.m. or slowly i.v.

In hepatic failure small doses can cause coma (see *drugs and the liver*), and it may be dangerous in hypothyroidism. Hypotension can occur

in myocardial infarction and with antihypertensive drugs, also vagal bradycardia (treatable by atropine 0·3 to 0·6 mg i.v.).

In respiratory insufficiency (emphysema, asthma) it is dangerous, see above; also in diverticulitis, pancreatitis and after cholecystectomy, see above.

Interaction. Morphine is potentiated by neostigmine, chlorpromazine (perhaps) and monoamineoxidase inhibitor and tricyclic antidepressants (probably).

Unwanted effects have been mentioned and discussed. Dependence and overdose are treated below.

Opiate dependence (see also ch. 13). It is now known that physical dependence begins to occur within 24 hrs if morphine is given 4-hrly, and some postoperative patients may be unwittingly subjected to a withdrawal syndrome that passes for general postoperative discomfort.

Tolerance occurs to the depressant, but not to some stimulant effects (e.g. miosis, constipation). It is acquired with continued frequent use and there is cross-tolerance with chemically related drugs and pethidine. Acquired tolerance may rapidly reach a high degree, an exceptional addict taking 600 mg or more several times a day. An average addict is more likely to take about 300 mg. Duration of tolerance after cessation of administration is variable for different actions, from a few days to weeks. Little is known about it. Children are often said to be naturally intolerant of morphine, but this is not true, and it is invaluable in heart failure in children (maximum dose s.c. 0·2 mg/kg). The aged and infants are intolerant.

Morphine dependence is more disabling physically and socially than is opium dependence. It is said, and there is reasonable support for it, that the use of opium by Eastern peoples presents about as serious a social problem as the abuse of alcohol by Western peoples. All are agreed, however, that dependence on the pure alkaloids causes results so detrimental to society that such misuse cannot be left unchecked.

The typical **withdrawal syndrome in morphine dependence** consists largely of effects which are opposites to the normal actions.

"When an addict misses his first shot, he senses mild withdrawal distress ('feels his habit coming on') but this is probably more psychological than physiological, for fear plays a considerable role in the withdrawal syndrome. At this stage a placebo may give relief. During the first 8 to 16 hrs of abstinence the addict becomes increasingly nervous, restless and anxious; close confinement tends to intensify these symptoms. Within 14 hrs (usually less) he will begin to yawn frequently; he sweats profusely and develops running of the eyes and nose comparable to that accompanying a severe head cold. These symptoms increase in intensity for the first 24 hrs, after which the pupils dilate and recurring waves of goose flesh occur. Severe twitching of the muscles (the origin of the term 'kick the habit') occurs within 36 hrs and painful cramps develop in the backs of the legs and in the abdomen; all the body fluids are released copiously;

vomiting and diarrhœa are acute; there is little appetite for food and the addict is unable to sleep. The respiratory rate rises steeply. Both systolic and diastolic blood pressure increase moderately to a maximum between the third and fourth day; temperature rises an average of about one deg F, subsiding after the third day; the blood sugar content rises sharply until the third day or after; the basal metabolic rate increases sharply during the first 48 hrs. These are the objective signs of withdrawal distress which can be measured; the subjective indications are equally severe and the illness reaches its peak within 48 to 72 hrs after the last shot of the opiate, gradually subsiding thereafter for the next 5 to 10 days. Complete recovery requires from 3 to 6 months with rehabilitation and, if needed, psychiatric treatment. The withdrawal syndrome proper is self-limiting and most addicts will survive it with no medical assistance whatever (this is known as kicking the habit 'cold turkey'). Abrupt withdrawal is inhumane, but with the development of such drugs as methadone, it is possible to reduce the distress of withdrawal very considerably",* for though there is cross-tolerance, methadone withdrawal is less unpleasant than morphine or heroin withdrawal. For further discussion see under *drug dependence.*

It is usual to cover the withdrawal period (about 10 days) with morphine-like drugs perhaps supplemented with chlorpromazine and barbiturates. Withdrawal symptoms occur in infants born to dependent mothers. There is a risk of making patients seriously dependent if prolonged treatment is given (the more widely the doses are spaced the less the risk), and whilst this may matter little in those who are dying, it can present a grave problem in, for example, patients with trigeminal neuralgia or recurrent urinary lithiasis. It is impossible to give any rule as to how quickly a patient can become seriously dependent, but it is generally a matter of weeks or months, though slight physical dependence can occur in a day if the drug is given intensively.

Overdose. Death from overdose is due to respiratory depression. Blood pressure is usually well maintained, if the patient is supine, until anoxia causes circulatory failure. At this point the pupils, whose small size is a useful diagnostic indicator, may dilate. Correct diagnosis is vital, for nalorphine (5 to 12 mg i.v. or i.m.), or levallorphan (0·2–2 mg) are specific antagonists. If an addict is suffering from acute overdose, only 25% of these doses should be given, for fear of inducing a dangerous withdrawal syndrome. Nalorphine has a powerful antagonistic effect against the respiratory depression, lasting 2 to 3 hrs, which is shorter than the duration of action of the morphine, so that the nalorphine may have to be repeated. Arousal from coma does not usually occur in man, although nalorphine restores consciousness in some animals. The guide to therapy is the state of respiration, not of consciousness.

If respiration is not adequate 5 mins after the antagonist, a second dose

* From MAURER, D. W. and VOGEL, V. H. (1962). *Narcotics and Narcotic Addiction.* Courtesy of Authors and Charles C. Thomas, publisher, Springfield, Ill.

(50 to 75% of the first) should be given. Repeated small doses may be needed, up to a total of 40 to 100 mg. Too much nalorphine may actually increase the respiratory depression due to morphine. Respiratory stimulant drugs are not ordinarily needed, artificial respiration being preferable. Picrotoxin should not be used because its effects are synergic with the stimulant effect of morphine on the spinal cord and promote convulsions. Apart from nalorphine the general treatment is the same as for overdose by any cerebral depressant drug.

Preparations of Opium and its Derivatives

Chloroform and Morphine Tincture (B.P.C.), (chlorodyne), 0·3 to 0·6 ml orally, is useful in diarrhœa. Tincture of Opium (laudanum), 0·3 to 2 ml, is used in enemas to relieve diarrhœa in severe ulcerative colitis and orally to control diarrhœa and cough for short periods. Nepenthe is a proprietary liquid preparation of opium that can also be injected, but there is no good reason for using such preparations when pure drugs whose pharmacology is better understood are available. Squill Opiate Linctus, B.P.C. (Gee's linctus), is used in cough. The squill, containing a digitalis-like glycoside, may act as an irritant expectorant, but it is more useful as a rat poison. Gee's linctus is a popular antitussive, but probably no more effective than the opium alone. Papaveretum (Omnopon), 10 to 20 mg, can be given by any usual route. It is a pure preparation of opium alkaloids. It has not been shown superior to morphine in any respect. Ipecacuanha and Opium Tablets, B.P. (Dover's Powders), are described above. Morphine sulphate, 10 to 20 mg, can be injected by any usual route; given orally it is less effective.

There are many other preparations including Kaolin and Morphine Mixture, B.P.C., and Morphine Suppositories, B.P.C.

The following drugs are considered in relation to morphine:

Codeine (methylmorphine) has similar properties to morphine but is only one-quarter to one-sixth as effective an analgesic. Most of its other actions are only about one-tenth that of morphine so that codeine is a valuable analgesic although it is inadequate against severe pain, however much is given. But it differs from morphine qualitatively in two other respects; large doses cause excitement, not narcosis, and dependence does not readily occur. It is widely used as an analgesic, antitussive and anti-diarrhœal agent in a dose of 10 to 60 mg of codeine phosphate (30 mg) orally. Combined with aspirin it provides relief that cannot be got with tolerable doses of either drug alone.

Codeine is seldom given by injection, more potent drugs being then preferred. There are numerous preparations including Aspirin, Phenacetin and Codeine Tabs, B.P. and Codeine Linctus, B.P.C. Large doses of codeine (60 mg) are commonly needed to control cough.

Pethidine (meperidine, Demerol) (50 mg) was introduced in 1939. It was discovered during a search for smooth muscle relaxants acting like atropine. Structurally, it is not obviously related to either morphine or atropine, though it is said that cognoscenti can discern resemblances to

both. When given to mice it caused the tail to stand erect (Straub phenomenon) a characteristic of morphine-like drugs which is due to spasm of the anal sphincter. This attracted attention and pethidine was examined for analgesic effect.

Pethidine cannot relieve such severe pain as can morphine but is effective against pain beyond the reach of codeine. Despite its substantial structural dissimilarity to morphine, pethidine has many similar properties including that of being antagonised by nalorphine.

Pethidine differs from morphine in the following ways:

It does not suppress cough usefully.

It does not cause constipation, but its effect in the upper small intestine is similar to morphine and there is spasm of the sphincter of Oddi.

The pupils are not constricted.

It has little hypnotic effect.

Pethidine causes vomiting about as often as does morphine; it has atropine-like effects, including dry mouth and blurred vision, and causes sedation, but overdose can cause CNS stimulation (tremors, convulsions).

There is disagreement on the extent to which pethidine depresses respiration. It is probable that in equianalgesic doses it is as depressant as morphine. Death from overdose is due to respiratory depression.

Pethidine dependence occurs, with some tolerance, especially to the side-effects, but its psychic effects are less constant and less marked than those of morphine. Pethidine has evident advantages over morphine for pain which is not very intense, and it is widely used. It is usually given orally (50 to 200 mg) or i.m. (50 to 150 mg), when its effects last 3 to 4 hrs. The solution is irritant and so it is not given s.c. Given i.v. (50 to 100 mg) it is used sometimes in anæsthetic practice to provide a state of "general analgesia". It is widely used in obstetrics.

Pethidine is **metabolised** in the liver and a little is **excreted** unchanged in the urine. The latter is substantially greater if the urine is acid and this can be put to practical use in treatment of poisoning and for obtaining evidence in suspected cases of pethidine dependence. Levorphanol is treated similarly.

Methadone (1946) (5 mg) is a synthetic drug chemically and pharmacologically similar to morphine. It is more reliably effective when given orally than is morphine. Vomiting is fairly common, though somewhat less than with morphine, especially if the patient is ambulant, and sedation is less. 5 to 10 mg are given about 4-hrly, orally or s.c. Dependence occurs) but this is less severe (slower onset and less severe withdrawal syndrome, than with morphine and heroin, and addicts to these drugs (by injection) are often transferred to oral methadone as part of their treatment.

Diamorphine (heroin) is a semisynthetic drug first made from morphine at St. Mary's Hospital, London, in 1874. It was introduced in 1898 as a remedy for cough and for morphine addiction and is very effective against both. Some years passed, however, before it was appreciated that

it "cured" morphine addiction by substituting itself as the addicting agent. Since then it has become a popular opiate drug with addicts and has achieved such a reputation that it is difficult now to discover whether addicts are attracted to it because it is pleasanter or because of its reputation, plus its ready availability from drug pedlars in some countries. It is converted to morphine in the body.

It is commonly stated that heroin is the "most potent" of all dependence-producing drugs. Weight for weight it is certainly more potent than morphine, and this is of importance in illicit traffic as heroin takes up less space, but in so far as efficacy in inducing dependence is concerned there is doubt. Indeed, it has been reported that some addicts have voluntarily preferred methadone to heroin.

In almost every country the manufacture of heroin, even for use in medicine, is now illegal. The first to try this prohibition as a remedy for widespread drug addiction was the U.S.A. which banned heroin manufacture in 1924, provoked by the magnitude of their addiction problem and not yet discouraged by their experience with alcohol prohibition (1919 to 1933). Such an approach to the illicit traffic in general and heroin in particular is futile, for contraband heroin has hardly ever been legally manufactured heroin which has been diverted to illegal uses. It is heroin made by a simple process from smuggled opium or morphine. The solution to the spread of heroin addiction lies in the suppression of illegal opium traffic, not in stopping legal manufacture and use of heroin.

When in 1953 the British Government proposed to follow suit with a similar prohibition of heroin in medical practice (*36*) it was pointed out that British legally manufactured heroin had never contributed to the international illicit drug traffic, so that, whether or not the drug was useful in therapeutics, a ban on its use by the medical profession was pointless in that it would not prevent abuse. This reasonable argument was lost in a flood of vigorously expressed opinion on the advantages of heroin, which was based solely on clinical impressions. These opinions, unsupported as they were by any scientifically obtained data, together with the fact that in the U.S.A. patients, though not addicts, had been without heroin for 29 years, did not form an impressive body of evidence in favour of retaining heroin solely on grounds of clinical necessity.

Even now, after heroin has been in use for over 70 years, it is still not known for certain whether it has unique therapeutic properties; but the U.S.A. White House Conference on Narcotic and Drug Abuse (1962) (*38*) had no doubts: "There is a widespread misconception that heroin has effects significantly different from those of morphine. It does not, and this misconception should be dispelled permanently." If there are advantages, they are slight, such as less liability to cause dysphoria and vomiting; but these are not trivial for a patient with myocardial infarction, or to one painfully dying. No doubt disagreement will continue, especially as the availability or not of heroin can be made the occasion for attacking government authority by those who have an inclination to it.

Heroin is still available to doctors in Britain, but is no longer exported.

Heroin is **used** chiefly to control severe pain and cough and to comfort the dying. It, like morphine, induces dependence and so should be used with due regard to this hazard. The initial oral dose of heroin hydrochloride is 5 to 10 mg (s.c. 3 to 6 mg).

Phenazocine (Narphen) is a benzmorphan that was at first thought to be both potent and non-addicting. When it was found that it was not superior to morphine, a series of antagonists were made, because the morphine antagonist, nalorphine, is a potent analgesic. *Pentazocine* is one of these.

Pentazocine (Fortral, Talwin) is an opiate antagonist; it can induce a withdrawal syndrome in addicts; it can also induce physical dependence (for it has agonist opiate activity too) but rarely and weakly and it can be regarded as an important advance in separating the property of potent analgesia from that of producing dependence.

Its *analgesic efficacy* approximates to that of morphine, but its *potency* (weight for weight) is about one-third of morphine.

Adverse effects include: nausea, vomiting, dizziness, sweating, hypertension, palpitations, tachycardia, CNS disturbances (euphoria, dysphoria), and all are more likely with the higher peak plasma concentrations achieved after injection.

Uses are those of morphine (excepting in diarrhœa), and also for lesser and chronic pain where morphine would be avoided for fear of dependence.

Transfer from morphine or pethidine. If a sudden change is made after prolonged use of morphine or pethidine which has induced dependence, an unpleasant abstinence syndrome may occur. Gradual transfer or an interval of 48 hrs should suffice to avoid this.

Dosage. Pentazocine Tabs, B.N.F. (25 mg), 25 to 100 mg, 3 to 4 hrly: Pentazocine Inj, B.N.F., 30 to 60 mg, i.m., 6 to 8 hrly.

Pentazocine compared with morphine

Dependence liability: very much less (risk only important when injected frequently).

Effect on opiate dependence: induces withdrawal syndrome.

Oral efficacy: pentazocine good: morphine poor.

Respiratory depression and sedation: less.

Duration of action: shorter.

Overdose respiratory depression: for morphine, use nalorphine (or naloxone).
for pentazocine; naloxone is effective.

Nausea and vomiting: similar.

Constipation and spasm sphincter of Oddi: less.

Cardiovascular effects (chiefly important in myocardial infarction:
morphine: hypotension, bradycardia.
pentazocine: hypertension (systemic and pulmonary), tachycardia.

Some Other Analgesic and Antitussive Drugs Related to Morphine

Name (*Tablet size in mg*)	*Oral dose* (*Injected dose*)	*Antagonised by nalorphine*	*Remarks*
dextromethorphan (Romilar) (15)	15–30 mg	no	Used in cough, similar to codeine but fewer side-effects. No significant respiratory depression.
hydrocodone (Dicodid) (5)	5–15 mg	probably	Similar to codeine but more effective, a useful antitussive.
dihydrocodeine (D.F. 118) (30)	30–60 mg (20–50 mg s.c.)	yes	Few side-effects. A little less effective than morphine.
levorphanol (Dromoran) (1·5)	2–3 mg (2–3 mg s.c.)	yes	Less drowsiness than morphine.
pholcodine (Ethnine)	5–15 mg	no (*but see naloxone*)	Used as a syrup in cough, less constipating than codeine. Insignificant respiratory depression.

The doses given are those of the commonly used salts. All the drugs are chemically related to morphine. Since they are rather irritant in solution and, like morphine, release histamine in the tissues, they are better given by deep s.c. injection or even i.m., when not given orally. Claims of substantial superiority have been made. The continued wide use of codeine and morphine is sufficient answer to many of them.

Dextropropoxyphene (Doloxene) (65 mg) is chemically close to methadone and differs in that it is less analgesic, antitussive, and less dependence-producing. Its analgesic usefulness approximates to that of codeine. The oral dose is 65 mg, and it is combined with aspirin, phenacetin and caffeine as Doloxene Compound–65, and with paracetamol as Distalgesic. It has been found equivalent to placebo in some studies.

Fentanyl is a synthetic opiate both more potent and having a briefer action than morphine; it is used i.v. alone (Sublimaze), or mixed with droperidol (Thalamonal) for "neuroleptanalgesia" (which see); phenoperidine (Operidine) is similar.

Analgesics and antitussives not mentioned in the table or above include: hydromorphone (Dilaudid): methyldihydromorphinone (Metopon): phenadoxone (Heptalgin): dipinanone (Pipadone) and, combined with an antiemetic (Diconal): dextromoramide (Palfium): anileridine (Alidine): alphaprodine (Nisentil): oxycodone (Proladone): ethoheptazine (contained in Zactirin); advantages claimed for these have not been proved.

Noscapine (narcotine) has antitussive effect, but little else, it is said to be non-addicting and can be used instead of codeine. It does not constipate,

is not narcotic and, like papaverine, is only included here because it is an alkaloid of opium. Oral dose 15 to 30 mg.

Papaverine differs from the more important opium alkaloids in that its only useful effect is relaxation of smooth muscle throughout the body, especially in the vascular system when injected. Oral preparations exist. It is occasionally injected into an area where local vasodilatation is desired, especially into and around arteries and veins to relieve spasm during vascular surgery and when setting up i.v. infusions.

Selective Narcotic Antagonists (*29, 34, 40*)

Nalorphine (N-allylnormorphine, Lethidrone). The antagonistic effect of a related substance on opiate-induced respiratory depression was described in 1915, but the opportunity of introducing a specific antidote into clinical practice was not taken until 35 years later.

Nalorphine is closely related to morphine and has generally weaker but similar effects, though it will antagonise some of these effects when induced by morphine. Thus it is both agonist and antagonist. It was used as an analgesic in the hope that it would be non-addictive, but it caused unpleasant effects on mood (dysphoria) and hallucinations.

Clinically, morphine antagonism is best seen in severe respiratory and circulatory depression. There may be no antagonism to slight degrees of such depression, indeed there may even be synergism. Raised biliary pressure and miosis are reversed; heavy sedation may be relieved, but the subject may not wake from coma. Interaction of narcotic and antagonist are complex, and care is necessary when treating narcotic poisoning lest respiratory depression be made worse.

Nalorphine antagonises morphine by competing with it at the site of action; it is not itself an analeptic and so it does not oppose other respiratory depressants, such as the barbiturates, which are not chemically related to it. Antagonism is unequal for all the effects of morphine.

Nalorphine induces a withdrawal syndrome in addicts, and this can be dangerous, so it should not be used in diagnosis of dependence except by the experienced. Sophisticated addicts know about this and refer to nalorphine as "draino" or "climaline".

Nalorphine antagonises the respiratory depression of all morphine-like drugs and pethidine. It does not antagonise pentazocine.

In obstetrics, when morphine or pethidine has been given to the mother, there is a risk of respiratory depression in the child at birth. This can be prevented by giving nalorphine to the mother (5 to 10 mg i.m. or i.v.) before birth, or to the child at birth (0·2 to 0·5 mg into the umbilical vein).

Levallorphan is chemically to levorphanol (see table) what nalorphine is to morphine. It has similar properties and uses to nalorphine. **Cyclazocine** is similar, i.e. has agonist as well as antagonist effects.

Naloxone (Narcan) is a pure antagonist, i.e. it is without agonist action; it should probably replace nalorphine.

Opiate and antagonist mixtures, e.g. pethidine plus levallorphan

have been tried, in the hope of getting analgesia without respiratory depression, especially in childbirth; but they have not been proved superior. It is probably best to use narcotic analgesics alone and to give an antagonist separately whenever it is clinically indicated.

DRUGS AND THE DYING (*79-81*)

Although the dying are not necessarily in pain, it is convenient to discuss the subject here.

No definitive scientific drug comparisons in this protean* situation have been made, so that guidance can only be based on the too-scarce reports of extensive personal experience.

While the skilful use of drugs can provide incalculable relief and deserves careful study, this must not hide the fact that the manner, attentiveness and human feeling of the attendants are dominant factors once any grosser physical and mental aberrations have been controlled by drugs. The needs of the dying have been summarised as security, companionship, symptomatic treatment, and medical, nursing and domestic care. Nearly half of the deaths in England and Wales occur in the patient's own home.†

In painful diseases analgesics should be given regularly to prevent pain and not only to suppress it. Suppression requires larger doses, particularly where the pain has generated anxiety and fear.

It is kind to leave a dose of analgesic accessible to the patient, especially at night, when unnecessary suffering may result from reluctance to call a nurse or disturb a relative.

By reducing anxiety associated with anticipation of pain, as well as by reducing pain itself, dosage of narcotics may be kept within bounds and serious dependence avoided. Naturally, drug dependence matters less in the dying than in potential survivors, but it can be manifested as an "emotional and demanding" state (*79*) which is distressing to both patient and attendants. Addition of a tranquilliser (diazepam, chlorpromazine) may help to control the psychological aspects of pain so that less analgesic may be needed and severe dependence avoided. Combinations of narcotic and non-narcotic analgesics and alcohol can be devised to suit each case.

To promote sleep, alcohol and other sedatives and hypnotics may be combined usefully.

For anorexia, stout and sherry have a probably deserved reputation before meals and may even be acceptable to those with nausea and vomiting. Fizzy drinks, whether lemonade or champagne, may help too.

Mental distress may be helped by barbiturate-amphetamine mixtures as well as by alcohol-cocaine-heroin mixtures, or antidepressants, or tranquillisers, according to circumstances.

* Protean=having many changing shapes or forms: after Proteus, a sea-god, who "was difficult of access, and when consulted refused to give answers by assuming different shapes . . . and eluding the grasp" (Lemprière).

† HUGHES, H. L. G. (1960) Peace at the last. Calouste Gulbenkian Foundation, London.

A patient may too easily be drugged into uncomplaining silence, but it does not follow that he is not still in deep distress—

". . . the grief that does not speak
Whispers the o'er-fraught heart, and bids it break".*

Restlessness and confusion may respond to chlorpromazine, hyoscine (though this occasionally confuses the old) and other tranquillisers.

For nausea or vomiting, see *antiemetics.*

For dyspnœa, respiratory depressants (sedatives, opiates) bronchodilators may give relief.

For cough see index. *For raised intracranial pressure* see index.

Constipation will occur with continuous use of sedatives and opiates and deserves early and continuous attention to avoid fæcal impaction—bulk purgatives and fæcal softeners are useful, but stimulant purgatives may be needed. Enemas are undignified, unpleasant and prodigal of nursing time; they can often be avoided by early attention to constipation.

Rattling breathing due to excessive mucus may abate with atropine 1 mg i.v.

NON-NARCOTIC ANALGESICS AND ANTIRHEUMATICS (*42–57*)

These are mostly orally-active weak *analgesics* with little to choose between them except that some are more toxic than others.

They also have an antipyretic effect and some have an *anti-inflammatory* or "antirheumatic" action. Serious dependence does not occur. Where patients get into the habit of taking them, in the absence of physical disease that can be physically benefited, it is because they have an emotional need for a "medicine", and this group of drugs happens to be particularly readily accessible.

The group includes:

Salicylates

Aniline derivatives: phenacetin, paracetamol, acetanilide

Pyrazolone derivatives: phenylbutazone, phenazone, amidopyrine

Others: indomethacin, mefenamic acid, chloroquine, gold.

Salicylates (*42–50, 69, 77, 83, 85*)

Willow bark, which contains salicin, was used for fevers in the 18th century as a cheap substitute for imported cinchona (quinine) bark. It was tried because both willow trees and agues occurred in marshy places and because, according to the "doctrine of signatures", where a disease was found, so there would be a remedy nearby, provided by a beneficent Nature. This success is regarded now as the result of chance, though it was then considered to provide evidence in favour of the hypothesis of "signatures".

The latter half of the 19th century saw the first use of sodium salicylate

* WILLIAM SHAKESPEARE. (1564–1616) *Macbeth*, Act 4, Scene 3.

in acute rheumatism and the preparation and introduction of acetylsalicylic acid (aspirin).

"The British eat about two thousand tons (> 2 million kg) of aspirin yearly. This makes 6,000 million tablets, or two tablets every week for every citizen. In Connecticut, U.S.A., 37% of all bottles of blood collected came from donors who had recently eaten aspirin" (*50*).

Mode of action (*42*, *45*). It is known that aspirin, salicylate, indomethacin, etc. inhibit the synthesis of prostaglandins. There is evidence that prostaglandins are important mediators of inflammation and perhaps of pain (e.g. headache) and pyrexia. Evidence is accumulating that this single effect may be responsible for a number of actions of aspirin. Salicylate is a less effective inhibitor of prostaglandin synthesis; it is also a less effective analgesic than aspirin.

The principal actions of salicylates are listed below.

1. Analgesic
2. Antipyretic
3. Anti-inflammatory
4. Respiratory stimulation
5. Metabolic effects
6. Prevention of uric acid reabsorption in the kidney (uricosuric)
7. Hypoprothrombinæmia and reduced platelet aggregation
8. Cardiovascular effects
9. Gastro-intestinal effects

1. **Analgesic effect** is mild, being less than that of codeine. There is no evidence of any central effect on the psychic reaction to pain that plays so important a part in the action of the narcotic analgesics. Analgesia seems to be due to both central and peripheral action. Aspirin is most effective against mild pain of somatic origin; it is superior to sodium salicylate.

2. **Antipyresis.** Fever results from resetting of the hypothalamic body thermostat mechanism to a higher level. There is both increased heat production and decreased elimination. Aspirin acts in the hypothalamus to reset the thermostat lower (it has insignificant effect on a normally functioning thermostat). Though sweating is usual it is not essential to the antipyretic effect. Paradoxically salicylate poisoning can cause hyperpyrexia (see below). Nowadays, when antipyretics are seldom used for the purpose implied by their name, there is less interest in this effect, but before antimicrobials existed the physician could often do nothing else to show his power over disease. The efforts previously devoted to reducing fever are now turned more profitably to removing its cause.

3. **Anti-inflammatory** (antirheumatic) effect (see above).

4. **Respiratory stimulation** is characteristic of salicylate intoxication. It occurs as a result of both increased CO_2 production due to increased

peripheral cellular metabolism and of direct stimulation of the respiratory centre. In severe poisoning, of course, toxic depression can occur.

5. **Metabolic effects.** As the plasma salicylate concentration rises, the following sequence of events occurs. This is important in understanding, and therefore in the management of, poisoning—

(a) *Increased peripheral O_2 consumption* due to a direct stimulant effect on cellular metabolism, with increased CO_2 production, leading to increased respiration.

(b) *Direct stimulant effect on respiratory centre.*

(c) *Respiratory alkalosis* results from (a) and (b).

(d) Because of (c), *blood pH tends to rise* and this is compensated by the kidney which secretes bicarbonate which is necessarily accompanied by Na and K ions as well as water. This reduction of plasma bicarbonate is only of importance in that the body is deprived of one of its buffering systems and so becomes particularly vulnerable to metabolic acidosis which only occurs at high doses and chiefly in children.

(e) *Metabolic acidosis* occurs as a result of several factors including: accumulation of organic acids due to toxic interference with carbohydrate metabolism (see below): renal insufficiency due to vascular collapse, and dehydration (no fluid intake, hyperpyrexia): salicylic acid in blood: increased catabolism (see above) with depression of enzymes that break down acid products.

There is also toxic respiratory depression causing CO_2 retention.

Carbohydrate metabolism. Salicylates can lower the *blood sugar*, perhaps by increasing peripheral utilisation of glucose, and they have been used in diabetes mellitus. However, with heavy doses, hyperglycæmia may occur, perhaps due to depression of aerobic glycolysis, increased hepatic glycogenolysis and increased adrenal cortical activity.

Serum cholesterol is reduced by high doses taken for at least 2 weeks.

6. **Renal tubular reabsorption of uric acid** is reduced and salicylate can be used to deplete gouty patients of uric acid. However, high doses (5 to 8 g/day) are needed, and few patients can tolerate these. The uricosuric effect is greater in an alkaline urine. Low doses of salicylate (less than 2 g/day) cause urate retention (see gout).

Salicylate antagonises all other uricosuric drugs.

7. **Hypoprothrombinæmia** occurs with large doses; it is unlikely at less than 5 g of aspirin or sodium salicylate a day. It is preventable and reversible by vitamin K_1. Severe hæmorrhage is rare. The mechanism of action is unknown. The bleeding described below is independent of hypoprothrombinæmia. *Platelet aggregation* is also inhibited.

8. **Cardiovascular effects** of therapeutic doses are only important in rheumatic fever with active carditis; in these cases congestive heart failure or pulmonary œdema may be induced. The following factors conspire to cause this: increased oxygen consumption (by as much as 45%) with increased peripheral uptake of oxygen (there is an increase in arterio-venous difference). This is met by increased cardiac output. There

is an increased plasma volume (of uncertain cause) which may be enhanced by increased sodium intake where sodium salicylate and not aspirin has been used.

Patients with active carditis should therefore probably not be given full doses of salicylate, particularly as there is no evidence that it reduces late cardiac complications.

9. **Gastro-intestinal disorders** (*43*, *46*, *47*). About 1 in 15 of the population cannot take aspirin without risking symptoms (heartburn, epigastric distress, vomiting); part of these can be attributed to an action on the central nervous system, especially if high dose is being given, but the local effects are more important.

If a particle of aspirin is placed on human buccal mucosa, within 30 mins the mucosa becomes white, opaque and wrinkled and a slough that readily peels away is formed. Gastroscopic studies in man reveal congested, hæmorrhagic areas where particles are lodged, and these may occur in the absence of symptoms.

Aspirin (and phenylbutazone) do not act merely as local chemical irritants where a particle lodges, they increase gastric mucosal cell shedding (so do alcohol and mustard) and alter the quality and quantity of gastric mucus. The normal stomach mucosa sheds 0·5 million cells/min and it is not surprising that interference with such an active process causes trouble. The characteristic aspirin-induced lesion is a superficial erosion.

Occult blood loss (usually 2 to 6 ml/day) occurs in 50 to 70% of people taking aspirin. It is estimated by injecting radioactive chromate labelled erythrocytes i.v. and measuring the radioactivity of fæces passed subsequently. Sometimes larger amounts of blood are lost and iron-deficiency anæmia occurs, especially in those predisposed (women who menstruate).

The site of blood loss is predominantly the stomach and it seems that anything that reduces the concentration of aspirin applied to the mucous membrane or increases ionisation (so that it is less lipid soluble and less will penetrate gastric mucosal cells) lessens the liability to bleed and/or the amount of blood lost. Therefore, pharmaceutical ingenuity can reduce the risk, and a rapidly dispersing tablet, or one that makes a buffered solution and is then swallowed with much fluid, is least likely to cause trouble, though most preparations do not have enough buffering power to be useful. None of these preparations is free from irritant effect and in some subjects they are no safer than ordinary aspirin. Enteric coated aspirin causes less blood loss, for the small intestine is less affected than the stomach, but absorption is delayed for 6 or more hours, so that this preparation is unsuitable for occasional analgesia, though well suited for long-term medication, as in rheumatoid arthritis. A reliable preparation is essential or the tablet may disintegrate too soon, or not at all. Sodium salicylate may cause less blood loss, but it is a less effective analgesic.

A history of taking aspirin recently is more common in patients with overt gastroduodenal hæmorrhage, and it may be a causative factor in as many as 50% of cases, particularly those with acute erosions.

Alcohol increases gastric hæmorrhage from ordinary aspirin, but negligibly with buffered aspirin.

Because aspirin is a valuable drug, for which there is no adequate substitute, because it is free from patent restrictions and because pharmaceutical formulation is unusually important in reducing gastric toxicity, there is a plethora of commercial preparations, plain, buffered, soluble, effervescent, enteric coated.

A properly compounded **Aspirin Soluble Tablet B.P.** (300 mg) (dose 300 to 900 mg) and a reliable **enteric coated** preparation will meet all needs. The soluble tablet contains aspirin, citric acid and calcium carbonate. When it is put in water the citric acid reacts with the calcium carbonate to form calcium citrate solution, and this dissolves the aspirin to form calcium acetylsalicylate. The reason for this roundabout approach is that calcium acetylsalicylate is hygroscopic and, unless effectively protected from moisture, the drug is hydrolysed.

There are many tablets containing mixtures of aspirin, phenacetin, codeine and caffeine. Details can be found in any formulary.

Aspirin is plainly best avoided in patients with disease of the upper gastro-intestinal tract, but any proposal that the drug should be abandoned in favour of newer analgesics ignores the fact that it has been used successfully for decades by the public and the medical profession, despite this effect. Considering that thousands of tons are eaten annually, significant toxic effects from aspirin are uncommon.

Pharmacokinetics. Aspirin is well absorbed from the stomach, for at the acid gastric pH it is unionised and so is lipid soluble. After entering the mucosal cell, the change to higher (body) pH renders it more ionised and so less diffusible. It therefore accumulates in the cells and it is not surprising that it can damage the mucosa. Such cellular concentration does not occur in the intestine where the pH gradient is less. Aspirin caused gastric bleeding can be substantially reduced by reducing gastric absorption (raising gastric pH, use of enteric coatings). It might be thought that at high pH in stomach and intestine there might be serious failure of absorption, but this is not so, for two reasons; first, aspirin is more soluble in alkaline medium, and, second, the enormous absorptive area of the small intestine more than counterbalances the adverse effect of pH. But if enough alkali is given to raise urine pH, there will be greatly enhanced excretion.

Salicylates are about 60% bound to plasma protein (aspirin is less bound). It displaces thyroxine from its carrier protein so that there is a fall in protein bound iodine and thyroid function tests can be misleading, but this is insignificant with occasional small doses.

Salicylate and aspirin are partially conjugated in the body. They are excreted by the kidney unchanged and as conjugates. The proportion excreted as free salicylate varies with urinary pH (from 10% to 80%). Females metabolise aspirin slower than males and are more liable to adverse effects (*83*).

A reasonably steady plasma concentration can be maintained if salicylates are given orally 6-hrly, which is about the half-life of the drug in normals, though this also can vary enormously with urine pH. But the half-life also varies with dose, and in cases of poisoning can be as long as 20 hrs.

The practical importance of pH is shown by the fact that the amount of salicylate in urine at pH 8 is four times that at pH 7. Therefore, if it is desired to get salicylate out of the body quickly an alkaline diuresis will be useful, and this can be employed in the treatment of poisoning. The technique is described in relation to phenobarbitone (which see).

Adverse reactions include *gastric bleeding* (see above); *allergy* (asthma, angioneurotic œdema, urticaria, rashes, rhinorrhœa) occurs; aspirin may aggravate chronic urticaria.

Aspirin is the commonest drug to cause asthma and the incidence is greatest in middle-aged women with nasal polypi, but this may not be a true allergy (see under *drug allergy*).

Patients allergic to aspirin are seldom allergic to sodium salicylate.

Salicylates cause *renal irritation* (cells, casts and albumin in the urine). The effect is proportional to the dose and can be responsible for erroneous diagnosis of renal disease. If the patient takes salicylate continuously the renal effect passes off in about a week. It is uncertain whether significant or permanent renal damage occurs.

The typical clinical picture of moderate **overdose** consists of nausea and vomiting, tinnitus, deafness, hyperpnœa, headache, sweating, restlessness and mental confusion. If administration has been prolonged there may rarely be hæmorrhage due to hypoprothrombinæmia. Presence of occult blood in the fæces is usual. It is probably best to give some vit. K_1.

With a big overdose these symptoms may be followed by mania, hyperpyrexia, convulsions and coma, with severe dehydration and ketosis.

Metabolic changes in salicylate poisoning are complicated and not entirely understood, but have an important bearing on therapy (see above).

The interaction of these factors determines the blood pH. When the metabolic effects dominate, acidosis results; when the respiratory effects dominate, there is alkalosis.

The age of the victim of poisoning is related to what happens.

In children, especially those poisoned during therapeutic use for fever, *metabolic acidosis* dominates.

In adults, especially those, physically healthy, who have taken a single large dose, *respiratory alkalosis* dominates, blood pH rises and tetany may occur.

The reason for this difference is unknown; it may be a true age-difference in response, or it may be due to the different circumstances in which poisoning occurs, whether during prolonged therapy or a single large dose.

In severe poisoning the plasma pCO_2, standard bicarbonate and blood pH must be measured. Blood pH must be measured because a false

conclusion may be drawn if pCO_2 and bicarbonate alone are measured. Patients showing alkalosis or mixed alkalosis/acidosis with normal pH need no therapy directed to changing the blood acid-base balance. The low plasma bicarbonate content does *not* alone indicate acidosis, and if sodium bicarbonate is given the patient may develop severe alkalosis with tetany.

If the patient has a mixed alkalosis/acidosis with acid blood pH,* small doses of sodium bicarbonate (2 to 4 m/mole per kg) may be given, and controlled by plasma standard bicarbonate and blood pH measurements. Lack of facilities to measure these and/or of ability to interpret the results, greatly increases the dangers of salicylate poisoning.

In an emergency, without guidance of laboratory measurements a patient thought to be acidotic may be given an i.v. infusion of Sodium Lactate Compound Inj. B.P. (Ringer-Lactate) (rather than Sodium Lactate Inj. B.P.), or a similar solution containing an amount of bicarbonate equivalent to the lactate. A patient thought to be alkalotic may be given Sodium Chloride and Dextrose Inj. B.P.

Correction of dehydration, which can be severe due to sweating, vomiting and overbreathing, is of the first importance, and so is reduction of hyperpyrexia by sponging. No attempt should be made to stop hyperventilation. Dextrose may be given, despite hyperglycæmia, for starvation contributes to ketosis.

Removal of salicylate from the body by alkaline diuresis is rational, and has been used successfully (*49*) even in alkalotic adults (for technique of forced alkaline diuresis see under barbiturate pharmacokinetics). Good results can be got by combining acetazolamide and sodium bicarbonate, e.g. the half-life of salicylate may be reduced from about 20 hrs to about 6 hrs. In practice a high plasma salicylate concentration may be halved in about 8 hrs. See also *dialysis*.

A random serum salicylate level is not a reliable guide to the severity of poisoning because it gives no indication of the course of the poisoning before it was measured.

However, a level above 40 mg/100 ml. can be taken as confirming the diagnosis, and if it is above 70 mg/100 ml in a patient who took the drug hours previously the case is severe. Serial levels, measured hourly, give more information.

Hæmodialysis, peritoneal dialysis or exchange transfusion (infants) can be done in specially equipped centres. These techniques are indicated in severe cases and the decision to use them should not be left until the patient is moribund. Patients, particularly children, poisoned by salicylate, can die in a very few hours. There are about 200 deaths per annum in England and Wales.

The similarity between salicylate poisoning and diabetic ketosis can be very close (hyperglycæmia, ketosis and reduction of Benedict's solution by the urine, the latter due both to glucose and to glucuronides of

* Specific alkali therapy is only needed if acidosis is severe (blood pH less than 7·2).

salicylate). Salicylate gives a brighter violet colour with ferric chloride than do ketones, and the colour due to salicylates is not influenced by first boiling the urine, which process removes the volatile ketones and destroys the non-volatile acetoacetic acid present in diabetic ketosis.

Uses. Apart from their use in minor pain and fevers, the principal use of salicylates is in rheumatic fever and rheumatoid arthritis (which see).

Aloxiprin (Palaprin) is a condensation product of aspirin and aluminium hydroxide: it is an alternative to soluble aspirin.

Benorylate (Benoral) is an ester of aspirin and paracetamol. It causes less blood loss than does aspirin.

Salicylamide is similar to salicylates. Claims that it gives equal therapeutic effect for less toxicity have not been firmly established.

Methyl salicylate (oil of wintergreen) is too irritant to be used internally. It is used in counter-irritant liniments. Its smell sometimes attracts children; if they drink it, treatment is urgent.

Aniline Derivatives

Phenacetin (acetophenetidin) is an effective mild analgesic which is commonly used in combination with others. It has antipyretic, but no useful antirheumatic, effect. It is an important ingredient of many analgesic mixtures used for somatic pain, usually in combination with aspirin, caffeine or codeine. The fact that it is rarely taken alone has made it difficult to delineate its long-term adverse effects (see below).

Phenacetin is converted into p-acetomidophenol in the body; this is probably the active analgesic substance and is available as paracetamol, see below.

Chronic over-dosage can also cause met- and sulphæmoglobinæmia, with hæmolysis. But continuous use at doses ordinarily regarded as safe for short periods can cause renal damage and phenacetin is being replaced by paracetamol although the safety of paracetamol remains uncertain.

Analgesic nephropathy (*51–56*). Mixtures of non-narcotic analgesics taken continuously over years can cause grave and often irreversible renal damage. At first phenacetin alone was suspected, but other drugs, e.g. aspirin and caffeine, have been found to cause shedding of renal tubular cells in the urine in normals; a wide range of drugs can cause renal papillary necrosis in rats. Drugs are greatly concentrated in this part of the kidney.

Analgesic nephropathy is most common in severe chronic rheumatism and in patients with personality disorder. Kincaid-Smith* describes them as characteristically sallow, middle-aged women who smoke heavily, cannot sleep without sedatives, have recurrent ill-health and who have "suffered dreadfully" from headaches for as long as they can remember.

* KINCAID-SMITH, P. (1970). *Prescr. J.*, **10**. 8.

They have commonly had a broken marriage and may have attempted suicide. The disease manifests itself as renal symptoms, particularly nocturia and renal colic; anæmia and hypertension are common; proteinuria may be only slight; sterile pyuria is common.

Phenacetin abuse and toxicity. Although phenacetin was introduced in 1887, it was not until 1953 that suspicion was aroused that it might cause renal damage. Certainty was not easily attained because, as well as the difficulties of interpreting associations discovered by retrospective enquiry, phenacetin is almost never used alone and it is hard to separate the effects of the several ingredients of mixtures. These mixtures have been widely abused, particularly on the European mainland, being used for any trivial discomfort. The remarkable extent to which people can become dependent on them is shown by events in a Swedish town (*68*), and these illustrate that drug abuse has emotional and social as well as pharmacological aspects.

During the influenza pandemic of 1918 a physician to a big factory in the town prescribed a powder containing phenacetin (0·5 g), phenazone (0·5 g) and caffeine (0·15 g). There was substantial mortality from the epidemic, but survivors thought they felt fitter and reinvigorated during convalescence if they took the powder. They continued to take it after recovery, in the expectation of becoming stronger and "more nimble of finger", so that they would earn more in the factory.

Use of the powder, which could be got without prescription, spread through the town. Consumption increased and "many families could not think of beginning the day without a powder'." It became almost as usual to offer a powder as a cigarette. When visiting friends in hospital, a powder "was as welcome as flowers, fruit or chocolate, whatever the nature of the illness. Attractively wrapped packets of powder were often given as birthday presents." Doctors regarded the habit "as something of a joke".

The phenacetin consumption of the town was about 10 times as great as in a comparable Swedish town. The deaths from renal insufficiency rose in the phenacetin town, but not in the control town, and in the decade 1952–61 they were more than three times as many.

An investigation was resisted by the factory workers and there was even an instance of organised burning of a questionnaire on powder-taking. It was eventually discovered that most of those who used the powders did so, not for pain, but to maintain a high working pace, from "habit", or to counter fatigue.

There is no reason to think phenacetin or phenazone effective for these, but each powder contained enough caffeine to give a noticeable effect, and as many as 10 to 12 a day were sometimes taken. The workers developed a considerable emotional dependence on the powders in the exact form in which they were accustomed to take them. Any slight change in the appearance of the powder rendered it, they thought, useless. Along with warnings of the danger of renal damage, a clinic was set up to help people break their habit. At first those who went to it were subjected to

"persecution and derision" by their colleagues, but eventually the rising death rate brought home to the consumers the gravity of the situation, a thing that has not yet been achieved with cigarette smoking.

In 1961 phenacetin was withdrawn from sale to the public in Sweden and could only be obtained on prescription. The devotees of the powder changed to a phenazone, caffeine formula. When asked, they usually replied "that it was quite useless, but that one had none the less to take a few now and then". Sales of this powder, however, remained about the same as those of the original phenacetin-containing powder.

Sudden withdrawal demonstrated that there was no physical dependence on the mixture, and the emotional dependence was probably a social, rather than a pharmacological phenomenon though the latter remains possible.

Similar abuse has occurred amongst workers in the Swiss watch industry.

Most of the evidence that phenacetin causes renal damage is circumstantial; attempts to reproduce the lesion in animals have been only partially successful. The characteristic lesion, interstitial nephritis with renal papillary necrosis, is most commonly seen in patients with diabetes or overt recurrent infection with or without urinary tract obstruction. Its occurrence in the absence of these factors is associated with a high incidence of heavy and prolonged phenacetin consumption. Pyelonephritis is often present, and the role of infection is disputed; whether it is a cause, or a consequence, of renal damage.

Patients present with acute or chronic renal failure and many improve when the analgesic mixture is withdrawn.

In addition, analgesic abusers may have a higher incidence of *renal pelvic tumours*. As with the nephropathy, phenacetin is particularly suspected.

Until these problems are thoroughly understood the wisest course may be always to enquire into analgesic-taking by patients with renal failure of obscure origin, to warn all renal patients to avoid such mixtures, to advise all diabetics to avoid them and to avoid long-term prescription of the mixtures for continuous regular use in anyone.

Paracetamol (57) (acetaminophen, Panadol) (0·5 g) is the metabolite of phenacetin that provides the analgesia. It is a useful analgesic that has largely replaced phenacetin (see above).

The plasma half-life of paracetamol is about 2 hrs in normals. Most of the drug is conjugated in the liver. In poisoning, liver damage occurs and prolongs the half-life to 8 hrs or more. Liver damage may be due to a metabolite rather than to the parent drug. Forced diuresis is unlikely to be useful in paracetamol poisoning both because the liver is damaged early and the renal excretion is rapid in relation to the usual time-course of organising treatment in such cases (57).

It is uncertain whether prolonged use causes renal damage. Paracetamol is less likely to cause methæmoglobin and hæmolysis than is phenacetin.

The oral dose is 0·5 to 1·0 g up to 5 times a day.

Acetanilide was introduced into medicine by mistake in 1886. It was intended to treat a pyrexial patient with intestinal worms by naphthalene, but acetanilide was given in error and the patient's temperature fell. It is an effective antipyretic and analgesic and is widely sold in proprietary preparations. It can be regarded as a more toxic form of phenacetin and since it has no compensating advantages it should be abandoned.

Pyrazolone Derivatives

Phenazone (antipyrine) is little used because of its toxicity which includes rashes, giddiness, tremors and sweating. It has no advantages to compensate for these, Because a lot is known of its pharmacokinetics it is used as a standard drug in measuring differences in hepatic microsomal enzyme capacity.

Amidopyrine is perhaps the most effective of the antipyretic analgesics, with a potent anti-inflammatory effect. However its propensity for causing agranulocytosis has led to its abandonment in Britain.

Phenylbutazone (Butazolidin) (100, 200 mg) (59) was used as a solvent for amidopyrine injections. In 1949 it was noticed that, in patients with rheumatoid arthritis, better clinical results were obtained when amidopyrine was given by injection than by mouth, despite the fact that blood levels of the drug were similar in each case. The only difference was the injection solvent (phenylbutazone) and this was then tried alone and found to have *potent "antirheumatic"* effects and to be a weak analgesic in addition.

Pharmacokinetics. Phenylbutazone is well absorbed from the gut. About 98% is bound to plasma protein and it competes for binding sites with other drugs, leading to clinically important interactions (which see). When injected i.m. it is slowly absorbed because it binds to protein locally and the peak plasma concentration is reached only after about 8 hrs instead of after the usual 2 hrs with oral administration.

The plasma half-life is about 72 hrs so it is not necessary to give it 3 times a day to maintain steady plasma concentrations, but such frequent administration may reduce gastric bleeding from the drug and is advisable.

Phenylbutazone is a potent liver enzyme inducer, and thus is a cause of interactions. For this reason, too, there is no purpose in exceeding the recommended doses, for the blood level does not increase concurrently, due to increased metabolism of the drug with increased dose. The blood levels with 1,600 mg and 800 mg a day are the same, but toxic effects increase with the dose. 800 mg a day can be given without great risk for a short time in many patients if they are watched carefully. Generally it is undesirable to exceed 400 mg a day total (in 3 doses) orally. Suppositories are available.

Phenylbutazone is almost entirely metabolised. Two important metabolites are oxyphenbutazone which has little uricosuric effect and is used as a drug, and another which has the uricosuric effect (but which is not

used in therapeutics as it is not absorbed from the gut). Like other uricosuric agents, phenylbutazone, in low dose, may actually cause retention of uric acid. This can be masked by hæmodilution due to salt and water retention (see below).

Uses: as anti-inflammatory and analgesic in rheumatoid arthritis, ankylosing spondylitis, gout and in superficial vein thrombosis; it may possibly benefit giant cell arteritis. It is also an effective uricosuric in gout.

Adverse effects are common except at low doses, and can be fatal. They include gastro-intestinal upsets with bleeding, perforation of peptic ulcers, hæmatemesis and melæna and phenylbutazone should not be given to patients with indigestion or peptic ulcer.

Œdema occurs, due to a renal effect in reducing sodium and water excretion and this may precipitate heart failure: it should not be given if there is renal or cardiac disease. Rashes, vertigo, insomnia, visual disturband and agranulocytosis or aplastic anæmia also occur. Hepatic damage is rare. Whether the reported association of phenylbutazone with leukæmia is causal remains unproved.

Active search continues for compounds with the therapeutic activity of phenylbutazone but without its toxicity. Several have been produced but have not yet been shown to be superior, e.g. oxyphenbutazone (Tanderil), nifenazone (Thylin).

Indole Derivative

Indomethacin (Indocid) is a potent anti-inflammatory agent without intrinsic analgesic activity. It is an alternative to phenylbutazone and it differs chiefly in having a higher incidence of adverse effects on the gut and CNS and less on the blood. Long-term use carries a high incidence of unwanted effects including the eye. It is best avoided in the presence of disease of the CNS, gut or kidney and in infections. Tablets and suppositories are available.

Others

Methotrimeprazine (Veractil) is a phenothiazine. It is a potent analgesic and sedative. It depresses respiration less than morphine and may not induce dependence.

Mefenamic acid (Ponstan) and **flufenamic acid** (Arlef) are analgesics similar in power to aspirin but they compare unfavourably for adverse effects, particularly diarrhoea.

Ibuprofen (Brufen), ketoprofen (Orudis) and alclofenac (Prinalgin) are alternative anti-inflammatory analgesics.

Innumerable non-narcotic preparations are available, some of which do not belong to the above chemical groups and are not antipyretics, for the market is vast and profitable. No indispensable drug has been omitted from the account above, and some that could be dispensed with have been included.

DRUG TREATMENT OF ACUTE RHEUMATISM (*58*, *70*, *76*, *78*)

So effective are salicylates in relieving pain and inflammation in acute rheumatism that failure to respond within 48 hours throws doubt on the diagnosis. Dispute has long existed about whether the late cardiac and other long-term complications of acute rheumatism can be prevented by salicylates. This now seems unlikely.

From their introduction into therapeutics adrenal steroids have been used. They also provide dramatic relief and the problem has been to decide whether salicylates or steroids or both together give the best therapeutic result, particularly regarding the prevention of late complications.

Illingworth and his colleagues (*70*) have compared five different treatments on a total of 200 patients against an untreated group:

Group 1 had no specific treatment
" 2 " low doses of sodium salicylate
" 3 " high doses of sodium salicylate
" 4 " adrenal steroid or corticotrophin
" 5 " adrenal steroid plus low doses of sodium salicylate
" 6 " adrenal steroid plus high doses of sodium salicylate.

They conclude that the best treatment of the acute attack is adrenal steroid plus high doses of salicylate. The benefits conferred are a more rapid fall of the erythrocyte sedimentation rate (E.S.R.), a shorter duration of arthritis, new rheumatic manifestations during treatment are fewer, temperature falls sooner and more cardiac murmurs disappear. It is probably best to use a steroid in patients with established heart failure or who are in danger of heart failure (cardiac hypertrophy) and also in those with pericarditis which does not respond to salicylate.

In a large international study (*58*) over 10 years there was no evidence that the prognosis was influenced by whether the patient was treated with aspirin, corticotrophin or cortisone.

Rheumatic fever may be treated initially with oral sodium salicylate 100 mg/kg total/day in four doses. It is probably not necessary to use the maximum tolerated dose or to keep the plasma salicylate concentration between 30 and 40/mg/100 ml as was previously recommended. The guide to dosage is relief of symptoms.

Soluble aspirin at similar dose may be preferred because it is undesirable to give extra sodium if there is likely to be any heart failure or if a steroid is being used. Bicarbonate should not be given with the salicylate as it only increases the turnover.

Phenylbutazone (600 mg/day for 4 days: 400 mg/day for 2 weeks: 200 mg/day for at least 2 weeks) may be better tolerated than aspirin and may give quicker control.

In addition an adrenal steroid may be given, say prednisolone, 60 mg on the first day, then 40 mg a day for 4 days, 20 mg a day for 16 days,

12·5 mg a day for the fourth and fifth week and 10 mg a day for the sixth week and after.

Treatment should be continued for at least 6 weeks or until the E.S.R. is normal for three consecutive weeks, whichever period is shorter. A 10-day course of penicillin should be given to kill any streptococci. Prophylaxis of streptococcal infection in patients who have had rheumatic fever is described in ch. 8.

DRUG TREATMENT OF RHEUMATOID ARTHRITIS (*60–65, 71–73, 75*)

Best results are obtained with early treatment, rest, physiotherapy and drugs.

The aims of drug therapy are to relieve pain and muscle stiffness and to suppress inflammation.

Relief of pain and muscle stiffness. Aspirin (2 to 6 g a day) is the drug of choice, but the high dose needed (usually just below that which induces tinnitus) means that gastric intolerance is common. Other forms of aspirin, e.g. aloxiprin may suit individuals better. Enteric-coated aspirin at night is useful to reduce early morning muscle stiffness.

If aspirin fails, phenylbutazone can be tried, but it is more toxic. The third choice is indomethacin. Paracetamol is less effective than aspirin.

Suppression of local inflammatory process

Though aspirin, phenylbutazone and indomethacin have anti-inflammatory effect, they are far inferior to adrenal steroids.

Systemic adrenal steroids are in no way curative. Their effects are only temporary and administration must generally continue indefinitely if relief is to be maintained. Some patients become refractory. Joint destruction may progress even in the presence of symptomatic relief. Chronic use also exposes the patient to the unwanted effects of the steroids which can be very troublesome. Therefore steroid therapy should not be lightly begun. It is not a substitute for other treatments, should only be used when these others have failed and it should be withdrawn after 2 months, if possible. Patients must be mentally stable and co-operative and prepared to accept partial improvement, if this is all that can be obtained without unwanted effects, as it well may be. Those who have had the disease for more than two years are liable, once a steroid has been started, to need it indefinitely, because attempts at withdrawal are followed by brisk exacerbation.

A steroid will not help patients whose disability is due to irreversible joint damage. There is evidence that prednisolone is superior in therapeutic effect to cortisone and to aspirin (*71*) and that the dose should not exceed 10 mg a day over long periods. The decision to use a steroid in rheumatoid arthritis is best taken by a physician who has made a special study of the disease.

Corticotrophin may be used instead of an oral steroid; it has both advantages and disadvantages.

Attempts to get the benefits of adrenal steroid therapy without its long-term hazards, by using repeated short courses of corticotrophin or occasional large dose of an oral steroid have not proved successful.

Intra-articular injection of hydrocortisone, or another steroid (prednisolone, dexamethasone) may be used when one joint is relatively more severely affected than others or when there are contra-indications to systemic therapy, such as pregnancy, diabetes or tuberculosis. Benefit from one injection may last many weeks (shorter in active cases). Aseptic precautions must be extreme, for the steroid will suppress inflammatory response and any introduced infection may spread dramatically. With repetition, enough may be absorbed into the blood to cause pituitary suppression. The placebo-effect of intra-articular injection is great (75).

Excessive therapy may lead to destruction of weight-bearing joints, perhaps because the relief of symptoms encourages greater use than the diseased joint can support without damage.

Gold and antimalarials are used in patients with active, progressive disease in whom anti-inflammatory analgesics have failed and in whom it is wished to avoid beginning an adrenal steroid, or to reduce steroid requirement. *Gold* has actions on collagen and synovial membrane and *chloroquine* has anti-inflammatory effects, but details of their therapeutic effect remain obscure. Onset of benefit occurs over weeks.

Gold salts were first used in rheumatoid arthritis in 1929 in the mistaken belief that the arthritis was a tuberculous manifestation. Opinions on the therapeutic merit of gold have fluctuated, but there has never been any doubt about its dangers, which can be serious. Gold is said to be the most effective agent for preventing progression of the arthritis, best results being obtained in early cases. The decision to employ gold should only be undertaken by physicians with special experience of the disease.

Gold is heavily plasma protein bound. It is concentrated in the kidney (by which it is slowly excreted) and can damage it severely. Weekly injections are cumulative so that at the end of a course the patient has such a high gold reserve that it will take as long as a year to eliminate it.

Sodium Aurothiomalate Injection, B.P., is given i.m. weekly, say 10 mg for 2 weeks, 20 mg for 2 weeks and then 50 mg weekly until one gram has been given. Benefit appears after 6 to 12 weeks. If there is none after one gram, it should be stopped. If there is benefit, 50 mg may be given monthly, indefinitely, until the disease becomes inactive.

Toxic effects. In skilled hands these occur in less than 5% of cases. They include pruritus, dermatitis, glossitis and stomatitis, most commonly, and also blood disorders, hepatic and renal damage, peripheral neuritis and encephalopathy. The patient should be warned to report any untoward symptoms at once. Serious effects are rare if the patient is carefully observed and the drug stopped at the earliest sign of toxicity. The urine should be examined for albumin before each injection. Gold should be stopped at

once on the appearance of any toxic effect and should not be given again unless the reaction was trivial, in which case it may be recommended at lower dose after the toxic effect has disappeared, but not before 6 weeks have passed. Any serious effect, or one which does not subside rapidly, should be treated with a chelating agent; dimercaprol is probably preferable to penicillamine. Adrenal steroids may be useful, as at least some of the toxicity is due to allergy.

Antimalarials of the chloroquine group (4-aminoquinolines) were tried in rheumatoid arthritis following improvement of the arthritis of discoid lupus erythematosus during antimalarial treatment of the skin manifestations. They offer an alternative to gold and adrenal steroids.

Benefit is not seen for about 4 weeks; up to 50% of patients may respond usefully.

Chloroquine accumulates in many organs, including the eye. It interferes with pigmentation generally and this effect may be related to its retinal toxicity which is, it seems, confined to the less pigmented races. Retinal damage can occur or progress after cessation of therapy.

After prolonged dosage small amounts of chloroquine are found in the urine for months or even years. The plasma half-life is about 6 days immediately after stopping continuous therapy and rises to over 2 weeks a month later when plasma concentrations are low.

Early toxicity includes gastrointestinal upsets, vertigo, malaise and depression; these may wear off. Later effects include rashes, bleached hair, myopathy and, most important, corneal opacities and retinal damage.

The *corneal* opacities, seen with a slit-lamp and evidenced by misty vision and haloes round bright lights, may occur about 4 weeks after therapy begins. They disappear over about 3 months if therapy is stopped. *Retinal* damage, first shown by central field defect, is rare unless therapy continues above a year; it can result in serious permanent damage to sight.

An attempt should be made to withdraw the drug, slowly, in less than a year. If it is necessary to continue, dosage should be minimal and the patient's vision monitored by an ophthalmologist 6-monthly.

Eighth nerve damage occurs rarely. Chloroquine may damage the fetus (chiefly sight and hearing). Omission of the drug for 3 months every 4 to 6 months may allow prolonged therapy safely. Hydroxychloroquine is an alternative. **Penicillamine** may benefit advanced cases.

Immunosuppressive drugs, e.g. azathioprine, have been used and can produce improvement. It is uncertain whether this is due to suppression of an autoimmune process alone or also to a non-specific anti-inflammatory effect. Inevitably, unwanted effects are troublesome and the treatment needs to be carefully monitored by physicians who have made a special study of it. Immunosuppressives are carcinogenic and the magnitude of this risk, which is particularly important in younger patients with a long life expectancy is uncertain; they are also mutagenic and teratogenic so that precautions over reproduction whilst taking the drugs are essential for both sexes.

Choice of drugs in rheumatoid arthritis can be summed up as the use of anti-inflammatory analgesics first and the introduction of the more toxic agents, chloroquine, gold and, finally, an adrenal steroid or immuno-

suppressive only when they fail. Chloroquine and gold may be used during attempts to withdraw a steroid.

Other aspects of the treatment of this disease are important but are outside the scope of this book.

Osteoarthritis

Aspirin, phenylbutazone and indomethacin give symptomatic relief. Severely affected large joints, especially when acutely exacerbated by trauma, benefit from intra-articular hydrocortisone.

Ankylosing Spondylitis

Phenylbutazone is the most effective drug. In severe cases where it gives relief but causes gastrointestinal toxicity, suppositories may be substituted for oral therapy.

Both phenylbutazone and indomethacin are superior to aspirin for symptomatic relief. Adrenal steroids are not useful and the place of radiotherapy is controversial. Physical methods of treatment are of the first importance to prevent deformity.

DRUGS AND GOUT (*66, 67, 74*)

Drugs with analgesic or anti-inflammatory effect: colchicine and demecolcine; **phenylbutazone;** indomethacin; adrenal steroids and corticotrophin.

Uricosuric drugs that usefully increase elimination of urate: probenecid, sulphinpyrazone and ethebenecid.

Drugs that block uric acid synthesis: allopurinol.

Drugs that may precipitate acute gout by blocking renal elimination of urate: thiazide diuretics, ethacrynic acid, frusemide; acetazolamide; all uricosuric agents in small doses (probably); pyrazinamide, clofibrate.

Colchicine (0·5 mg) **and demecolcine** are alkaloids from the autumn crocus. They are antimitotic agents of little use in neoplastic disease, but valuable in gout, in which they relieve the pain and inflammation in a few hours. Such rapid relief is considered to confirm the diagnosis, because non-gouty arthritis is unaffected, though failure does not prove the patient has not gout. An ingenious explanation of the specificity of colchicine has some experimental backing (*74*), though it lacks firm proof.

Crystals of monosodium urate are deposited from hyperuricæmic body fluids—the detailed factors that start this process are still largely obscure—and a local inflammatory response with phagocytosis of the crystals, occurs. It is known that actively phagocytic leucocytes produce lactic acid, and this promotes urate crystallisation, for urates are less soluble in an acid medium. With more crystallisation there is more inflammation and more phagocytosis with more lactic acid production, and a "self-propagating, self-stimulating inflammatory reaction" results.

Inflammation is also enhanced by digestive enzymes released from leucocyte lysosomes.

Colchicine suppresses leucocyte phagocytosis and, by reducing lactic acid production, prevents the pH change in the tissues that causes more crystallisation; thus it interrupts the inflammatory cycle. It also stabilises leucocyte lysosomes.

Colchicine is absorbed from the gut, some is metabolised in the liver and some is excreted unchanged in the bile and reabsorbed from the gut. This enhances its gut toxicity.

Effects of **overdose** may be severe. Gastro-enteritis occurs, with abdominal pain, vomiting and diarrhœa which may be bloody after both oral and i.v. administration. It is probably due to inhibition of mitosis in the rapidly reproducing cells of the intestinal mucosa. Renal damage can occur and, rarely, blood disorders. Large doses cause muscular paralysis.

In **acute gout** colchicine, 1 mg orally, may be given, followed by 0·5 to 1 mg 2-hrly until either relief or toxic effects occur. Benefit is usually felt in 2 or 3 hrs and is marked within 12 hrs. 4 to 8 mg total are usually needed, and it is unwise to exceed 10 mg, but colchicine, like all drugs, sometimes fails. If gastro-intestinal side-effects are severe the patient may tolerate demecolcine, the dose of which is the same. The results of colchicine therapy are best if the drug is given early in an attack. Once the effective dose is known for any patient he can take half the total at once when he feels an attack coming on, and then 0·5 mg hourly.

Injection i.v. should never be necessary; extravasation should be carefully avoided, even though a court of law is uncertain just how damaging it can be.*

Colchicine is an effective **suppressant prophylactic** against gout in doses of 0·5 to 1 mg a day, or on alternate days.

Probenecid (Benemid) (0·5 g) is a uricosuric agent. It is not an analgesic. It was discovered as a result of a search for agents that would prevent **penicillin excretion** by the renal tubule and so enable high penicillin plasma concentration to be maintained by small doses. Probenecid does this effectively, but as penicillin has become so cheap there is no longer any particular advantage in not adopting the alternative and simply increasing the dose. Probenecid is however occasionally used in infections where exceptionally high penicillin plasma concentration is desired, as in some cases of bacterial endocarditis, in children in whom large and frequent injections are specially unpleasant, and where the maximum effect is needed from a single dose treatment, e.g. in gonorrhœa where patient default is common. Probenecid also blocks tubular excretion of cephalothin and cephalexin; but cephaloridine is only little excreted by the tubule and so not importantly affected.

Probenecid, because it interferes with renal tubular excretion of penicillin (and PAS as well as other substances) and reabsorption of urate, is

* *Brit. med. J.* (1964), 1, 992.

clearly *interfering with active renal tubular acid transport* processes, probably by competition. It does not affect the excretion of other antibiotics. It does interfere with excretion of dyes used for intravenous pyelography.

Urate in the glomerular filtrate is virtually entirely reabsorbed in the proximal tubule, and that in the urine (about 7% of that in plasma) derives from secretion by the distal tubule. Unfortunately, it seems that salicylate and probenecid can interfere with both processes, for their action is to block energy-requiring transport, and the end result depends on which process is most affected. At high doses, the dominant effect is on proximal tubular reabsorption, but at low doses distal tubular secretion may be most affected, which would account for the fact that low doses can cause urate retention. However, this is only of practical importance with salicylate.

During about the first 4 weeks of therapy there is increased risk of acute gout, despite a reduction in blood urate. This may be due to a falling and fluctuating plasma urate concentration encouraging the solution and perhaps intermittent recrystallisation of urate from tophi. Colchicine may be used as a suppressant during this period, and patients should be warned of the possibility, for it can create an unfavourable impression if the patient, who has only been told that the drug will prevent his gout, promptly has a severe attack.

Probenecid is well **absorbed** from the alimentary tract. It is partly metabolised and partly excreted unchanged in the urine. It causes gastrointestinal upset in a few patients and allergy occasionally.

To prevent gout probenecid is given orally, 0·5 g or occasionally 1 g, twice a day. The blood urate concentration falls rapidly at first and then levels off at about two-thirds of the initial concentration. Crystals of urate may appear in the urine and so it should be made alkaline (with potassium citrate or sodium bicarbonate) and a high fluid intake (3 l/day) taken for the first month of probenecid (or any other uricosuric) administration to avoid the dangers of mechanical obstruction or stone formation. Care should be exercised if this is done, because some gouty patients have renal insufficiency.

Probenecid may fail if there is renal failure (see allopurinol).

The benefits to be anticipated from lowering plasma urate are reduction in frequency of attacks of gout, prevention of the formation of new, and reduction in the size of existing, tophi and prevention of renal damage.

Sulphinpyrazone (Anturan) (100 mg) is related to phenylbutazone. It is potent, and alkalinisation of the urine and high fluid intake are necessary at first to avoid crystalluria. For this reason dosage may begin with 50 mg orally 12-hrly, rising to 100 mg 6-hrly over a few weeks. It may be possible to reduce it to half that dose later. Sulphinpyrazone causes gastric upset and is contra-indicated in peptic ulcer.

Ethebenecid (Urelim) is similar to probenecid.

Plasma protein binding of urate and drugs. About 30% of urate is plasma protein bound and this is reduced markedly by aspirin, phenylbutazone, probenecid, all uricosuric agents. It is not known if this plays a part in their clinical effects, including precipitation of acute gout. The following drugs do not importantly alter urate binding, sulphinpyrazone, indomethacin, colchicine (*66*).

Allopurinol (100 mg) is not uricosuric. It is an isomer of hypoxanthine which blocks the production of uric acid by competing for the enzyme (xanthine oxidase) that converts xanthine and hypoxanthine to uric acid; thus it is a xanthine oxidase inhibitor. Patients taking allopurinol excrete less uric acid and more xanthine and hypoxanthine in the urine; these compounds are both more readily excreted in renal failure and are more soluble than uric acid so that xanthine stones rarely form. Allopurinol was first used in leukæmia therapy to prevent the oxidation of the active drug 6-mercaptopurine to an inactive metabolite, and its effect on uric acid synthesis was noticed. If an ordinary dose of 6-mercaptopurine be given to a patient whose gout is being treated with allopurinol, dangerous potentiation occurs.

Allopurinol is indicated where there is renal failure, where urate lithiasis has occurred or where tophi are extensive, in blood diseases where there is spontaneous hyperuricæmia, and during treatment of leukæmia where, due to destruction of leucocytes with release and degradation of nucleic acids, high renal urate load occurs (with risk of deposition in the kidney, or stones). Allopurinol prevents hyperuricæmia due to diuretics. It can be combined with a uricosuric.

Allopurinol is readily absorbed from the gut, it is metabolised in the liver to alloxanthine which is also a xanthine oxidase inhibitor; it is excreted unchanged and as alloxanthine by the kidney.

The dose is usually 200 to 300 mg total/day (in 2 or 3 doses), but up to 600 mg or even more total may be given in severe cases.

Adverse effects: acute gout may occur early in therapy, perhaps for the same reason as with uricosurics (see probenecid above). Other adverse effects include: allergies of various kinds including blood disorders, and gut upsets and liver damage.

Aspirin and salicylates should be avoided in gout (the patient should be warned of the ubiquity of aspirin in proprietary preparations) because small or tolerable doses cause urate retention and also interfere with the efficacy of uricosurics.

DRUG TREATMENT OF GOUT

Acute gout. Colchicine, phenylbutazone and indomethacin are highly effective in acute gout, terminating the attack in a few hours. It is important to begin treatment as early as possible. Colchicine is traditional, but it has to be given in maximum tolerated dose and phenylbutazone is generally preferred as less toxic. Colchicine may be drug of first choice in a *first* attack of severe monarticular arthritis, as a good response helps make

the diagnosis which can be difficult. Other anti-inflammatory drugs are non-selective.

Administration of colchicine, see above. Phenylbutazone can be used thus, a loading dose of 600 mg orally is followed by two doses of 200 mg 2-hrly and then 100 mg 6 to 8-hrly. Improvement often begins in a few hours and recovery is usually complete in 1 to 4 days, but may take up to 2 weeks. If gastric symptoms occur phenylbutazone may be given i.m.

Phenylbutazone and colchicine can be used together and relief may be quicker than with either alone, but it is suggested that this should only be done if experience shows that the response to both drugs used singly is unsatisfactory, for both are toxic. Indomethacin is also effective.

If these drugs fail, an adrenal steroid or corticotrophin may be used. Relapse may follow withdrawal, and may be minimised by covering the withdrawal with colchicine.

Recurrent and progressive gout may be prevented by probenecid or one of the other uricosurics. They should be used if the serum urate consistently exceeds 8 mg/100 ml.

Therapy should be begun in a quiescent period. *Salicylates must not be given concurrently with other uricosurics* as they interfere with their action (see above). Paracetamol may be used as an analgesic without interfering with therapy.

Impaired renal function, provided it is mild, does not contra-indicate uricosurics, but they may fail. Allopurinol is then preferable. They may be combined.

Colchicine also prevents gout, probably by suppressing acute attacks at their inception. It has no effect on urate excretion. Not surprisingly a combination of probenecid and colchicine (Colbenemid) has been found to give good results, the true prophylactic effect of probenecid being combined with the suppressant anti-inflammatory action of colchicine. Colchicine is especially useful at the start of uricosuric prophylaxis, to stop an acute attack, which often occurs during the first 4 weeks; and the urine should be made alkaline, and the volume maintained high (see above).

Once a patient is taking a uricosuric drug, the plasma urate level will fall to normal weeks before therapeutic benefit occurs. Medication should be adjusted to keep the plasma urate in the normal range. It can rarely be abandoned.

Colchicine prophylaxis alone is undesirable, for the plasma urate remains high allowing the disease process to continue (tophi, renal damage).

Chronic tophaceous gout. Tophi can sometimes be reduced in size and even removed by the use of uricosuric agents and allopurinol.

Acute pyrophosphate arthropathy responds similarly to acute gout.

Precipitation of gout by drugs

Any vigorous diuresis may precipitate acute gout, but the thiazide

diuretics selectively cause urate retention by inhibition of distal renal tubular excretion of urate and so do other potent oral diuretics: the effect is antagonised by uricosurics and allopurinol: diuretics that do not induce hyperuricæmia include mercurials, triamterene, amiloride and spironolactone. Pyrazinamide and clofibrate rarely precipitate gout.

Alcohol, diet and gout

The belief that alcohol induces acute gout is widely held, of long standing and has been celebrated in verse:

> A taste for drink, combined with gout,
> Had doubled him up for ever.
> Of *that* there is no manner of doubt—
> No probable, possible shadow of doubt—
> No possible doubt whatever.*

The poet's certainty of the association and of its severity may go a little further than the evidence warrants. But alcoholic intoxication is associated with a rise in plasma urate concentration, perhaps due to a raised lactate concentration competing for the renal tubular organic acid excretion path. Also, starvation (a feature of some cases of chronic alcoholism) raises the blood urate. Indeed obese patients on starvation treatment may develop gout and some advocate a uricosuric.

Caffeine gives rise to methylated uric acid in the urine. This is irrelevant to gout and there is no reason to prohibit caffeine-containing drinks.

Purine-containing foods (beers, liver, pancreas) contribute to formation of uric acid, but since the advent of uricosuric drug therapy dietary restriction has become unnecessary except occasionally in renal failure.

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Chapter 13

NON-MEDICAL USE OF DRUGS, DRUG DEPENDENCE, TOBACCO, ALCOHOL

"ALL the naturally occurring sedatives, narcotics, euphoriants, hallucinogens, and excitants were discovered thousands of years ago, before the dawn of civilisation. . . . By the late Stone Age man was systematically poisoning himself. The presence of poppy heads in the kitchen middens of the Swiss Lake Dwellers shows how early in his history man discovered the techniques of self-transcendence through drugs. There were dope addicts long before there were farmers."*

The drives that persuade or compel a person more or less mentally normal to resort to drugs to obtain "chemical vacations from intolerable selfhood" (*1*) will be briefly considered here, as well as some account of the pharmacological aspects of drug dependence.

"That humanity at large will ever be able to dispense with Artificial Paradises seems very unlikely. Most men and women lead lives at the worst so painful, at the best so monotonous, poor and limited that the urge to escape, the longing to transcend themselves if only for a few moments, is and has always been one of the principal appetites of the soul" (*1*). The dividing-line between legitimate use of drugs for social purposes and their abuse is indistinct for it is not only a matter of *which* drug, but of *amount* of drug and of whether the effect is directed anti-socially or not. "Normal" people seem to be able to use alcohol for their occasional purposes without harm but, given the appropriate degree of mental abnormality and environmental adversity, man may become dependent on it, both emotionally and physically.

The discussion in this chapter is confined to psychotropic drugs, i.e. drugs which alter mood, consciousness or other psychological or behavioural factors (*10*); they include opiates, sedatives, hypnotics, tranquillisers, stimulants and hallucinogens.

Abuse potential of a drug is related to its capacity to produce *immediate* satisfaction, e.g. amphetamine and heroin give immediate effect, anti-depressants do not.

Some terms used

Drug abuse. What constitutes abuse is determined by the opinions generally held in a particular society. Thus, in Britain, temperate use of tobacco and alcohol to insulate from environmental stress and to ease social intercourse is generally accepted; a substantial minority do not consider occasional taking of cannabis to be abuse; a small minority do

* HUXLEY, A. (1957). *Ann. N.Y. Acad. Sci.*, 67, 677.

not consider all use of LSD or heroin to be abuse. Thus, **non-medical** (or social) drug use (i.e. all drug use that is not on generally accepted medical grounds) may be a term preferable to abuse. Non-medical use means the continuous or occasional use of drugs by the individual, of his own choice, to achieve his own well being, or out of curiosity or to obtain an experience. The latter would not appropriately be included under the term dependence, which implies not only a need, but also some regularity and frequency of use (see below).

Drugs used for non-medical purposes are often divided into two groups, **hard** and **soft**. Hard drugs are those that are liable seriously to disable the individual as a functioning member of society by inducing severe emotional and, in the case of cerebral depressants, physical dependence. The group includes heroin, morphine and its analogues, and cocaine.

Soft drugs are less dependence-producing. There may be emotional dependence, but there is little or no physical dependence except with very heavy doses of depressants (alcohol, barbiturates). The group includes sedatives and tranquillisers, amphetamines, cannabis, hallucinogens, alcohol, tobacco.

As with many attempts to make convenient classifications, this fails, for it does not recognise individual variation in drug use. Barbiturates can be used in heavy, often i.v., doses that are gravely disabling and induce severe physical dependence with convulsions on sudden withdrawal; i.e. for the individual the drug is "hard". But there are many middle-aged people mildly dependent on them as hypnotics and sedatives who retain their position in home and society. Similarly, amphetamines can be used in ways that cause doubt whether they should be described as "hard" or "soft".

The motives for non-medical drug use include (*9*, *10*):

1. Relief of anxiety, tension and depression; relief of personal psychological problems.
2. Search for self-knowledge and for meaning in life, including religion. The cult of "experience" including æstheticism, sex and "genuine", "sincere" interpersonal relationships, "belonging".
3. Rebellion against or despair about orthodox social values and the environment.
4. Fear of missing something, and conformity with own social subgroup.
5. Fun, amusement, recreation, excitement, curiosity.

Two claims for the non-medical use of psychotropic drugs may be mentioned, (1) that there is such a thing as a "**drug culture**", and (2) that drugs provide **mystical or religious experience.**

The phrase "drug culture" implies that drugs can provide the spiritual, emotional and intellectual experiences and development that are the basis for a way of life that can be described as a "culture".

It is not only intrinsically unlikely that chemicals could be central to a constructive culture but no support for the assertion has yet been produced. (That chemicals might be central to a destructive culture is another matter.) That like-minded people practising what are often illegal activities will gather into closely knit sub-groups for mutual support, and will feel a sense of community, is to be expected, but that is hardly a "culture". Even where drug-using sub-groups are accepted as representing a culture (or sub-culture), it may be doubted if drugs, are sufficiently central to their ideology to justify using "drug" in the title, i.e. drug use is a secondary associated, and not a primary phenomenon. But claims for the individual and social value of drug experience must surely be tested by the criterion of fruitfulness for the individual and for society,* and the judgement of the individual concerned alone is insufficient; it should be confirmed by others. The results of illegal drug use do not give encouragement to press for a large-scale experiment in this field. To justify such an experiment (as with any other clinical trial) it would seem necessary to show reason to believe that what are universally agreed to be good human qualities, e.g. love of neighbour expressed in effective, practical action, are either likely to be promoted, or at least unlikely to be diminished by a drug. (Love of neighbour is incompatible with driving a car over him). That drugs, including alcohol, can induce states of vague benevolence and feelings of spirituality is undoubted, but the test is not only how a person feels, but what he does in response to the feeling.

The other claim is that drugs provide **mystical experience** and that this has valid religious content, so that it has great value and importance for the individual. If mysticism is to be discussed at all, it must be defined. *Mystical experience* is perhaps best defined by listing its characteristics; these are feelings of:

1. Unity: a sense of oneness with nature and/or God.
2. Ineffability: the experience is beyond the subject's power to express or describe.
3. Joy, peace, sacredness.
4. Knowledge: insight into truths of life and values, illuminations, revelations of enormous significance.
5. Transcendence of space and time.

Mystical states are both transient and passive (the subject feels his will is in abeyance).

There are three *forms of mysticism*†:

1. *Nature mysticism:* "an intuition, which is sometimes so vivid as to appear to be a vision, of reality and unity in the world 'outside' the mind

* This criterion is not new: St. Matthew's Gospel, **7**, 5. St. Paul's Epistle to the Romans, **12**, 4–5.

† Definitions from:
KNOWLES, D. (1971). *What is Mysticism.* London: Sheed and Ward.
HAPPOLD, F. C. (1963). *Mysticism.* Penguin Books.

. . . it is associated with natural beauty and sublimity, or with a quasi personified 'nature' as its object."

2. *Soul mysticism:* the soul or spirit strives to enter, not into communion with God or Nature, but into a state of complete isolation from everything other than itself. The chief object is the quest of a man's own self and of knowledge about it.

3. *God mysticism:* the spirit is absorbed into the essence of God or achieves some form of union with God. There is an inexpressible knowledge and love of God or of religious truth.

Naturally such experience is attractive so that there is a demand for any easy means to deliver it. But, it must be stated that there can be no guarantee that a mystical experience will occur with any drug.

Mystical experience is not a normal pharmacodynamic effect of any drug, its occurrence seems to depend on many factors, the subject and his environment, and any preparation he may have undergone. The drug *facilitates* the experience, it does not *induce* it; drugs can also facilitate very unpleasant experiences. It is not surprising that mystical experience can occur with a wide range of drugs that alter consciousness:

". . . I seemed at first in a state of utter blankness . . . with a keen vision of what was going on in the room around me, but no sensation of touch. I thought that I was near death; when, suddenly, my soul became aware of God, who was manifestly dealing with me, handling me, so to speak, in an intense personal, present reality . . . I cannot describe the ecstasy I felt". This experience occurred in the 19th century* with chloroform, which is not a drug recommended by contemporary mystics.

There is no good evidence that drugs can produce experience that passes the test of *results*, i.e. fruitfulness (above). Indeed, reliance on repeated drug experience may even inhibit the development of independence from the things of this world, which is vital for anything that can be described as freedom of spirit.

Whether a single administration of a drug can be used to initiate or trigger experiences that may result in an individual gaining beneficial insight is unproved. If emotional shock is acceptable in religious conversion there seems no obvious reason why a drug should not also be used once after careful preparation. Plainly there is a risk of the experience becoming an end in itself rather than a means of development.

It is interesting to note that the double-blind controlled trial has been attempted in the field of spiritual experience and knowledge where, it has been pointed out, the passion with which a belief is defended is commonly in inverse proportion to the strength of the evidence that can be adduced for it.

Twenty well-prepared Christian theological students received, by random allocation, either psilocybin (a hallucinogen) or nicotinic acid (as an "active" placebo). They attended a Good Friday church service

* Quoted in JAMES, W. (1902). *Varieties of Religious Experience.* London: Longmans. Many subsequent editions of this classic.

lasting 2½ hrs and wrote accounts of their feelings, completed questionnaires and were interviewed to elicit evidence of mystical experience (see above). It was concluded that psilocybin facilitated mystical experience.* While such work is of great interest it may be remembered that religious experience "means the whole of life religiously interpreted, rather than isolated feelings. A religious man is not one who has 'experiences' . . . but one who takes all life in a religious way . . . religious experience . . . is not the isolated outbreak of abnormal phenomena in this or that individual (though to read some psychological treatments of religious experience one would suppose so)".†

Conclusions on non-medical drug use

The above brief discussion does little more than raise issues that deserve serious consideration. Drug-induced experience can only be discussed in terms of attitudes and beliefs held by the individual as to the nature of man, his purpose (if any), his obligations (if any) and his relationship to a transcendant being or God (if any). An author in this field has a choice of attempting an impartiality which is almost certainly spurious, or of deliberately allowing his views to obtrude. The latter course seems preferable, as less misleading. The writer's views on the **three major areas of non-medical drug use** are as follows:

1. *For relaxation, recreation, protection from and relief of stress and anxiety; relief of depression:* moderate use of some "soft" drugs may be accepted as part of our society provided they do not detract from living fully, loving fully, and striving for good.

2. *For spiritually valuable experience:* justification is doubtful.

3. *As basis for a "culture" in the sense that drug experience* (a) can *be, and* (*b*) should *be central to an individually or socially constructive way of life:* a claim without validity.

Legalisation of drugs for non-medical use. The decision whether a drug is acceptable in medical practice is made after an evaluation of its safety in relation to its efficacy. The same principle should be used for drugs for non-medical or social use. But the usual medical criteria for judging efficacy against disease or discomfort are hardly applicable. The reasons why people want to use cannabis or other drugs for non-medical purposes are listed above. None of them can carry serious weight if the drug is found to have serious risks to the individual‡ or to society with either acute or chronic use. Ordinary prudence dictates that any such risks should be carefully defined before a decision on legalisation is made.

* PAHNKE, W. N. (1970). In *Psychedelics: the uses and implications of hallucinogenic drugs*. Ed. Aaronson *et al.* London: Hogarth Press.

† DODD, C. H. (1960). *The Authority of the Bible*. London: Fontana.

‡ Hazard to the individual is not a matter for the individual alone if it also has consequences for society.

Drugs and Sport

The rewards of competitive sport, both financial and in prestige, are the cause of determination to win at almost any cost. Drugs are used (hopefully) to enhance performance. Detection can be difficult where the drugs or metabolites are closely related to physiological substances, and where the drug can be stopped before the event without apparent loss, e.g. anabolic steroids.

Anabolic steroids are chiefly used to prepare for events where strength is primary, e.g. weight-lifting, hammer-throwing, though they are also being used for "explosive" events, e.g. sprinting, hurdling. The situation has been aptly summed up by one North American sporting editor, "How nutsy must one be to risk liver damage . . .?"* Also, efficacy is uncertain.

Other abuses include the use of amphetamines (which have probably caused death from hyperpyrexia in metabolically stimulated vasoconstricted subjects exercising to the utmost in a hot environment).

The problem raised by use of local anæsthetics for strains, hormonal regulation of menstruation, drugs for anxiety, etc., are ethical rather than medical, as is the use of hypnosis in the reported competition success of a swimmer who, it is alleged, had been persuaded under hypnosis into the belief that he was being pursued by a shark.

Caffeine can improve physical performance and it illustrates the difficulty of deciding what is "permissible" or "impermissible". A cup of coffee is part of a normal diet, but some might consider swallowing tablets (of caffeine) to be "doping".

Drug Dependence

Drug dependence is a state arising from repeated, periodic or continuous administration of a drug, that results in harm to the individual and sometimes to society. One or more of the following phenomena occur:

1. **Emotional (psychic) dependence:** the first to appear: there is emotional distress if the drug is withheld.
2. **Physical dependence:** follows emotional dependence in some cases: there is a physical illness if the drug is withheld (abstinence or withdrawal syndrome).
3. **Tolerance:** this also occurs to many drugs that do not induce dependence.

It was once customary to divide regular or continuous drug abuse into two categories, "addiction" and "habit". Attempts to draw firm distinctions between the graver addiction and the relatively trivial habit have been unsuccessful. It was said that in addiction the subject had a "compulsion" to take the drug, that he became both emotionally and physically

* *The Times*, London, Apr 12, 1972.

dependent on it and that his resulting state was detrimental not only to himself but to society. It was more serious than drug habit, in which the subject merely had a "desire" for the drug, on which his dependence was solely emotional, and the evil effects were virtually confined to himself. The distinction failed because of the impossibility of distinguishing between "desire" and "compulsion", the absence of any important physical dependence with cerebral stimulants (cocaine, amphetamine), which were generally agreed to be drugs of addiction, and the difficulty of separating damage to the individual from damage to society. Also the same drug could form a minor habit in one individual and be the subject of gross addiction in another. Alcohol is an obvious example. It provides an occasional pleasure or solace for some, it is taken regularly by others, who feel unhappy if they are deprived of it, and a minority of people disintegrate socially through its effects and are physically dependent to such a degree that they become gravely ill if they cannot get it.

In 1964 the World Health Organization Expert Committee on Addiction-producing Drugs (*13*) recommended that the term "**drug dependence**" should be substituted for both "addiction" and "habit". The various drug dependences are a group of diseases with some common features. It may well be that personality disorders and the socio-economic environment are the important determinants of whether dependence occurs and of the drug that is chosen. Drug dependence is not solely, or even mainly, a problem of pharmacology. This is supported by the fact that there are sometimes sudden changes in the drug of choice amongst drug-abusing groups, and there is evidence that rats which are offered morphine and choose to take it, develop greater dependence and a readiness to revert to it after withdrawal, than do rats to which morphine is arbitrarily administered.

The pharmacological properties of the chosen drug, the dose used and the frequency of administration are important factors in determining the speed of onset of and the degree of dependence, emotional and/or physical.

The use of the term "addict" or "addiction" has not been completely abandoned in this book because the new and sensible terminology can be cumbersome, especially when referring to drug-dependent individuals, and in distinguishing the severer forms of dependence, which present a problem as grave as tea-drinking is trivial. But the use of the term "drug dependence" is welcome, because it removes a distinction that was never a true difference, and it stops profitless arguments about whether some drugs, e.g. tobacco, are addictive or merely habit-forming.

The **mechanisms of physical dependence** on drugs and development of tolerance are ill understood, but various theories have been proposed. Physical dependence has been demonstrated in *in vitro* cultures of human epithelial cells (*15*). Evidently drugs can become essential to some normal metabolic functions.

Physical dependence develops with cerebral depressants, but is, for practical purposes, absent with stimulant drugs.

The distinction between physical and emotional dependence is not always clear, for the mental misery of the deprived habitual tobacco smoker may manifest itself in physical symptoms, such as digestive disturbances and tremors.

There is commonly **cross-tolerance** between drugs of similar, and sometimes even of dissimilar, chemical groups, e.g. barbiturates and alcohol.

Although "no drug possesses mysterious powers to subjugate a human being" (*2*), there is danger in experimenting with the more potent agents. It is said that a feeling of pleasure on first experience of a drug can be an index of "addiction proneness", and this was evidently so for that famous addict, Thomas de Quincey, who, in 1804, suffering from facial pain, "met a college acquaintance who recommended opium". He purchased some tincture and went home. ". . . I took it; and in an hour, O heavens! what a revulsion! what a resurrection, from its lowest depths, of the inner spirit! . . . That my pains had vanished, was now a trifle in my eyes; this negative effect was swallowed up in the immensity of those positive effects which had opened before me, in the abyss of divine enjoyment thus suddenly revealed. Here was a panacea . . . for all human woes; here was the secret of happiness, about which philosophers had disputed for so many ages, at once discovered; happiness might now be bought for a penny, and carried in the waistcoat-pocket; portable ecstasies might be had corked up in a pint-bottle; and peace of mind could be sent down by the mail" (*3*). Or, as a modern American addict has more succinctly, though less elegantly, put it, "They all think they can take just one joy-pop but it's the first one that hooks you" (*2*).

On the other hand many people experience nothing but unpleasantness with the opium group of drugs. In case these quotations should give an impression that there is anything amusing or romantic about severe opiate dependence, it may be categorically stated that it is, in virtually all cases, a ruinous, degrading and sordid state not only for the addict, who is a psychopath, but for his family and friends. Unfortunately the subject cannot decide for himself that his dependence will remain mild. The opinion of de Quincey is unsound, and his career as an addict was quite exceptional.

Despite the fact that the sale of opium to the public in Britain was not restricted by law until 1923 there was never a large body of opium addicts in the country. Restriction was inevitable, however, because of the ease with which morphine can be extracted from it, a standing temptation to unscrupulous people who in some countries promote addiction, even among juveniles, for gain. The argument of de Quincey in 1821, "what a man may lawfully seek in wine, surely he may lawfully find in opium" does not now arouse our sympathy. Nor are we as surprised as he was that fourteen insurance offices in succession "repulsed me as a candidate . . . on that solitary ground of having owned myself to be an opium-eater" (*3*).

Dependence occurs to any drug that alters consciousness however bizarre, e.g. muscarine (which see) and to some that, in ordinary doses, don't, e.g. non-narcotic analgesics, purgatives, diuretics.

Emotional dependence can occur merely on a tablet or injection, regardless of its content, as well as to particular drugs. Mild dependence does not require that a drug should have important psychic effects, the subject's beliefs as to what it does are as important. We are all physically dependent on food, and some develop a strong emotional dependence too, and eat too much.

General Pattern of Drug Dependence and Abuse

Under 25 year olds: hard drugs, chiefly heroin: extensive experimentation with multiple drugs including barbiturates and amphetamines: a demand for cannabis for use much as alcohol is used: some alcoholism: occasional use of LSD, etc.

Over 25 year olds: alcoholism: mild dependence on hypnotics and tranquillisers: occasional use of LSD.

Some topics

Size of the problem of "hard" drug dependence (chiefly heroin) in Britain, though still small numerically, grew rapidly from 1959 when the number of heroin addicts known to the Home Office was 68, until 1968 when the increase almost ceased. In 1972, 1,619 narcotic addicts were recorded (total population 55 million). The official figures are certainly substantial underestimates; but of addicts coming to a hospital Casualty Department (overdose, infections) less than a third were *not* officially known, so perhaps the underestimate is not as great as feared.

The increase was initially amongst males under 25 years old, but this has levelled and now young females are increasing in number. Narcotic abuse is associated not only with personality disorder but with psychological weakness and immaturity, and social stress, so that adolescents are specially vulnerable; they are generally first introduced to drugs by other users.

Multiple drug use (hypnotics, sedatives, amphetamines, heroin) is now a marked feature and the pattern of drugs used changes frequently.

Supply of drugs to addicts. In Britain heroin and cocaine may only be prescribed *for addiction* (during treatment or after cure has failed) by specially licensed doctors. Addicts are registered officially for this purpose. The drugs, and injection equipment if needed, are supplied on a National Health Service prescription. It is considered the lesser evil to supply pure drug to known people who remain in touch with responsible physicians. This also minimises the risk of infection, which, with overdose is a chief cause of the high mortality amongst addicts to hard drugs. If this procedure were not used it is thought that the illicit market, which is at present modest, would expand. The need for money to finance the market would cause the price to be substantial and addicts would

turn to persistent theft to pay for their addiction. But the matter remains speculative.

There is, at present, no technique of assessing the truth of an addict's statement that he needs x mg of heroin (or other drug), and the dose is negotiated intuitively by the doctor. This can result in the addict obtaining excess drug which he sells and may use to initiate new victims.

Withdrawal syndrome in opiate dependence. Whilst this can undoubtedly be very unpleasant (described in ch. 12) the notion that once "hooked" the addict continues to seek the drug *primarily* to avoid the unpleasantness of withdrawal may be false. The high relapse rate after full withdrawal suggests this; also, addicts are reported as seeking "super-normality" rather than normality, so that even after complete withdrawal the psychopathic or neurotic subject is left with unrealised expectations which cause him to seek relief in drugs.

Route of administration. With the i.v. route, much higher peak plasma concentrations can be reached than with oral administration. This accounts for the "kick" that abusers report and which many seek, likening it to sexual orgasm or better.

Escalation. A variable but small proportion of subjects who use amphetamines and cannabis eventually take heroin. The disposition to progress from occasional use of "soft" drugs through to dependence on "hard" drugs, when it occurs, is less likely to be due to pharmacological actions, than to psychological and social factors. Escalation may be more common among amphetamine than among cannabis users. See *cannabis*.

Unusual substances abused include petrol and glue solvents (by inhalation), levodopa and other antiparkinson (anticholinergic) drugs, in fact, anything that alters consciousness.

Treatment

Treatment consists of:

1. **Withdrawal** of the drug, perhaps the least important facet of therapy, followed by attempts at mental and social rehabilitation to prevent relapse, e.g. "therapeutic communities", the most important aspect. In the case of drugs which cause physical dependence, withdrawal may be gradual (over about 10 days), or sudden, provided that in the latter case steps are taken to control the abstinence syndrome. This may be done by judicious use of the same drug, but some prefer to use alternative drugs, generally, though not always, of similar kind; for instance a heroin addict can be given methadone: an alcoholic may be given chlormethiazole, chlordiazepoxide or paraldehyde. If a patient is in very poor physical condition withdrawal should be postponed until he is better.

2. **Maintenance.** Relapsed addicts who live a fairly normal life are sometimes best treated by supplying drugs under supervision. There is no legal objection to doing this in Britain, but naturally this course, which

abandons hope of cure, should not be adopted until it is certain that cure is virtually impossible. A less harmful drug by a less harmful route may be substituted, e.g. oral methadone for i.v. heroin. Addicts are often reluctant to abandon the i.v. route which provides the "immediate high" which they find so desirable.

Testing new drugs for power to induce serious dependence

The occurrence of physical dependence is an important indicator. Drugs are given regularly to animals (monkeys, dogs) for about 4 weeks and then withdrawn suddenly to see if an abstinence syndrome occurs. If the drug is related to morphine, physical dependence can also be shown by giving an antagonist (nalorphine). Power of a drug to suppress an abstinence syndrome is also evidence that it may itself induce serious dependence.

New drugs are also tested similarly in volunteer ex-addicts (*18*).

Types of drug dependence: the World Health Organization recommends that drug dependence be specified by "type" when under detailed discussion.

Morphine-type:
emotional dependence severe
physical dependence severe; develops quickly
tolerance marked
cross-tolerance with related drugs
nalorphine induces abstinence syndrome

Barbiturate-type:
emotional dependence severe
physical dependence very severe; develops slowly at high doses
tolerance less marked than with morphine
cross-tolerance with alcohol, chloral, paraldehyde, meprobamate, glutethimide, methyprylone, chlordiazepoxide

Amphetamine-type:
emotional dependence severe
physical dependence slight: psychoses occur during use
tolerance occurs

Cannabis-type:
emotional dependence marked
physical dependence absent; no characteristic abstinence syndrome
tolerance trivial

Cocaine-type:
emotional dependence present
physical dependence absent
tolerance absent

Alcohol-type:

emotional dependence severe
physical dependence with prolonged heavy use
cross tolerance with other sedatives

Tobacco-type:

emotional dependence strong
physical dependence slight

Drug mixtures:

Barbiturate–amphetamine mixtures induce a characteristic alteration of mood that does not occur with either drug alone
emotional dependence strong
physical dependence occurs
tolerance occurs
Heroin–cocaine mixtures: similar characteristics

Prevention of drug dependence after medical use of drugs

It is probable that many addicts who claim that their state is the result of misuse of drugs by their medical attendants are not speaking the truth, but trying to shift a feeling of guilt to other shoulders.

The risk of making a normal person addicted to narcotic analgesics during therapeutic use is small if drugs are handled properly, but it exists in chronic recurrent painful conditions. It is wise to withhold drugs of addiction from such people as long as possible and then, if they must be used, to space the doses as widely as possible. It may also sometimes be wise to conceal the nature of the drug, especially if the patient is mentally abnormal or unstable.

In patients who have only a brief expectation of life the production of addiction is of little importance and need not generally be taken into consideration when planning therapy.

TOBACCO

Tobacco was introduced to Europe from South America in the 16th century. For some time smoking* attracted a good deal of opprobrium and was forbidden by both Church and State, but this did not stop it and soon the State found that tobacco was a habit-forming drug of sufficient power to bear heavy taxation without causing habitues to abandon it, and yet of insufficient power to cause dangerous disruption of the community. This applies to alcohol as well, and it has been pointed out that "So excellently habit-forming are they in fact, from the Government's point of view, that they can now be made to pay for the whole of the National Health Service, including its vast hospital services and for

* "A habit . . . dangerous to the lung." King James I, 1604.

all the other free untaxed tranquillisers prescribed by doctors",* and a substantial sum be still left over.

The composition of tobacco smoke is complex (about 300 compounds have been identified in it) and varies with the type of tobacco and the way it is smoked. The chief pharmacologically active ingredient is nicotine. The amount absorbed varies from up to 90% in those who inhale, to as little as 10% in those who do not. Substances (polycyclic hydrocarbons) carcinogenic to animals have been identified in tobacco smoke condensates from cigarettes, cigars and pipes.

Cigar smoke is of pH 8·5, at which nicotine is relatively unionised (lipid soluble) so that it is readily absorbed from the mouth. Cigarette smoke is pH 5·3 and nicotine is more ionised and so less absorbed from the mouth. This difference may explain why cigar smokers inhale less than cigarette smokers, and have a lower death rate from lung cancer.

Tobacco dependence. The reasons people habitually smoke tobacco are certainly complex and "it is no easy matter to reach a simple and reasonable conclusion concerning the mental health aspects of smoking. The purported benefits on mental health are so intangible and elusive, so intricately woven into the whole fabric of human behaviour, so subject to moral interpretation and censure, so difficult of medical evaluation and so controversial in nature that few scientific groups have attempted to study the subject" (*2*).

A critic's prejudices will largely decide whether this "pharmacologic aid in (man's) search for contentment" (*2*) is viewed as acceptance of a genial social and solitary pleasure or as a humiliating surrender to self-indulgent vice.

The following notes throw a little light on the subject here and there.

There is no substantial and clear-cut personality difference between smokers and non-smokers. Cigarette smokers tend to be more extraverted, less rigid and perhaps more neurotic than non-smokers. Pipe smokers are notably introverted.

Smoking is associated with neuroticism but not with any important increased liability to psychosomatic illness.

Psychoanalysts have made a "characteristic contribution to the problem. 'Getting something orally', one asserts . . . 'is the first great libidinous experience in life'; first the breast, then the bottle, then the comforter, then food and finally the cigarette" (*9*). The common sight of a pipe-smoker with an empty or unlit pipe in his mouth would seem to lend support to this.

Starting to smoke may be linked with "self-esteem and status needs", but probably not to adolescent rebellion (*2*).

There is no difference in intelligence between smoking and non-smoking children, but the former are less academically successful.

* SARGANT, W. (1956). *Brit. med. J.*, **1**, 939.

Emotional stress is associated with heavier smoking amongst smokers rather than with starting to smoke by non-smokers.

Social environment plays a large part in determining smoking, and the offering and accepting of tobacco, as of alcohol, is important in the development of personal relations in business and in private life.

When considering the significance of the association of smoking with mental states and personality characteristics it is particularly important to avoid assuming explanations for which there is really no evidence, e.g. the fact that when under emotional stress a person smokes more, may be because stress is relieved by smoking—which is widely believed—or because smoking is merely an expression of stress.

Five types of smoking have been suggested (*21*):

1. *Psychological* smoking: characteristic of early stages of smoking in adolescence: but dependence on nicotine itself soon appears and the subject has embarked on a potentially life-long drug-dependence (only 18% of smokers become non-smokers at present).
2. *Indulgent* smoking: i.e. purely for pleasure when resting, reading, watching television, etc.: frequency is uneven.
3. *Tranquillisation* smoking: nicotine needed for sedation: oral gratification and use of hands to relieve tension is part of the satisfaction: smoking frequency varies with emotional state.
4. *Stimulation* smoking: nicotine used to maintain performance and reduce fatigue in monotonous or demanding tasks.
5. *Addictive* smoking: withdrawal symptoms felt when subject has been about 30 mins without smoking and he smokes to relieve this: frequency of smoking varies little.

Characteristics of dependence: psychological dependence is extremely strong and tolerance and some physical dependence occur. Transient withdrawal effects include, EEG and sleep changes and impaired performance in some psychomotor tests, though it is difficult to disentangle psychological from physical effects in these last.

Acute physiological effects of smoking tobacco have been elegantly summarised by Comroe (*13*).

Increased airway resistance occurs due to the non-specific effects of submicronic particles, e.g. carbon particles less than 1 micron across. The effect is reflex. Even inert particles of this size cause bronchial narrowing sufficient to double airway resistance. This is insufficient to cause dyspnœa, though it might affect athletic performance. Four to five-fold increase in resistance is necessary to cause noticeable dyspnœa and ten to twenty-fold increase to cause severe dyspnœa such as can occur in asthma.

Nicotine inhalations of strength comparable to that reached in smoking do not increase airway resistance.

Ciliary activity, after trivial stimulation, is depressed, and particles are removed from the lungs more slowly.

Carbon monoxide absorption is physiologically insignificant in healthy young adults, but may be significant in the presence of coronary heart disease (see below).

Nicotine. In large doses nicotine stimulates directly the endings of cholinergic nerves whose cell bodies lie in the central nervous system, i.e. it acts at autonomic ganglia and at the neuromuscular junction. This is what is meant by the term "nicotine-like" or "nicotinic" effect. Higher doses paralyse at the same points.

In addition, nicotine stimulates the central nervous system, including the vomiting centre, both directly and via the carotid body; tremors and convulsions may occur. As with the peripheral actions, depression follows stimulation. Thus nicotine can both stimulate and depress, depending on the dose. Nicotine causes release of the antidiuretic hormone of the posterior pituitary gland.

In low doses such as are taken in ordinary smoking, the effects of nicotine are probably largely reflex, from stimulation of sensory receptors (chemoreceptors) in the carotid and aortic bodies, pulmonary circulation and left ventricle. Some of the results are mutually antagonistic. The following account tells what generally happens after one cigarette, from which about 1 mg nicotine is absorbed, although much depends on the amount and depth of inhalation and on the duration of end-inspiratory breath holding.

On the cardiovascular system the effects are those of sympathetic stimulation. There is vasoconstriction in the skin and vasodilatation in the muscles, tachycardia and a rise in blood pressure of about 15 mm Hg systolic and 10 mm Hg diastolic. Ventricular extrasystoles may occur. Cardiac output, work and oxygen consumption increase. Coronary vascular resistance decreases and blood flow increases in men aged 20 to 50 years. However if the resistance is fixed by atherosclerosis, flow does not increase, though work and oxygen consumption do. This may be a mechanism of tobacco-induced angina pectoris. It is possible that nicotine stimulates the myocardium by releasing noradrenaline stored in it, but at present it seems likely that this effect only occurs with higher doses.

Nicotine increases fatty acid concentration in the blood, and also platelet stickiness. These may be factors in atheroma and thrombosis.

On the gastrointestinal tract there are no important effects either on movement or secretion. Nausea and vomiting occur in the novice, probably due to stimulation of the vomiting centre.

Appetite increases when smokers stop. The mechanism is uncertain.

It is well known that *tolerance* develops to nicotine and that a first experience commonly causes nausea and vomiting which quickly ceases with repetition of smoking.

A *sedative* or *stimulant* effect occurs in those who smoke regularly, according to dose, circumstances, psychological state, etc.; this deserves further study.

The pleasurable effects of smoking are derived from a complex mixture of multiple pharmacological and non-pharmacological factors.

Effects of Chronic Tobacco Smoking

The Royal College of Physicians of London feels it has a duty to pronounce "on a question of public health when action is required". In 1725 it offered advice "concerning the disastrous consequences of the rising consumption of cheap gin", and in 1962 on the effects of smoking on health.*

Its published reports (*1*) are models of clarity and brevity. Some of the data are shown in Figures 8–15 and the facts, which deserve close attention, will not be repeated in the text.

In 1964 and 1967 the U.S. Public Health Service published extensive reports (*2*).

The evidence for an association of smoking with various diseases consists both of retrospective surveys, in which the smoking habits of those who were ill were compared with those of a chosen control group, and of prospective surveys (fewer, because more difficult to do), in which the habits of a population sample were recorded and they were then followed and their fate determined. Retrospective studies are open to objection because of the risk of bias in selection of subjects and of controls to match them with, and it is therefore desirable that they should be supported by prospective studies to obtain convincing evidence as to whether an association is really one of cause and effect.

The importance of finding out just what smoking does or does not do is shown in this table:

Percentage of Men aged 35 who may Expect to Die before the age of 65 (*1*)

Non-smokers	15%
Smokers of 1–14 cigarettes a day	22%
Smokers of 15–24 cigarettes a day	25%
Smokers of 25 or more cigarettes a day	33%

Increases of mortality with cigar and pipe smokers are substantially less.

Statistical methods cannot, of course, provide proof of causal relationship. "The causal significance of an association is a matter of judgement which goes beyond any statement of statistical probability" (*2*). To decide whether an observed association is causal, several criteria, no one of which alone is sufficient, must be satisfied (*2*). These include:

1. *Consistency* of association—diverse methods of approach should give the same answer.
2. *Specificity* and *strength* of association—specificity means the precision

* It is not intended to imply that the College was unconcerned about public health between these dates.

with which the presence of, say, chronic bronchitis or lung cancer, can be used to predict that the victim smokes and vice versa—also the size of effect should be sufficient not to be obscured by any associated but non-casual factors, e.g. alcohol consumption, and a correlation of effect (disease) with dose (amount smoked) is also important.

3. *Temporal* association—the supposed cause (smoking), must operate before any evidence of the disease appears.

4. *Coherence* of association—the associated event should fit in with all known facts of the natural history of the disease.

An important prospective survey is that of Doll and Hill (*6*) who in 1951 sent a questionnaire on smoking habits to all registered medical practitioners in Britain (59,600) and arranged to be told of the practitioners' deaths and of the notified cause. They concluded in 1964* that "an association with smoking is found, in differing degrees, in men, for seven causes of death—namely cancer of the lung, cancers of the upper respiratory and digestive tracts, chronic bronchitis, pulmonary tuberculosis, coronary disease without hypertension, peptic ulcer, and cirrhosis of the liver and alcoholism".

These disease associations satisfy, to widely varying degrees, the criteria mentioned above.

General: hepatic microsomal **enzyme induction** occurs, probably from the polycyclic hydrocarbons in smoke.

Carbon monoxide in smoke is sufficient to reduce oxygen carrying capacity of the blood by 10% due to formation of carboxyhæmoglobin.

Lung cancer. The strong statistical association with cigarette smoking is most simply explained as one of cause and effect. Men are much more affected than are women; more men smoke more tobacco. This explanation has proved unacceptable to some, e.g. many smokers and the tobacco industry, and a number of ingenious alternatives have been suggested. Only the most important can be considered here.

It has been proposed that there is a genetically determined tendency both to smoke and to develop lung cancer. This requires that the tendencies are quantitatively related, because heavier smokers are more likely to get cancer, and that the tendency to give up smoking, as well as the tendency to smoke, is determined by heredity.

The recent increase of lung cancer in many countries must thus be explained either (a) by a sudden simultaneous development of this inherited liability in many countries, which is not seriously proposed by anyone, or (b) by invoking an inherited susceptibility "to some other unidentified environmental influence which has recently arisen in every country in which the incidence of lung cancer has increased. This indefinite hypothesis is unsatisfactory in itself" (*1*) and is also hard to reconcile with a study of lung cancer in Seventh Day Adventists, in the U.S.A.† It appears

* Recent controversy (see index to *Lancet*, 1972–3) does not invalidate these conclusions.

† WYNDER, E. L., *et al.* (1959). *Cancer*, **12**, 1016.

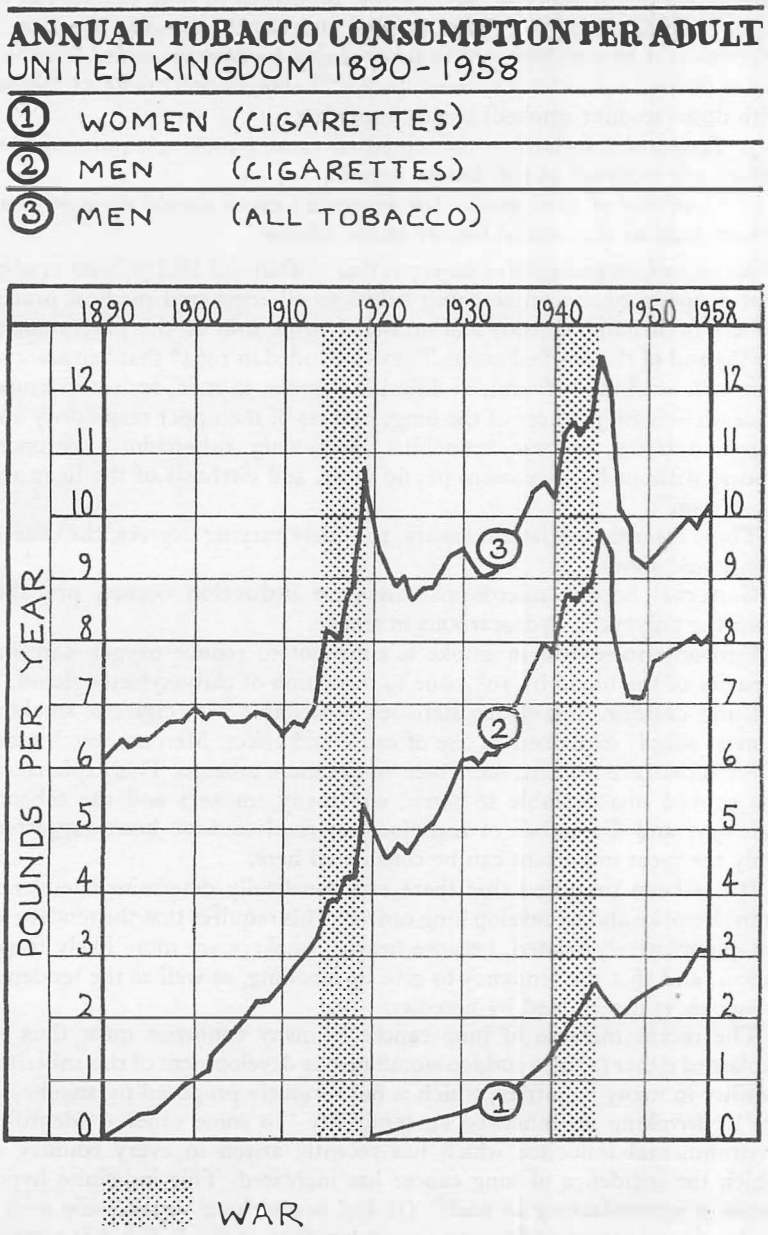


FIG. 8. By permission, after Royal College of Physicians Report (1962). Following this the number of cigarettes smoked by men dropped sharply, but has since risen to about its previous level. Women appear to have ignored the Report altogether.

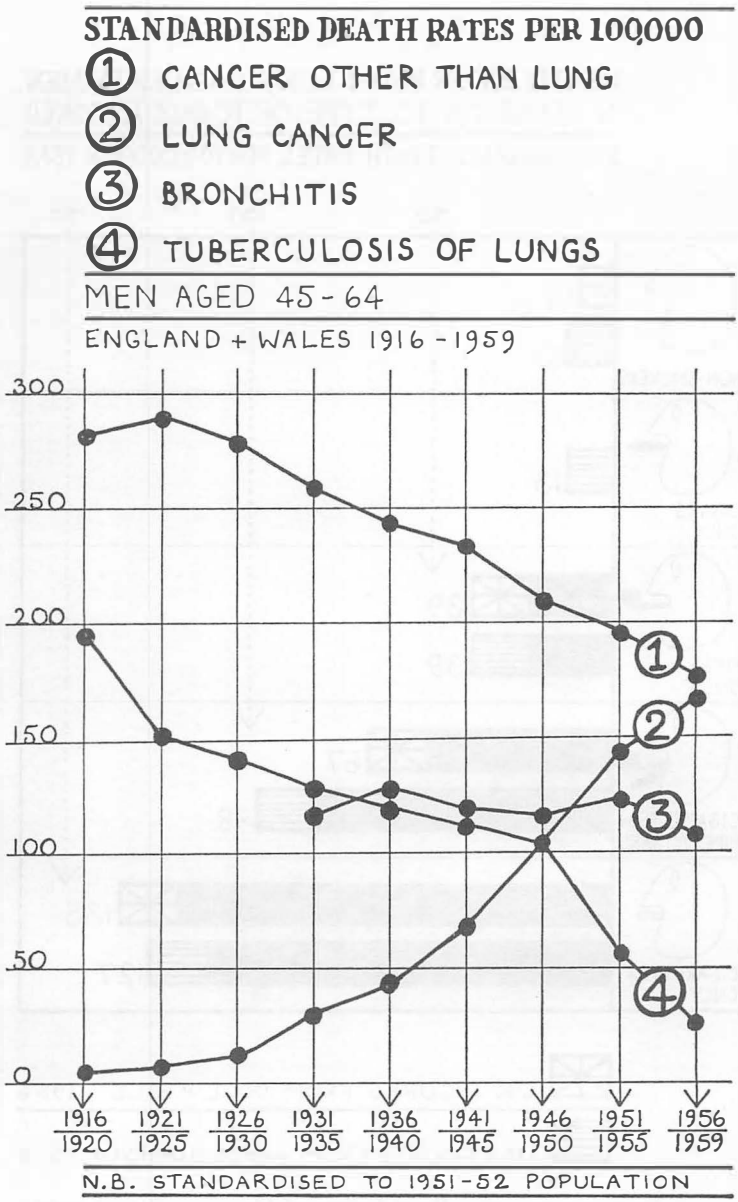


FIG. 9. The absence of figures for bronchitis before 1931 is due to different practice in death certification that renders them not comparable to figures since 1931. (By permission, after Royal College of Physicians Report, 1962. The graph has not substantially changed in the 1971 Report.)

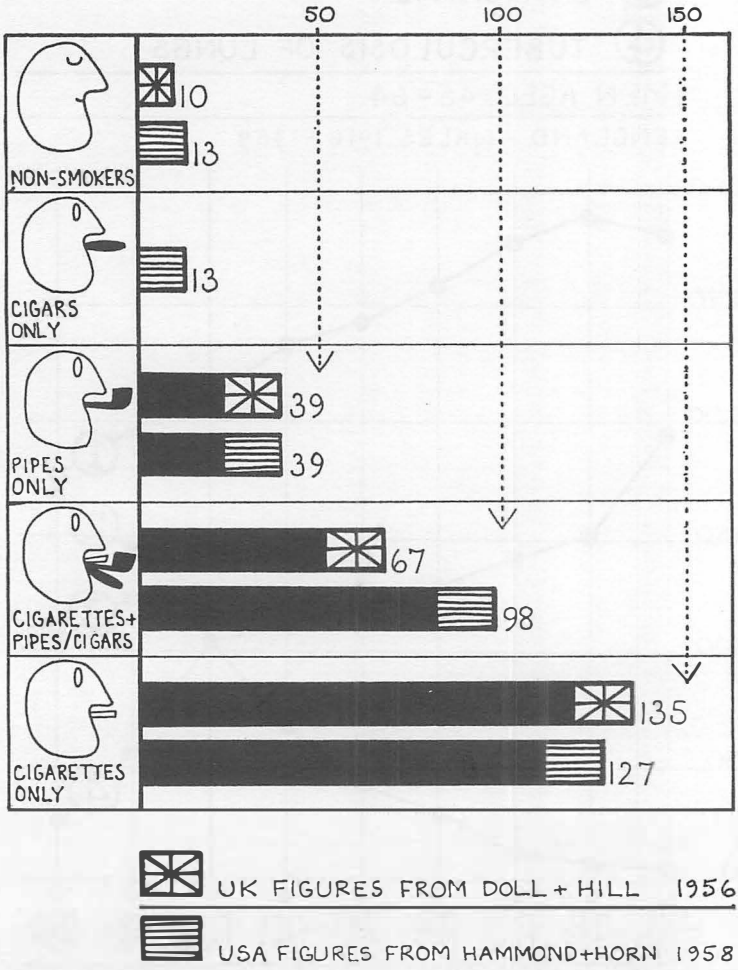


FIG. 10. By permission, after Royal College of Physicians Report, 1962.

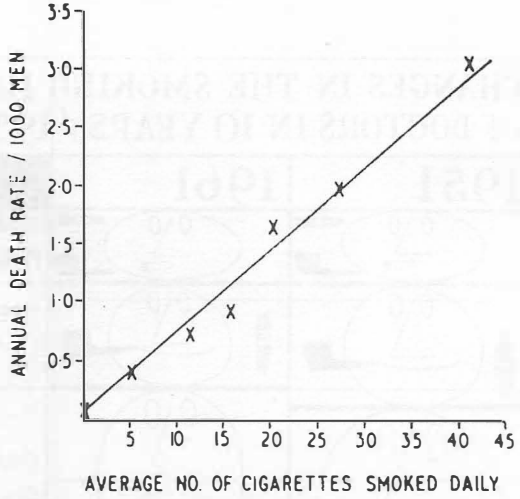


FIG. 11. The effect of smoking. Death rate from lung cancer, standardised for age, among men smoking different daily numbers of cigarettes at the start of the inquiry (men smoking pipes or cigars as well as cigarettes excluded).

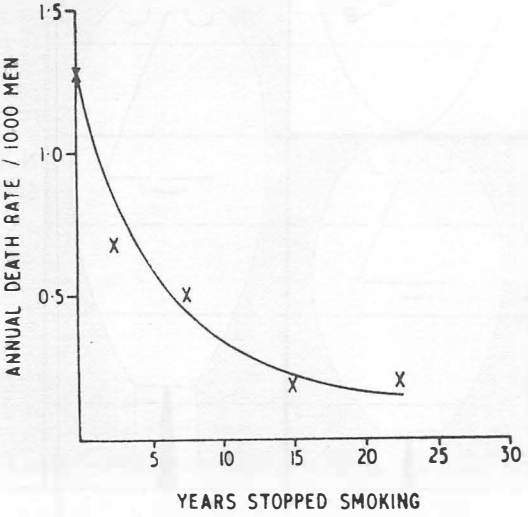


FIG. 12. The effect of giving up smoking. Death rate from lung cancer, standardised for age and amount smoked, among men continuing to smoke cigarettes and men who had given up smoking for different periods (men who had regularly smoked pipes or cigars as well as cigarettes excluded). The corresponding rate for non-smokers was 0·07 per 1,000.

From DOLL, R., and HILL, A. B. (1964). *Brit. med. J.*, 1, 1399, by permission of the authors and the Editor of the *Brit. med. J.*

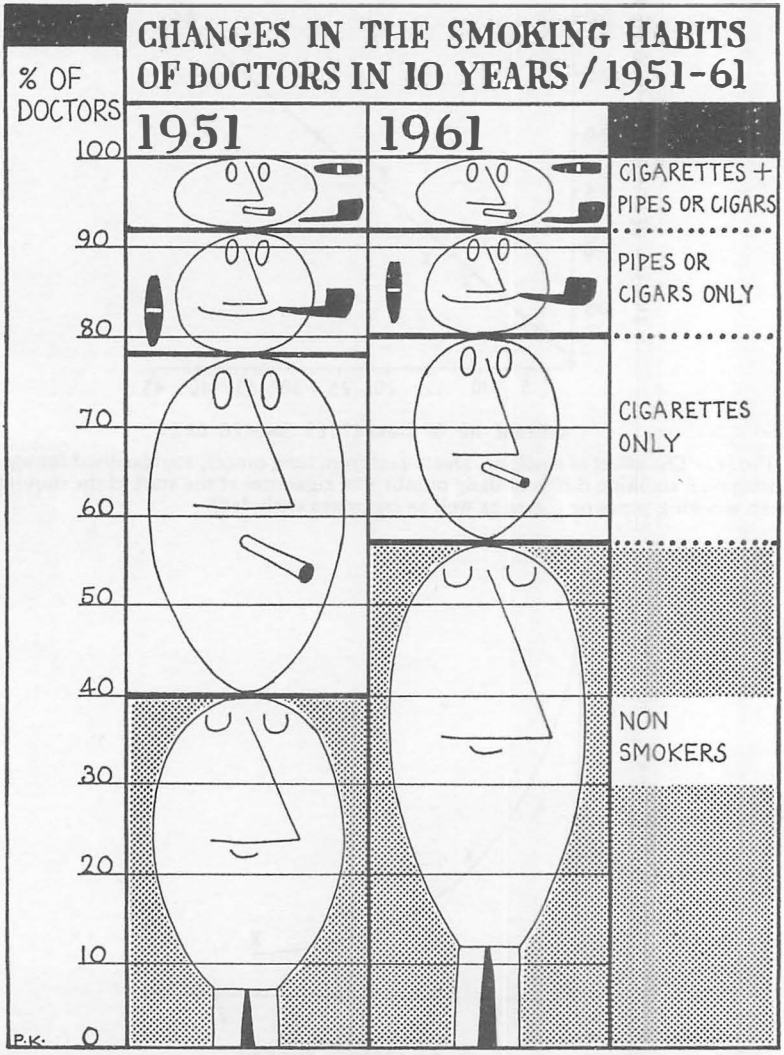


FIG. 13. The changes shown occurred after the dangers of cigarette smoking became known. There was no corresponding change in the smoking habits of the general population. British male doctors only. (Adapted from Royal College of Physicians Report, 1962. The tendency to abandon cigarettes has continued, 1971 Report).

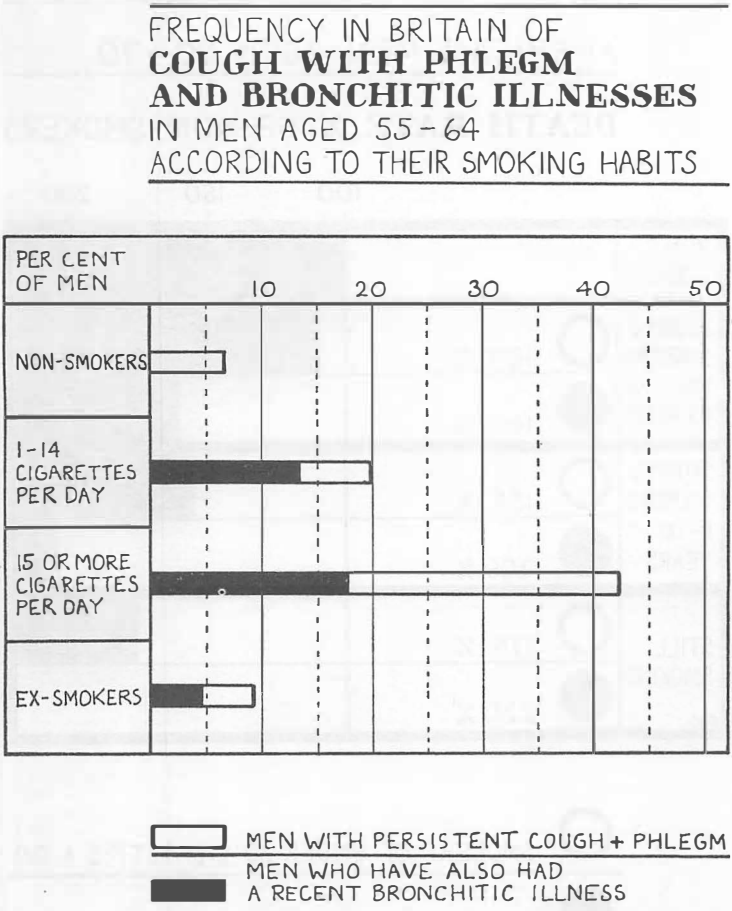


FIG. 14. Figures from HIGGINS, I. T. T. (1959). *Brit. med. J.*, **1**, 325. (By permission, after Royal College of Physicians Report, 1962).

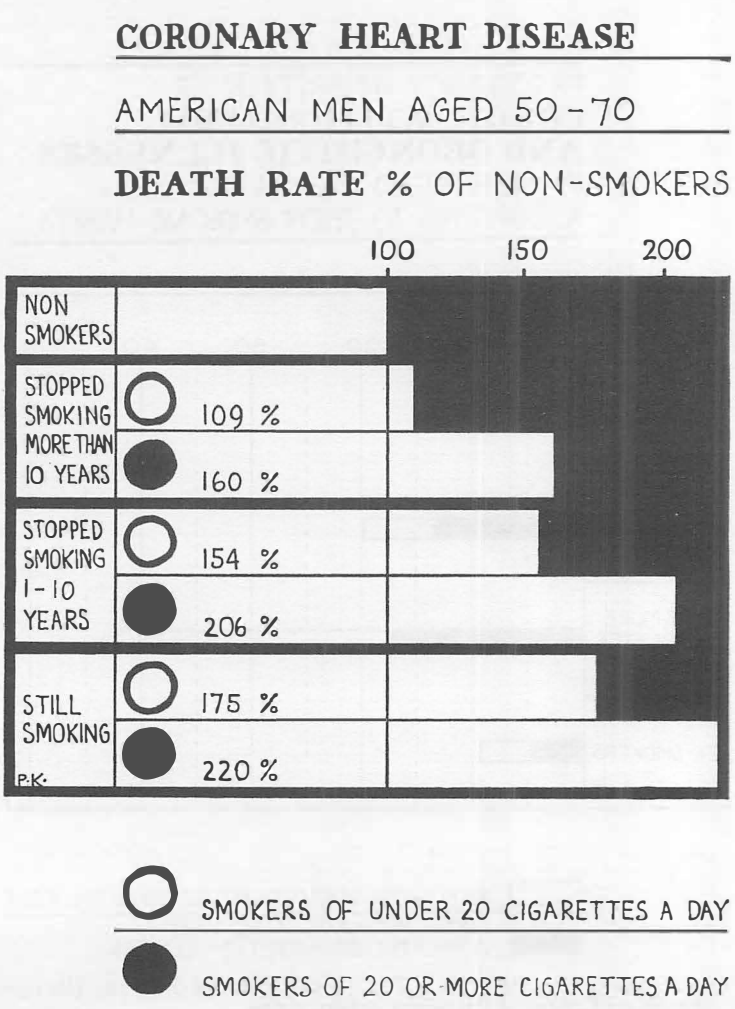


FIG. 15. Relationship of death rates from coronary heart disease to smoking habits. (Data from HAMMOND, E. C., and HORN, D. (1958). *J. Amer. med. Ass.*, **166**, 1159, 1294, after Royal College of Physicians Report, 1962.)

that members of this religious sect, which prohibits smoking, have an incidence of lung cancer one-eighth of that of non-members. Indeed the only two males with lung cancer were converts who had smoked cigarettes until middle age. In respect of cancer of sites not associated with smoking there was no difference from the control group, so that Seventh Day Adventists evidently have no general immunity from cancer. Therefore, to accommodate this evidence to the hypothesis of a genetic cause of both smoking and lung cancer, it would be necessary to stipulate that those born into the sect, but not those converted to it, inherit a low susceptibility to lung cancer.

"To many it will come as no surprise to learn that the benefits of religious observances are by no means restricted to the future life. But not often before can the evidence have been put on such a sure statistical basis".*

Support for the genetic hypothesis has also been forthcoming with evidence that there are personality differences between smokers and non-smokers. Cigarette smokers are more extraverted and rather less rigid than non-smokers. Perhaps they "live it up" more than non-smokers and so both lower their resistance to disease and expose themselves more to disease-producing conditions (7), so that smoking is incidental, not causal.

However, this attractive theory does not account for the disproportionate increase in lung cancer amongst smokers, compared with other cancers (1).

General air pollution is also relevant and it certainly appears to increase the incidence of lung cancer, but it is probably a minor factor, for at all levels of air pollution smokers suffer most, even in the most rural areas.

The proposition that increased accuracy of diagnosis and death certification is responsible for an apparent and not a real increase in lung cancer can be dismissed, as it cannot explain the faster rate of increase in men than in women.

"We are therefore left with the hypothesis that habitual cigarette smoking over many years, is a cause, in the ordinary sense, of lung cancer" (1).

This conclusion is now generally accepted, though disputes on individual studies continue. Indeed, to decline to accept the causal hypothesis, *to the extent* of agreeing to dissuade the young from beginning to smoke, inevitably raises the question of what motives are behind such a refusal. Motives, in this context, may be of several kinds, economic interest, emotional, or merely scientific vanity:

> To observations which ourselves we make,
> We grow more partial for th'observer's sake.†

* Editorial (1959). *Brit. med. J.*, **2**, 1465.
† ALEXANDER POPE (1688–1744). *Moral Essays*, Ep. 1.

Study of the evidence and opinions on smoking and lung cancer can be recommended to anyone wishing to exercise his intellect in assessing scientific evidence of several kinds, and human motives, and it has the added advantage of being a subject of huge social importance.

The changed habits of male British doctors (Fig. 13), no doubt the result of the evidence on lung cancer, probably account for the fact that amongst them between 1951 and 1965 the death rate from lung cancer fell by 38% whereas amongst the general male population, whose habits had not significantly changed, the death rate rose by 6%.

Bladder cancer is twice as common among smokers.

Chronic bronchitis is a major cause of death and disablement in Britain. Smoking and air pollution are potent factors. The manifest improvement in the condition that follows cessation of smoking does not allow of the disputes on causality that have been so troublesome and interesting in the case of lung cancer.

Coronary artery disease. Liability to this disease is about twice as great in cigarette smokers and is related to number smoked, to inhalation and to age of beginning to smoke. The risk is less in pipe and cigar smokers.

Thromboangiitis obliterans hardly ever occurs in non-smokers.

Peptic ulcer mortality is somewhat higher amongst smokers, and there is good evidence that healing is delayed by smoking (*8*).

Other associations with chronic smoking. Women who smoke during **pregnancy** have a higher incidence of abortion, babies 170 g lighter and with a late fetal plus neonatal mortality rate 28% higher than non-smokers (*23*). Later development is also retarded (*27*). Smokers are less often certified as dying of Parkinsonism than are non-smokers. Facial wrinkles above age 30 yrs correlate with amount smoked.

Tobacco amblyopia is rare. There is a characteristic centrocecal scotoma, particularly to red and blue. Nutritional deficiency may promote it and it is commonest in pipe and cigar smokers. Slow recovery is usual provided tobacco is abandoned. Hydroxocobalamin may help.

Whether smoking significantly affects blood clotting remains uncertain.

The demonstrable and suspected deleterious effects of heavy tobacco smoking are quite enough without there being any necessity for those who disapprove of the habit on moral grounds to invent others as has been done in the past. "An old dresser of mine at the hospital, of the name of Bain, who was an amiable attentive pupil, but never very efficient, smoked, I have since heard, a good deal when at the hospital, but after he left he was smoking nearly all day long. His debility was now so great that he was obliged to have a glass of bitter beer in the morning before he could rise. He was not addicted to drinking. . . . The whole of his ailments were produced by tobacco-smoke."*

* Solly, S. (1857). *Lancet*, **1**, 176.

Stopping Smoking

Contrary to what is widely believed it is not generally difficult to stop (66%), only 14% finding it "very difficult" (*21*). But ex-smoker status is unstable. The situation is summed up by the witticism, "Giving up smoking is easy, I've done it many times". There is no good evidence that any drug is effective other than as a placebo.

Such a use, however, is not to be despised and placebos can be reinforced by the physician's overt confidence as he prescribes them. But only harmless drugs should be used. Quinidine-containing anti-smoking remedies are potentially dangerous to the heart, perhaps especially if the patient exercises vigorously, for then the serum potassium level rises,* and cardiac arrest may occur. Lobeline is traditional. Ascorbic acid is harmless.

If the patient is heavily tobacco-dependent and anxiety and tension are concomitants of attempts to stop smoking, then a sedative or tranquilliser may be useful for a short time, but it is important to avoid substituting one drug-dependence for another.

Various astringents are used in the mouth to make the smoke taste bad.

In short, drugs have little place, and "the weaponry which may help the patient to hurdle his habit"† is divided between "appeals to sense and the psyche" and so is beyond the scope of this book.

Tobacco-dependence is more an emotional than a physical dependence. Patients are prone to solace themselves with food on abandoning the habit, and to gain weight in consequence. If appetite suppressants are used, the patients may become dependent on them.

Whether a patient should give up smoking depends on numerous factors, including the amount of evidence that smoking causes or aggravates disease in people in general and in the patient in particular, and the patient's attitude to his habit. Some people are so miserable without tobacco that the risk of disease is the lesser evil. To smoke, or not to smoke, is not primarily a problem of pharmacology, and this also applies to alcohol. There is ample evidence to warrant strong advice against starting to smoke, but doctors are not consulted on this by individuals. The problem with, say, the chronic bronchitic habituated to tobacco is different.

Over-hasty and unreasonable prohibitions of patients' pleasures or vices do no good. The pliable patient is made wretched, but most are merely alienated, as was D. G. Rossetti (1828–1882), who wrote

My doctor's issued his decree
That too much wine is killing me,
And furthermore his ban he hurls
Against my touching naked girls.

How then? Must I no longer share
Good wine or beauties, dark and fair?
Doctor, goodbye, my sail's unfurled,
I'm off to try the other world.

* ALEXANDER, M. K. (1964). *Lancet*, **1**, 226.

† SPRAGUE, H. B. Monthly scientific publication of the American Heart Association, Inc., October 1964.

Alternative smoking materials based on cellulose are being developed. They have been extensively tested on animals and are now being tried on man. Nicotine, or a proportion of tobacco, is added to provide satisfaction.

Medical Students' Attitudes Towards Smoking (*15*)

In a survey commissioned by the Department of Health which seems naively to have thought medical students to be both "interesting" and "influential", the following emerged:

"The smoking habits of medical students differ from those of the public in a number of ways. Male medical students are less likely to be smokers than male members of the public, and female medical students are also less likely to be so than female members of the public. If they do smoke, the amount smoked tends to be less."

"The control group analysis showed that not all the differences found between medical students and the public could be attributed to the training and specialised experience medical students receive, but were more probably due to educational differences between medical students and the public. The smoking habits of medical and non-medical students were similar except that the incidence of smoking was lower among female medical students than it was among the others and that pipe-smoking was more popular among medical students. There is little indication from these findings that medical training is influencing students very strongly. On the other hand non-medical students, though similar to medical students in certain of their attitudes to smoking, had far less desire than even preclinical students to give up smoking altogether, and fewer of them had ever tried to give up smoking at some time in the past. Preclinical and clinical students were far more knowledgeable than non-medical students about the illnesses associated with smoking and many more of them believed that smoking is definitely a cause of lung cancer. They also had a much greater tendency than non-medical students to believe that smoking might damage their future health; but if they believed that their own health was safe even though the health of other people could be affected, their rationalisations for this view were the same as those of non-medical students."

Snuff (*14*)

Snuff is powdered tobacco mixed with other substances. Prolonged use causes atrophy of the nasal mucous membrane with replacement of ciliated columnar by squamous epithelium. Some kinds used in Africa may be locally carcinogenic.

ETHYL ALCOHOL

"The services rendered by intoxicating substances in the struggle for happiness and in warding off misery rank so highly as a benefit that both individuals and races have given them an established position within their

libido-economy. It is not merely the immediate gain in pleasure which one owes to them, but also a measure of that independence of the outer world which is so sorely craved . . . We are aware that it is just this property which constitutes the danger and injuriousness of intoxicating substances . . ."*

Although the importance of alcohol in therapeutics is small its social significance is so big that a fuller account of its pharmacology is warranted than would otherwise be appropriate.

The history of alcohol is part of the history of civilisation "ever since Noah made his epoch-making discovery".† Perhaps its main use in therapeutics has been with opium as an analgesic and surgical anæsthetic before the introduction of ether.

Alcohol acts on the central nervous system in the manner of the inhalation anæsthetics.

Pharmacokinetics: *absorption* of alcohol taken orally is rapid, for it is highly soluble and diffusible, some from the stomach, but most from the small intestine. With moderate amounts the highest blood levels, as might be expected, are reached with stronger solutions.

However, solutions above 20% are absorbed relatively slowly because high concentrations of alcohol inhibit gastric peristalsis and cause pylorospasm, thus delaying the arrival of the alcohol in the small intestine. Large doses taken in very dilute solution are absorbed relatively slowly because of the large amount of water.

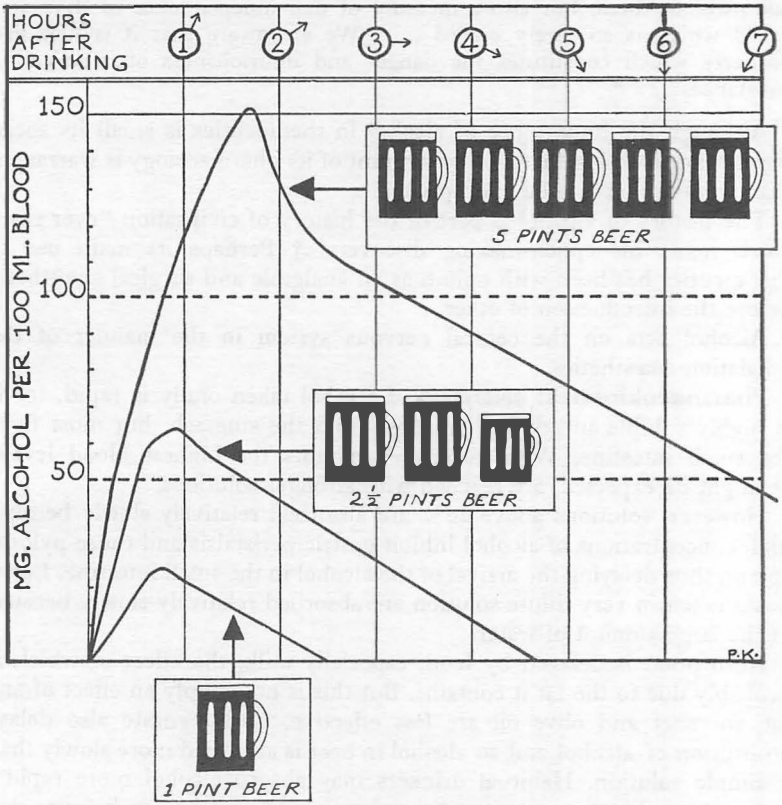
Absorption is delayed by food, especially milk, the effect of which is probably due to the fat it contains. But this is not simply an effect of any fat, for suet and olive oil are less effective. Carbohydrate also delays absorption of alcohol and so alcohol in beer is absorbed more slowly than a simple solution. Habitual drinkers may absorb alcohol more rapidly than others. They excrete it at normal rates, but metabolism is faster due to *enzyme induction*, though it also *inhibits* metabolism of other drugs.

After absorption alcohol rapidly diffuses throughout the body water and is not selectively stored in any tissue. It enters fat relatively slowly and women have higher blood concentrations as they have more body fat. If food is taken simultaneously alcohol disappears from the blood more rapidly than otherwise; it is not known how this happens.

Maximum *blood concentrations* after oral alcohol therefore depend on numerous factors including the total dose, the strength of the solution, the time over which it is taken, the presence or absence of food, the time relations of taking food and alcohol and the kind of food eaten, as well as on the speed of metabolism and excretion. A single dose of alcohol, say 60 ml. (equivalent to 145 ml whisky, five to six "whiskies", or three pints, 1,700 ml of beer) taken over a few minutes on an empty stomach will probably produce maximal blood concentration at from 1 to 1½ hrs

* FREUD, S. (1939). *Civilisation, War and Death, Psycho-Analytical Epitomes, No.* 4. Hogarth Press.

† *Genesis*, 9, 21; HUXLEY, A. (1957). *Ann. N.Y. Acad. Sci.*, **67**, 675.



Approximate blood levels after three doses of alcohol.

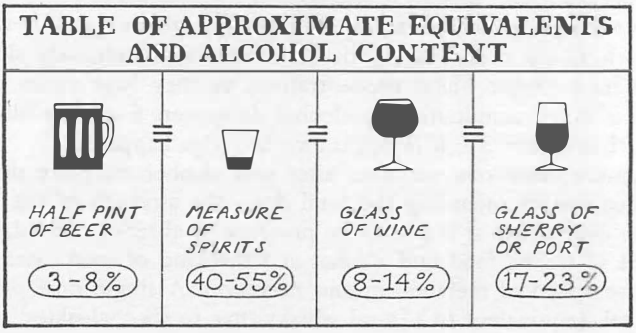


FIG. 16. Table of equivalent doses, with percentage alcohol content of some drinks. (Knowledge of blood alcohol level does not allow a reliable estimate of how much has been consumed to be made.)

and will not all be disposed of for 6 to 8 hrs. There are very great individual variations. About 90% of absorbed alcohol is **metabolised,** the remainder being excreted in the breath, the urine and the sweat; convenient methods of estimation of alcohol in all these are available. The rate at which alcohol is metabolised varies somewhat with the concentration in the body; it is generally in the region of 10 to 15 ml per hour in occasional drinkers regardless of plasma concentration; in tolerant individuals metabolism is faster, but this is not the sole explanation of their tolerance, which is also a tissue tolerance.

Alcohol is metabolised (oxidised) by enzyme systems in the liver, first into acetaldehyde and then to acetate which is metabolised to carbon dioxide and water. Some chemicals, for instance disulfiram (Antabuse), block the conversion of acetaldehyde to acetate so that the acetaldehyde accumulates and makes the subject feel ill. *Blood concentration* of alcohol has great medicolegal importance. *Alcohol in alveolar air* is in equilibrium with that in pulmonary capillary blood and reliable, easily handled devices have been developed to measure it (*5*), for this avoids "assaulting" the subject with a needle and can be used by police at the roadside.

Actions. The most important actions of alcohol are on the central nervous system in which it causes depression, like other anæsthetic agents. It is not a stimulant; hyperactivity, when it occurs, is due to removal of inhibitory effects. The concept of higher levels of the central nervous system dominating lower levels is naive, and it is now known that there is a complex interdependence of the various parts, so that changes at one "level" affect function at other "levels", "higher" or "lower". Alcohol, in ordinary doses, may act chiefly on the arousal mechanisms of the brain stem reticular formation (*6*). Direct cortical depression probably only occurs with high doses.

With increasing doses the subject passes through all the stages of general anæsthesia and may die of respiratory depression. Psychic effects are the most important socially, and it is to obtain these that the drug is habitually used in so many societies, to make social intercourse not merely easy but even pleasant. They have been admirably described by Sollmann; "The first functions to be lost are the finer grades of judgment, reflection, observation and attention—the faculties largely acquired through education, which constitute the elements of the restraint and prudence that man usually imposes on his actions. The orator allows himself to be carried by the impulse of the moment, without reflecting on ultimate consequences, and as his expressions become freer, they acquire an appearance of warmth, of feeling, of inspiration. Not a little of this inspiration is contributed by the audience if they are in a similar condition of increased appreciation. . . . Another characteristic feature, evidently resulting from paralysis of the higher functions, is the loss of power to control moods."*

* SOLLMANN, T. (1957). *Manual of Pharmacology.* 8th ed. Philadelphia: Saunders.

Environment, personality, mood and dose of alcohol are all relevant to the final effect.*

These and other effects that are characteristic of alcohol, have been celebrated in verse.†

Ho! Ho! Yes! Yes! It's very all well,
You may drunk I am think, but I tell you I'm not,
I'm as sound as a fiddle and fit as a bell,
And stable quite ill to see what's what.
I under *do* stand you surprise a got
When I headed my smear with gooseberry jam:
And I've swallowed, I grant, a beer of lot—
But I'm not so think as you drunk I am.

Can I liquor my stand? Why, yes, like hell!
I care not how many a tossed I've pot,
I shall stralk quite weight and not yutter an ell,
My feech will not spalter the least little jot:
If you knownly had own!—well, I gave him a dot,
And I said to him, "Sergeant, I'll come like a lamb—
The floor it seems like a storm in a yacht,
But I'm not so think as you drunk I am."

For example, to prove it I'll tale you a tell—
I once knew a fellow named Apricot—
I'm sorry, I just chair over a fell—
A trifle—this chap, on a very day hot—
If I hadn't consumed that last whisky of tot!—
As I said now, this fellow, called Abraham—
Ah? One more? Since it's you! Just a do me will spot—
But I'm not so think as you drunk I am.

ENVOI

So, Prince, you suggest I've bolted my shot?
Well, like what you say, and soul your damn!
I'm an upple litset by the talk you rot—
But I'm not so think as you drunk I am.

There is good reason to believe that, in general, efficiency, both mental and physical, is reduced by alcohol in any amount worth taking for social purposes. There is an important exception; the person who is so disabled by anxiety or nervous tension that his performance is gravely impaired may improve with the correct dose of alcohol. The alleviation of great anxiety may improve performance more than the alcohol depresses

* "That which hath made them drunk hath made me bold." Lady Macbeth in *Macbeth*, Act 2, Scene 2. W. SHAKESPEARE.

† By SIR J. C. SQUIRE (1884–1958). Quoted, by permission, R. H. A. Squire. To be fully appreciated, this poem should be read aloud.

it. Such people, mentally abnormal, are more liable to become alcohol addicts. Another exception is a minority of introverted people; it is referred to below.

Innumerable tests of physical and mental performance have been used to demonstrate the effects of alcohol. Results show that alcohol reduces visual acuity and delays recovery from visual dazzle, it impairs taste, smell and hearing, muscular co-ordination and steadiness and prolongs reaction time. It also causes nystagmus and vertigo. At the same time the subjects commonly have an increased confidence in their ability to perform well when tested and underestimate their errors, even after quite low doses. Attentiveness and ability to assimilate, sort and quickly take decisions on continuously changing information input, decline. This results particularly in inattentiveness to the periphery of the visual field, which is important in motoring. All these are evidently highly undesirable effects when a person is in a position where failure to perform well may be dangerous.

The effects of alcohol on **motor driving** have been the subject of a lot of well-deserved attention, and many countries have made laws designed to prevent motor accidents caused by alcohol. The problem has nowhere been solved. In general it can be said that the weight of evidence points to a steady deterioration of driving skill and an increased liability to accidents which begins with the entry of alcohol into the blood and steadily increases with blood concentration.

"Alcohol brings disaster on the road less because of lack of skill than because of defective judgement *in relation to* skill. . . . Furthermore, let us recognise that the danger may be less from the few who have imbibed a lot than from the many who have taken a little."*

Unfortunately it is not possible to observe and make measurements of driving skill in subjects who are both unaware that they are under observation and who are yet driving under normal traffic conditions. The undoubted tendency of alcohol to increase distractability, proneness to take risks and carelessness has not therefore been measured under normal conditions; in experimental conditions the well-known ability of an alcoholic to "pull himself together" and to perform well temporarily when he knows he is being tested will tend to give an unduly favourable picture of the effects of alcohol, but despite this, the evidence that its effects on driving are wholly evil is impressive.

In one study on Manchester bus drivers, all of whom were recipients of awards for safe driving, it was found that even with these experienced professionals there was no "safe" blood-alcohol level below which it was certain that no impairment of judgement would occur.

The drivers were invited to estimate through what gaps they *thought* they could drive their bus, were then given a driving test to determine the smallest gap through which they would *actually attempt* to drive and finally were told to drive through gaps regardless of their opinions. The

* COHEN, J. (1963). In *Alcohol and Road Traffic.* Brit. Med. Assoc., London.

main conclusion was that "the performance of the drivers deteriorated, they were involved in greater hazards, and they displayed a false confidence in their driving ability" (*2*).

In another study using a motor driving trainer it was found that alcohol even in small doses caused drivers to move away from the kerb and to tolerate steering swings towards the road centre but not towards the kerb, also steering wheel movement increased and its timing became more faulty. An attempt to correlate these responses with personality suggested that extraverts were not worried by the stress imposed by taking alcohol, they did not alter their speed greatly but were much less accurate. Introverts however appeared to try to compensate for the alcohol effect, earnestly striving to show that they were efficient, with the result that they over-reacted to the situation, moving the steering wheel more and changing speed, some slowing right down and others seemingly trying to show how quickly they could drive. In the introvert group 2 out of 9 subjects made fewer errors. No extravert made fewer errors (*3*).

There can be little doubt that alcohol plays a huge part in causing motor accidents, being a factor perhaps in as many as 50%. Youth is also associated with increased liability to road accidents. The adolescent who drives after drinking is thus a grave menace. Alcohol adversely affects the prognosis of head injuries (*8*). Increasingly, for public safety, stress is laid on measuring blood concentrations of alcohol; these are likely to be more widely employed as the serious impairment of judgement caused by even small amounts of alcohol is recognised and the consequences condemned by society. Schemes for clinical examinations for "intoxication" usually consist of general observations on behaviour and simple tests for physical inco-ordination. But the carelessness or lack of vigilance which follows even very small amounts of alcohol and which is probably a far commoner cause of accidents than is physical inco-ordination cannot be shown by any clinical tests that can reasonably be applied, for such people can easily "pull themselves together" when they realise that they are being examined with a view to a charge being brought against them, and in any case the experience of a motor accident is often quite enough to promote an appearance, and indeed a feeling, of sobriety.

For this reason, the compulsory use of a roadside breath test, followed by compulsory provision of a blood sample (or urine sample if the subject objects to blood being taken) is in the public interest. The breath test is not accurate enough to be used alone as evidence. In Britain a blood concentration exceeding 80 mg alcohol/100 ml blood whilst in charge of a car is a statutory offence. At this concentration, the liability to accident is about twice normal. Other countries set other concentrations, some lower, some higher.

Naturally, suspects are sometimes reluctant to provide evidence for their own conviction and refusal to undergo the breath test or to give blood or urine is deemed evidence of an alcohol concentration above the legal limit. One ingenious Englishman, having provided a positive breath

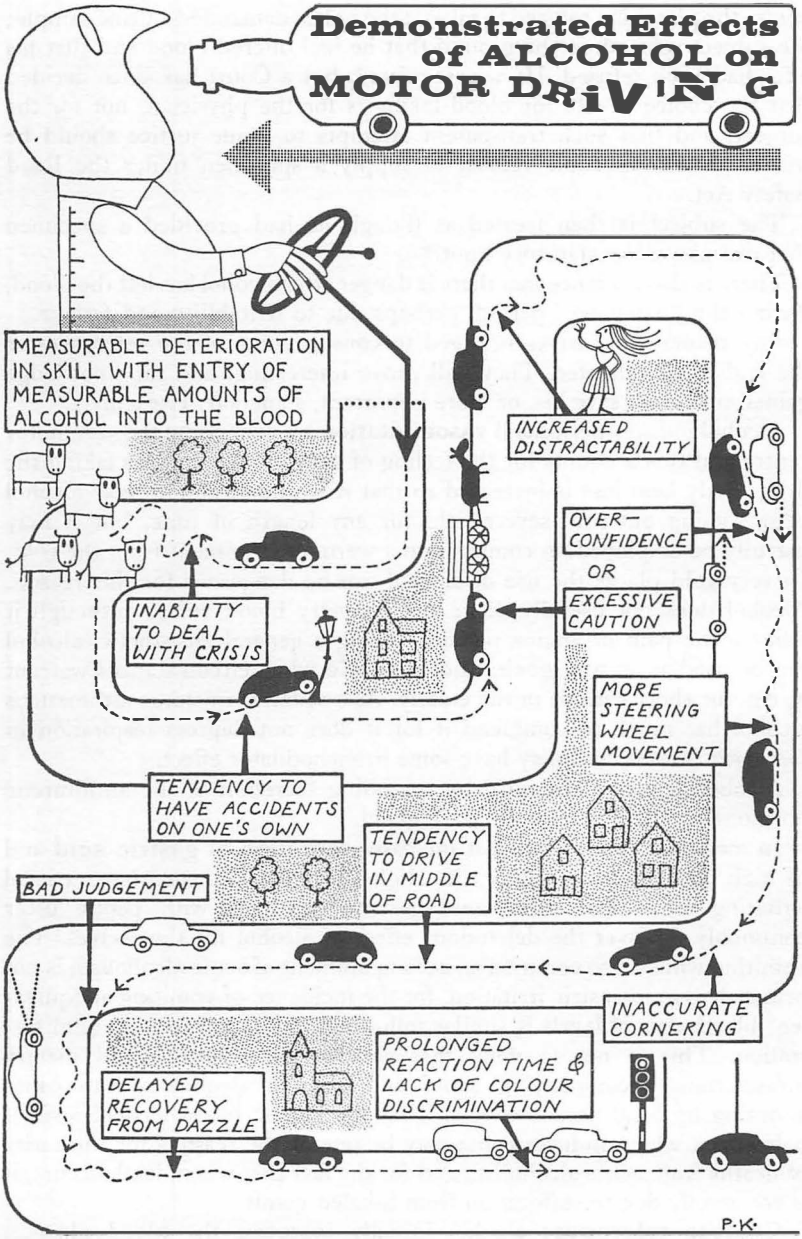

Demonstrated Effects of ALCOHOL on MOTOR DRIVING
MEASURABLE DETERIORATION IN SKILL WITH ENTRY OF MEASURABLE AMOUNTS OF ALCOHOL INTO THE BLOOD
INCREASED DISTRACTABILITY
OVER-CONFIDENCE
OR
EXCESSIVE CAUTION
INABILITY TO DEAL WITH CRISIS
MORE STEERING WHEEL MOVEMENT
TENDENCY TO HAVE ACCIDENTS ON ONE'S OWN
TENDENCY TO DRIVE IN MIDDLE OF ROAD
BAD JUDGEMENT
INACCURATE CORNERING
PROLONGED REACTION TIME & LACK OF COLOUR DISCRIMINATION
DELAYED RECOVERY FROM DAZZLE
P.K.

FIG. 17.

test offered a blood sample on the condition it should be taken from his penis; the physician refused to take it; the police demanded a urine sample; the subject refused on the ground that he had offered blood and that his offer had been refused. He was acquitted, but a Court has since decided that the choice of site for blood-taking is for the physician, not for the subject, and that such transparent attempts to evade justice should be treated as unreasonable refusal to supply a specimen under the Road Safety Act.

The subject is then treated as though he had provided a specimen that was above the statutory limit.*

There is also evidence that there is danger after alcohol has left the blood, during the "hangover" period, perhaps due to irritability and fatigue.

Any reader who drives is urged to consult some of the references at the end of the chapter. They will prove interesting, and the knowledge gained may even save his, or more important, somebody else's life.

Alcohol induces peripheral **vasodilatation** by depressing the vasomotor centre and this accounts for the feeling of warmth that follows taking the drug. Body heat loss is increased so that it is undesirable to take alcohol before going out into severe cold for any length of time, but it may usefully be employed on coming into a warm environment from the cold. In very cold places the use of alcohol can be dangerous for this reason. Alcohol does not usefully dilate the coronary blood vessels although it relieves the pain of angina pectoris. Being a general anæsthetic, alcohol can be used as an **analgesic and hypnotic** when circumstances warrant it, e.g. for short periods in the elderly. As a sedative in status asthmaticus alcohol has much to commend it for it does not depress respiration in *therapeutic* doses, and may have some bronchodilator effect.

Alcohol acts as a **diuretic** by inhibiting secretion of the antidiuretic hormone by the posterior pituitary gland.

In moderate concentration it increases **secretion of gastric acid** and in high concentration reduces it. High concentrations also have a local irritating effect and may cause gastritis. Patients with peptic ulcer commonly discover the deleterious effect of alcohol for themselves. The vomiting which is so common an accompaniment of acute alcoholism is not primarily due to gastric irritation, for the incidence of vomiting at equivalent blood alcohol levels is similar following oral or intravenous administration. This is not to deny that very strong solutions and dietary indiscretions accompanying acute and chronic alcoholism can cause vomiting by local gastric effects. That the emetic blood alcohol level is below that which induces coma may be one of the reasons for the rarity of deaths from acute alcoholism and for the fact that when death occurs, it is commonly due to suffocation from inhaled vomit.

Glucose tolerance: alcohol initially increases the blood glucose, due to reduced glucose uptake by the tissues. This leads to increased

* *Brit. med. J.* (1972), **2**, 600.

insulin output which may be responsible for the severe **hypoglycæmia,** especially if taken after vigorous exercise, that is a feature of some cases of acute alcoholism, especially in fasting subjects.

On **sexual function** nothing really new has been said since William Shakespeare wrote that alcohol "provokes the desire, but it takes away the performance." Performance in other forms of athletics is also impaired.

As a **food,** alcohol may be very useful in debilitated patients. It is rapidly absorbed from the alimentary tract without requiring digestion and it supplies seven calories per gram as compared with nine from fat and four from carbohydrate and protein. Heavy doses cause hyperlipidæmia in some people.

Tolerance to alcohol can be *acquired* and Gaddum has made the practical point that it costs the regular heavy drinker two-and-a-half times as much to get drunk as it would cost the average abstainer.* This is probably due both to enzyme induction and to adaptation of the CNS. There are also racial differences in *natural tolerance*; Caucosoids are more tolerant than Mongoloids.

Acute alcohol poisoning is a sufficiently familiar condition not to require detailed description. It is notorious that the behaviour changes, mental confusion, inco-ordination and even coma, which are characteristic, can be due to numerous other conditions and diagnosis can be extremely difficult if a sick or injured patient happens to have taken alcohol as well. Alcohol can cause severe hypoglycæmia. Anyone who is liable to find himself called upon, especially by the police, to diagnose drunkenness, or rather perhaps to exclude other causes as responsible for a person's behaviour, should consider his procedure very carefully. When applying clinical tests for drunkenness it is worth remembering that habitual physical skills can be retained to an advanced stage and that the results of performance tests cannot always be interpreted unambiguously.

"One evening a motorist, whose speech was slurred and who was excited, brought to my house a cyclist he had knocked over. I told him he had had too much to drink and advised him to leave his car and walk home. He was very incensed at this and demanded that I should call a policeman as I had insulted him. I rang up the police station, and asked the constable who arrived to persuade him to go home quietly without his car. The constable got him outside on the pavement, and after testing his walking, told him that he would be wise to follow my advice but that he was at liberty to make his own choice.

"The driver thereupon got into his car, started off at a fast speed down a hill, mounted the pavement on the opposite side of the road, returned to his own side, crossed the pavement there, and collided with the wall bordering the churchyard. He had no explanation to offer for this driving. He was arrested, brought back to my house, and I was asked

* GADDUM, J. H. (1956). In *Lectures on the Scientific Basis of Medicine,* 1954–55. London: Athlone Press.

to certify him. I refused to do this, and he was examined later at the station by a colleague who told me the rest of the story. After submitting the defendant to various inconclusive tests and fortified by the history, he told him he was drunk. He was then asked by the motorist: 'Doctor, could a drunk man stand up in the middle of this room, jump into the air, turn a complete somersault, and land down on his feet?' My colleague was injudicious enough to say, 'Certainly not'—and was then and there proved wrong."*

When a person is behaving in an excited or violent fashion due to alcohol it is very dangerous to attempt to control him with barbiturates or opiates because of the risk of inducing severe respiratory depression as a result of synergism of the drugs. Paraldehyde, chlorpromazine or diazepam are safer. In patients who are comatose the stomach may be emptied by tube; emesis, either therapeutic or due to the alcohol, is dangerous in any patient with impaired consciousness. Respiratory stimulants, e.g. nikethamide, or controlled respiration are used as required: circulatory failure may occur.

Large doses of **fructose**† i.v. enhance alcohol metabolism but also induce lactic-acidosis. Claims that a dose of fructose swallowed during and/or at the end of an evening's drinking can render a subject who is unfit to drive, fit to do so, are dangerously misleading.

Chronic alcohol dependence (alcoholism) is liable to cause a variety of psychotic states and, after many years, nutritional deficiencies, especially of thiamine. The latter occur because alcoholics suffer anorexia with chronic gastritis, may be taking nearly all the calories they need as alcohol and may have no money to spend on food. Alcoholic hepatic cirrhosis due to a direct toxic effect on liver cells which is probably enhanced by nutritional deficiency (*12*). Stopping drinking improves survival only in *early* cases. When wine rationing was introduced in Paris in the 1939–45 war deaths from hepatic cirrhosis dropped to about one-sixth the previous level; 5 years after the war they had regained their previous level. A similar, though less, effect was seen during Alcohol Prohibition in the U.S.A. (1919–33). Exacerbations of drinking may precipitate an acute hepatitis. The serum transaminase rises after alcohol in alcoholics, but not in normals. Chronic myocardial failure also occurs, as does peripheral neuropathy. It is reported that in one case the cerebrospinal fluid tasted of gin; this needs confirmation.

The end-stage, of dementia with memory loss, deterioration in social habits, slurred speech and gait and "blackouts", which may be epileptic, is typical. More florid chronic psychotic conditions with delusions and hallucinations are probably the result of abnormal previous personality rather than any intrinsic effect of alcohol on the nervous system.

* WORTHING, C. L. (1957). *Brit. med. J.*, **1**, 643.

† Sucrose is hydrolysed to dextrose and fructose in the intestine, but this takes time.

FIG. 18. By permission, after GLATT, M. M. (1963). *Proceedings of the 2nd International Conference on Alcohol and Road Traffic.* Brit. med. Assoc.: London.

Sudden **withdrawal of alcohol** from an addict who has developed physical dependence, such as may occur when an ill or injured alcoholic is admitted to hospital, can precipitate an acute psychotic attack (*delirium tremens*).

Withdrawal is less unpleasant if the patient is sedated, e.g. with chlorpromazine, chlordiazepoxide or paraldehyde. Chlormethiazole (Heminevrin), an anticonvulsant sedative has a reputation as specially effective, but such a claim is hard to prove one way or the other.

Psychosocial therapy is more important than drugs, which are only of limited use. "The surprising beneficial effect of any therapy in the initial period of its trial is explained by the enthusiasm of the therapist combined with insufficient length of follow-up" (*6*).

It is usual to administer vitamins especially thiamine, in which alcoholics are commonly deficient. Corticotrophin and hydrocortisone may be useful if there is collapse. The general subject of drug dependence is discussed earlier in this chapter.

Disulfiram (Antabuse). In alcoholics who are fairly well and co-operative, an attempt may be made to discourage drinking by the use of disulfiram. This blocks the metabolism of alcohol at the stage where acetaldehyde is formed. The accumulation of this substance in the blood is so unpleasant that the patient does not wish to experience it again: disulfiram thus reinforces his perhaps otherwise ineffective will power. Such therapy by intimidation, whether self-administered or thrust on the patient, is not to be expected to play an important part in the treatment of alcoholism, a disease which is primarily a manifestation of psychological disorder. When a patient is given disulfiram it is important to give a test dose of alcohol under supervision, so that he can be taught what to expect and also to induce in him an aversion from alcohol. That this is not a treatment to be lightly undertaken is shown by the fact that, though rare, deaths have occurred following the "test drink". A typical reaction of medium severity comes on about 5 mins after taking alcohol and consists of generalised vasodilatation and fall in blood pressure, sweating, dyspnœa, headache, chest pain, nausea and vomiting. Severe reactions include convulsions and circulatory collapse.

It is clear that no patient should be given disulfiram without the fullest previous explanation and the certainty that he understands the possible serious consequences of drinking a lot of alcohol in a few minutes.

The disulfiram-alcohol interaction has long been known to workers in the rubber industry in which the substance is used, but it was not applied to therapeutics until after the chance experience of two Danish pharmacologists. "Dr. Hald suggested that disulfiram could be employed as an anthelmintic because it had a very strong fixation to copper ions. It was probable that some enzymes of the oxidation system of intestinal worms were copper containing, and copper-containing enzymes are known in . . . higher animals, including man." The drug was tested on rabbits infected with worms and results were sufficiently encouraging to warrant clinical trial.

"According to the custom in this house we never give a new drug to patients before we have taken at least double the recommended dose ourselves. During this routine procedure Dr. Hald and I discovered that we had

developed a hypersensitivity to alcohol. We compared symptoms and found them identical. The only thing we have in common was the tablets. A test on a third person in our laboratory confirmed the observation."*

Further investigation disclosed the mechanism of the effect.

Calcium carbimide (Abstem) is similar.

Emetics, administered after drinking, are used in the "aversion" treatment of alcoholism, to establish a conditioned dislike.

Alcoholic drinks. The pharmacology of alcoholic drinks is not the same as the pharmacology of alcohol. The drinks contain other ingredients which may reduce the rate of absorption of alcohol (carbohydrate in beer), act as a carminative (essential oils), or diuretic (juniper oil in gin). It is certainly widely believed that the toxicity of all varieties of alcoholic drinks is not solely dependent on their alcoholic content and that ill-effects are likely to be more severe if several varieties are taken within a short time; this is expressed as advice "not to mix your drinks". There is no conclusive evidence on this point, but there is reason to believe that the effects of ethanol in some drinks is prolonged by the presence of other substances (propyl to octyl alcohols, ethers, aldehydes, etc.) which delay ethanol metabolism by occupying the same metabolic paths (i.e. competition) (*10*). These other ingredients are themselves hardly more toxic than ethanol. It should be remembered that when enough alcoholic drink has been taken to cause 'hangover" the subject has commonly debauched himself in other ways too, with tobacco, food, polluted atmosphere and fatigue, and in addition is expected to feel ill the next day.

Since there are many more important subjects for research, the final elucidation of this point in the near future is unlikely, and indeed very strong evidence would be needed to shake, although not to confirm, the faith of most people that this or that drink or combination is harmless or harmful, for the effects of alcoholic drinks are part of the folklore of society.

Alcohol and other drugs. *All cerebral depressants* (hypnotics, tranquillisers, antiepileptics, antihistamines) can either potentiate or synergise with alcohol, but this is seldom important at *ordinary* doses in relation to car driving. But, when supplies of hypnotics are given to patients known to drink heavily, they should be warned to omit the drugs when they have been drinking. Deaths have occurred from this combination.

Alcohol dependent people with a physical tolerance are relatively tolerant of some other cerebral depressant drugs (hydrocarbon anæsthetics and barbiturates), but of course the synergism with these drugs still occurs. There is no significant acquired cross-tolerance with the morphine group of drugs.

Sulphonylureas (antidiabetics) cause a disulfiram-like reaction, as may *metronidazole.*

Oral anticoagulants: control may be disturbed by alcohol inhibiting

* Dr. Erik Jacobsen. Personal communication.

hepatic metabolism directly or enhancing it by enzyme induction: moderate drinking is unlikely to cause trouble.

Anticonvulsants can be metabolised faster due to enzyme induction and this may contribute to its well-known adverse effect on epilepsy.

Miscellaneous uses. In addition to those already mentioned its use in strong solutions as an irritant has given alcohol a reputation as a restorative in fainting. When such stimulation is indicated a slap in the face is just as irritant, cheaper, always handy and cannot enter the lungs and cause pneumonia. Alcohol precipitates protein and is used to harden the skin in bedridden patients. Local application also reduces sweating and may allay itching. As a skin antiseptic 70% by weight (76% by volume) is most effective. Stronger solutions are less effective. Alcohol injections are sometimes used to destroy nervous tissue in cases of intractable pain (trigeminal neuralgia, carcinoma involving nerves).

METHYL ALCOHOL

Methyl alcohol is of clinical importance because it is sometimes consumed as a substitute for ethanol. Its acute toxicity is slightly less than ethanol, that is, it makes the subject a little less "drunk", but it is metabolised at only about a fifth the rate of ethanol and it is the toxic metabolites produced over a long period which make methanol intoxication so serious.

Methanol poisoning may appear with or without initial symptoms similar to those of ethanol. There is severe malaise, vomiting and abdominal pain. Pancreatitis has been found at autopsy on poisoned patients and so morphine should not be used if it is avoidable. Muscle cramps also occur. Coma and circulatory collapse may follow. A prominent symptom is visual disturbance with scotomata and total blindness, which may occur early or late. The mechanism is uncertain and partial or complete recovery can occur, although permanent blindness with optic atrophy is common. Very small doses can cause blindness and large doses sometimes have failed to do so, which has given rise to the suggestion that the eye changes may be due to an idiosyncrasy. Unfortunately they cannot reliably be reproduced in animals.

The characteristic symptoms of acute methanol poisoning may be delayed for many hours, or even a day or more if much ethanol has been consumed with it, as is often the case. This is because both alcohols are metabolised by the same enzymes and the rate at which each is metabolised depends on the amount of the other present, i.e. substrate competition. This can be made use of in treatment, the less toxic ethanol being added to delay metabolism of the methanol so that more of the latter is excreted unchanged in urine and breath and the amount of metabolites formed is less.

Methanol is metabolised into formaldehyde and then formate which produces an intense acidosis. To combat this is the most urgent need if the most effective treatment, dialysis, is not available.

There is reason to think that the prognosis may depend on the acidosis, which may be reversed by i.v. 5% sodium bicarbonate solution (over 100 g in a few hours may be needed). One-sixth molar sodium lactate (1·87%) may be used instead. Measurement of the plasma bicarbonate and blood pH are of great value in controlling therapy. In their absence, and in severe cases, it is better to risk overtreatment than undertreatment. Mild cases may

be treated by oral administration. As methanol is so slowly metabolised a patient may relapse if sodium bicarbonate administration is stopped too soon.

Experiments in animals and clinical observations suggest that administration of ethanol to delay methanol metabolism is beneficial. It is suggested that up to 10 ml of ethyl alcohol should be given hourly, for this is about the amount that can be metabolised, but the dose must be regulated by the patient's response, in view of the fact that he probably has unknown amounts of various alcohols in him. A darkened room is reputed to benefit the eye changes.

Guide to Further Reading

On Non-Medical Use; Drug Dependence

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Chapter 14

DRUGS AND MENTAL DISORDER

Background to the Use of Drugs in Mental Disorder

WITH the increasing recognition of mental illness as a common cause of disability, interest in the possibilities of drug therapy has naturally increased. Chemists have responded by making innumerable substances for investigation, hoping that some of them may prove to be drugs. One snag is the difficulty of predicting therapeutic efficacy from the animal experiments which must necessarily precede clinical trial; another is how to determine by clinical trial whether a genuine therapeutic effect has been achieved and, if so, whether it was in fact due to the drug. It is not surprising that no exact animal parallels for human mental disorders exist and that, as a result, "the major problem of replicating in the laboratory the actions of potential tranquillisers in human psychoses and neuroses remains almost completely unsolved".*

There is, however, great activity in this field, for both the potential benefits to humanity and the financial rewards are great, and laboratory workers are busy doing their best with experiments of an almost incredible variety. A therapeutic effect in human mental disease is hoped for if a chemical affects any part of the brain known to be related to behaviour; if it interacts with substances known to occur in the central nervous system, such as noradrenaline, 5-HT and acetylcholine; if it antagonises substances which produce abnormal behaviour, e.g. lysergic acid diethylamide, or if it modifies animal behaviour in situations which resemble those known to induce fear or anxiety in man. This diversity of approach indicates how little is known of the pathology of mental disorder.

Some of the animal techniques used in *the search for tranquillisers* to test in human mental disorder include general observation of the effects on behaviour alone and in groups, reaction to observers' presence and to handling, taming effects in monkeys, reduction of fighting amongst mice, prevention of epileptic fits caused by sound (audiogenic fits) in mice, prevention of drug-induced convulsions, reduction of amphetamine toxicity, reduction of drug-induced hyperactivity in animals, modification of "sham rage", of the shape of a spider's web and of the behaviour of Siamese fighting fish. There is also a wide range of methods involving conditioning. For example, animals can be taught to press a lever or to jump away at a signal, and so to avoid the electric shock which would otherwise ensue; drugs can sometimes modify such avoidance responses in ways which suggest that the animal has become less afraid.

* RILEY, H., *et al.* (1958). *J. Pharm.* (*Lond.*), **10**, 657.

A major difficulty in interpreting the results of animal experiments is that it is impossible to know how an animal feels. For example, an animal may cease, after a drug, to show signs of the fear which had been induced in it during a conditioning experiment. The explanation may be that the drug is a true tranquilliser and has allayed fear selectively, leaving the animal virtually normal, or the animal might no longer show fear because it feels too ill or else has forgotten the recently learned routine, so that the whole situation is different.

In laboratories where *tranquillising drugs* are sought it is usual to employ a number of tests simultaneously, so obvious is it that no one test can possibly be expected to reveal important new therapeutic agents. Attempts are also made to correlate animal experimental results with clinical efficacy. A drug shown clinically to be beneficial in, say, schizophrenia, would be carefully examined in a great many animal tests and those tests in which most activity was shown would be used as a battery for screening further new chemicals for possible clinical trial.

Drugs for use in depression are sought by examining compounds for their ability to stimulate the central nervous system in some way, e.g. by effect on the spontaneous activity of small animals in cages suspended so that they respond to any movement of the occupant (jiggle-cages), or by counting the pecking frequency of pigeons, reversal of ptosis due to reserpine or by testing for antagonism of depressant drugs. Antidepressants have also been found to block instinctive mouse-killing (muricidal) behaviour in rats, and this has been proposed as a screening test.

The search along these lines for better drugs is reasonable on current knowledge, but it is a crude process. The problems involved in psychiatry are more difficult than in many other branches of medicine where animal experiments can often be devised to approximate to human disease. Animal experiments which throw light on the function of simpler nervous systems should not be despised, although care must obviously be taken to avoid over-enthusiastic extrapolation from them to man. Most of those working with these tests are acutely aware of the difficulties involved.

A rational approach to the drug therapy of mental disease is the present intensive study of the biochemistry of human mental disorder. If characteristic metabolic abnormalities can be found in any disease then it may well become possible, in some cases, to make drugs that will modify or even rectify them. This may offer greater hope of therapeutic success in the psychoses in which behaviour differs from normal in kind, rather than in the neuroses in which it differs mainly in amount.

Clinical evaluation is done by recording drug effects on behaviour. Opinions of the patient himself and of his family and nurses and doctors are used as well as psychological tests and rating scales. In this field, bias is particularly likely and studies should be double-blind wherever practicable.

When a drug is ready for clinical trial in mental disease, a principal difficulty is to find a homogeneous group of patients on whom to try it.

Psychiatric diagnosis is less precise than that in most other branches of medicine; indeed it has even been suggested that the usual criteria of what constitutes a "disease" may not be applicable in psychiatry. The performance of well-designed clinical trials in psychiatry also presents many difficulties (*29*), in the use of the double-blind technique, assessment of results and avoidance of interference by factors other than the drug under investigation. Unfortunately many published clinical studies, even a majority, are so designed that no conclusion can legitimately be drawn as to the value of the drug, although a conclusion commonly is drawn nonetheless. ". . . totally uncontrolled studies of the effects of a new drug, especially when the dependent variable is something as amorphous and elusive as anxiety, can be misleading. A striking testimonial to the validity of this statement is the way in which the popularity of new drugs typically runs through the well-documented cycle of panacea, poison, pedestrian remedy. The high incidence of uncontrolled studies is not a feature confined to drugs affecting behaviour. It seems characteristic of clinical research. . . . When one considers that the principles of the controlled experiment were written about by Bacon, in 1620, and Pascal in 1648 . . ., an examination of the literature in 1958 can be somewhat discouraging" (*13*). It has got a little better since.

Some of the hazards of uncontrolled studies have been demonstrated. In one case patients and hospital staff were told that two new drugs were to be tried, an "energiser" and a "tranquilliser". The tablets were orange and yellow respectively, and were available in 25 mg and 50 mg "sizes". Improvement was reported in 53% of patients taking the "energiser" and in 80% of those taking the "tranquilliser". In fact both "drugs" were lactose, made to taste bitter with quinine (*2*).

Even where a careful double-blind technique is used successfully, bias due to the personality and beliefs of the physicians about the remedies can still affect the result. In a study on relief of anxiety by two active drugs and a placebo, the results varied according to which of two physicians was treating the patients.

Dr. A. was youngish in appearance, he expected no difference between the three treatments and his attitude to the patients was non-committal. No difference between the treatments was found.

Dr. B had greying hair and a fatherly appearance and he expected that the pharmacologically active substances would prove superior to the placebo. Patients reported that he was "helpful" and "dependable". A difference in favour of one of the active drugs appeared in his patients.

When both groups were added together there was no significant difference (*26*).

It is probable that effects of doctors' personalities and opinions can influence even the best conducted studies, and this may be more likely to happen where the drug is an adjuvant, and not the mainstay of therapy. The fact that endeavours to eliminate bias are not always completely successful has been used as an argument against attempting controlled

techniques in psychiatric comparisons. The logic of this is obscure. The special problems of assessing therapy in psychiatry will continue to be debated for a long time, for they will not be easily or quickly solved.

The enthusiasm with which drugs are welcomed by patients and used by doctors should make us pause. "Is it not possible that the use of these drugs represents a modern version of the 'furor therapeuticus'—a traditional 'occupational disease' of the physician? The last several decades have brought us, in rapid succession, various forms of 'shock treatments', psychosurgery, and, lastly, the tranquillising drugs. All have in common the fact that they provide socially sanctioned patterns of medical action and thus help the physician to do something when he is faced with a psychiatric problem" (*14*).

The physician is not necessarily treating only the patient when he gives a drug. He may be treating himself.

Mechanisms of action: depression: there is evidence that a deficiency of amines (5HT, catecholamines) accompanies depression and that drugs that induce depression reduce the amount of noradrenaline at the synapses, e.g. reserpine is a tissue amines depleter. Antidepressant drugs may act by increasing the amount of free amine present (*31*). L-tryptophan, a 5-HT precursor, has some antidepressant effect.

The time between onset of sleep and the first REM period (see *sleep*) is shorter than normal in depression. Tricyclics, MAOIs and lithium all lengthen this time (REM latency) (*76*).

Anxiety. The biochemical mechanisms of anxiety are even more obscure than those in depression. There is a hint that cyclic AMP may be involved. But there are also peripheral mechanisms such as increased voluntary muscle tone (reduced by a drug with central muscle relaxant effect, e.g. diazepam) and tachycardia (reduced by β-adrenoceptor block). Relief of these peripheral phenomena may help by breaking the somatopsychic cycle of anxiety → peripheral effects → more anxiety → more peripheral effects, and so on.

Psychoses: the mechanisms of depression and of anxiety may be involved, but there may be added biochemical disturbances. Phenothiazines and butyrophenones interfere with central catecholamine mechanisms (transport and effect). Lithium alters noradrenaline metabolism.

Psychotropic drugs provide symptomatic treatment only; they do not rectify disease processes, but it is possible that by reducing a symptom, a vicious circle may be broken, allowing the patient to re-establish contact with his environment and thus to become accessible to social and psychotherapy.

The effects of all drugs acting on mental processes vary greatly with the circumstances and the dose and the attitude of the prescriber.

Warning. A patient with "endogenous depression" became very much better during 3 or 4 weeks following prescription of an antidepressant drug. The physician reminded her of the importance of

continuing therapy despite the improvement. The patient smiled and said, "Oh, doctor, the tablets did not agree with me, so I stopped taking them after the first two or three days".* N.B. (1) antidepressants require about 10 days to produce benefit; (2) there is a great deal more to treating most diseases than simply prescribing drugs, and this is particularly true of psychological disorders; (3) when a patient improves following a prescription, it cannot be assumed that it is because of the prescription.

Classification of Psychotropic† Drugs

"Drugs are available which will increase the over-all output of patients with too little behaviour, and other drugs are available which reduce the output of patients with too much behaviour".‡ This bald statement usefully emphasises the depth of ignorance which is the most prominent feature of the background to the use of drugs to influence behaviour.

So little is known about the biochemical basis of mental disorder that no classification based on mechanisms of action can be offered. Drugs are perhaps best classified provisionally according to the symptoms they are used to relieve, but there is no general agreement and the following will have to serve. The main headings are those used by a World Health Organization Scientific Group.§

1. **Neuroleptics** (antipsychotics, major tranquillisers,¶ ataractics) are drugs with therapeutic effect on psychoses. They can produce extrapyramidal symptoms.

(a) *phenothiazines:* chlorpromazine (Largactil), perphenazine (Fentazin), fluphenazine (Modecate), prochlorperazine (Stemetil), promazine (Sparine), thioridazine (Melleril), thiopropazate (Dartalan), trifluoperazine (Stelazine), pericyazine (Neulactil).
(b) *butyrophenones:* haloperidol (Serenace), trifluperidol (Triperidol), benperidol (Anquil).
(c) *thioxanthenes:* chlorprothixene (Taractan), thiothixene (Navane), flupenthixol (Depixol).
(d) *reserpine*, *tetrabenazine* (Nitoman).

2. **Anxiolytic sedatives** (minor tranquillisers¶) are drugs that reduce pathological anxiety, tension and agitation but do not have therapeutic effect on disturbances of cognition and perception. They commonly have anticonvulsant effect, and are liable to induce dependence. They do not produce extrapyramidal symptoms.

* Merry, J. (1972). *Lancet*, **1**, 1175.
† Psychotropic = affecting the mind.
‡ Dews, P. B. (1958). In *Pharmacology in Medicine*. Ed. V. Drill. New York: McGraw-Hill.
§ World Health Organization (1967). *Tech. Rep. Ser.*, **371**.
¶ The word *tranquilliser* is used elsewhere in this book without qualification because it is useful to cover both groups 1 and 2 (neuroleptics, anxiolytic sedatives).

(a) *benzodiazepines:* diazepam (Valium), chlordiazepoxide (Librium), oxazepam (Serenid-D), medazepam (Nobrium), lorazepam.
(b) *meprobamate* (Equanil).
(c) *barbiturates.*
(d) *miscellaneous:* benzoctamine (Tacitin), oxypertine (Integrin), tybamate (Benvil), hydroxyzine (Atarax), chlormethiazole (Heminevrin), opipramol (Insidon).

In addition to the above, members of other groups can be useful:

(a) *antidepressants:* their inclusion may seem inappropriate, but some have sedative properties, e.g. doxepin (Sinequan, trimipramine (Surmontil), amitriptyline (Tryptizol), and patients are not necessarily *either* anxious *or* depressed, they may be both.
(b) *β-adrenoceptor blocking drugs* (to block cardiovascular effects of anxiety).

3. **Antidepressants** (thymoleptics) are drugs effective in treatment of pathological depression.

(a) *tricyclics:* imipramine (Tofranil), desipramine (Pertofran), trimipramine (Surmontil), amitriptyline (Tryptizol), protriptyline (Concordin), nortriptyline (Aventyl), doxepin (Sinequan), dothiepin (Prothiaden), dibenzepin (Noveril), clomipramine (Anafranil).
(b) *monoamine oxidase inhibitors:* phenelzine (Nardil), isocarboxazid (Marplan), nialamide (Niamid), tranylcypromine (Parnate), tofenacin (Elamol).

4. **Psychostimulants** increase the level of alertness and/or motivation.

(a) amphetamines, methylphenidate (Ritalin), pemoline (Kethamed).
(b) caffeine.

5. **Psychodysleptics** (hallucinogens, psychedelics, psychotomimetics) produce mental phenomena, particularly cognitive and perceptual.

6. **Miscellaneous.**

(a) *lithium:* for mania and manic depressive psychosis.
(b) *Combinations* of psychotropic drugs are sometimes useful. Initially at least the drugs should be given separately, e.g. first an anti-anxiety agent and then a phenothiazine added and the dose adjusted to suit the patient. Fixed-dose combinations are unsatisfactory, chiefly because of this need to adjust the doses; but patients are less likely to take two separate drugs reliably. The first fixed-dose combination to be introduced was barbiturate + amphetamine (e.g. Drinamyl). It causes euphoria and is particularly liable to dependence and abuse. Other examples include phenothiazine + MAOI (Parstelin), tricyclic + phenothiazine (Motival, Triptafen-DA), tricyclic + benzodiazepine (Limbritol), etc.
(c) L-tryptophan (Optimax): see *mechanism of depression*, above.

Dosage of Psychotropic Drugs

Because of the difficulty in measuring responses in psychiatry, and the variability caused by environmental factors, drugs are commonly given in arbitrarily fixed, or at least crudely adjusted, doses. This militates substantially against precise clinical evaluation and against achievement of optimum therapeutic effect, unless plasma concentrations can be measured.

In the case of tricyclic antidepressants standard doses may produce steady state plasma concentrations varying by a factor of ten or more (*32*). The ideal therapeutic response may occur at intermediate plasma concentrations, falling off as the concentration rises above an optimum. It is plain that where a patient does not respond, knowledge of plasma concentration will be valuable in order to allow a decision whether this is a true therapeutic failure or whether the dosage is wrong. This information is at present seldom available.

Neuroleptics

Phenothiazine group

Chlorpromazine. As a result of investigation of phenothiazine compounds for possible anthelmintic effect, first promethazine, the useful sedative and antihistamine, was discovered and then chlorpromazine (1951). This illustrates what is still so often the case, that useful drugs are commonly found accidentally.

Chlorpromazine has a large number of actions, but the mechanism of most of them is obscure. Practical therapeutics might be better served if they were distributed amongst three or four drugs instead of being concentrated in one. They include:

Central nervous system. The term *neuroleptic* was introduced to describe the characteristic emotional quietening, indifference and psychomotor slowing induced by chlorpromazine.

There is evidence that chlorpromazine acts in the hypothalamus and brain-stem reticular formation. In animals chlorpromazine quietens wild and angry monkeys and prevents the hyperthyroidism that ordinarily occurs in wild hares caught and exposed twice a day to barking dogs. It has a remarkable ability to control hyperactive and hypomanic states without seriously impairing consciousness, and it modifies abnormal behaviour in schizophrenic states. It is ineffective against depression unless this is accompanied by agitation and indeed may make it worse. Normal people often feel sleepy, apathetic and indifferent to the environment after taking chlorpromazine and it also induces some indifference to pain. In large doses chlorpromazine causes a Parkinsonian syndrome, but small doses can sometimes relieve Parkinsonian tremor. In moderate doses it controls the muscle spasm of tetanus, but very large doses may make it worse. This is probably an effect on the reticular formation where stimu-

lation of one area activates, and of another depresses, spinal reflexes. Chlorpromazine also reduces muscle spasticity due to other neurological lesions. Epilepsy may be precipitated in predisposed people, but the drug has been used with success in epileptics with schizophreniform illness.

Chlorpromazine is an anti-emetic effective against both drug and disease-induced vomiting, but ineffective against motion sickness.

The α-adrenoceptor blocking effect is moderately strong, and postural hypotension may occur. The peripheral vasodilatation induced by this action of chlorpromazine causes heat loss, and body temperature may fall, as with other long-acting vasodilators, especially if the patient is anæsthetised. Some central effect on the temperature regulating mechanism is probable. The use of the term "artificial hibernation" in connection with the use of chlorpromazine, with or without other drugs, is particularly inappropriate for there is no general slowing down of bodily processes; if anything the circulation is more, not less, active.

Potentiation of other drugs. Chlorpromazine potentiates all cerebral depressants including alcohol, analgesics, hypnotics, and anæsthetics, and curare. These effects can have clinical importance, but usually only if the drugs are being used in large doses.

Miscellaneous actions. Chlorpromazine has weak atropine-like, antihistamine, ganglion-blocking and quinidine-like actions (it can produce ECG changes). It is a local anæsthetic, but in solution it is very irritant.

Chlorpromazine is well *absorbed* from the alimentary tract and demonstrable effects of a single dose last about 8 hrs. However, therapeutic effect on behaviour may be delayed for as long as 4 weeks, benefit may last months after cessation, and metabolites may be excreted for months.

Chlorpromazine is probably chiefly *metabolised* in the liver.

Unwanted effects include drowsiness and lethargy, though the patient remains rousable, postural hypotension, dry mouth, and the Parkinsonian syndrome (which is amenable to anticholinergic antiparkinsonian drugs). In addition, curious dystonic reactions occur (limbs, face, tongue) and, particularly where there is organic brain damage, they may be permanent. The dystonia can mimic tetanus and misdiagnosis has resulted. Akathisia (an irresistable urge to move about) occurs. These are very frightening to the patient. Phenothiazines should not be used for minor conditions.

Blood disorders and rashes, sometimes photosensitive, occur, and with prolonged use there may be permanent pigmentation. Fits may occur and, rarely, lactorrhœa and lens opacities.

The most serious effect is obstructive jaundice, in which cellular damage is generally trivial, the principal impact being on the bile canaliculi which show cellular infiltration and biliary stasis. Jaundice most commonly occurs 2 to 4 weeks after starting therapy but relapse can occur at once on restarting it in a patient who has had chlorpromazine jaundice. This and its irregular occurrence suggest that it is an allergic reaction. Recovery is almost invariably complete within a few weeks, but permanent liver damage has been reported. Hepatic biopsy has revealed lesions in patients

taking chlorpromazine who are free from jaundice. The possibility of liver damage or blood disorder is sufficiently high to make casual use of chlorpromazine reprehensible. Great care is necessary if there is a history of alcoholism.

Chlorpromazine is used in mental disorders (see below), as an antiemetic, to potentiate narcotics and to aid the production of hypothermia. It is used in severe pain, both to potentiate other drugs and to induce indifference to pain by altering the emotional response. It may relieve the abdominal pain of porphyria, but use should be brief to avoid causing liver damage. It is worth trying in persistent pruritis. It can also be tried against intractable *hiccup*, as may a very wide variety of drugs including carbon dioxide, pethidine, methamphetamine, hyoscine, quinidine, orphenadrine, amitriptyline and metoclopramide, which indicates that the physiology of hiccough is not understood.

Dosage varies widely (see table). Starting doses may be 25 mg orally, i.m. or i.v. (not s.c. as it is irritant) 4 to 6-hrly; dosage may be increased every 3 to 4 days.

Other phenothiazines

There is a great variety available. Although most of those advocated in psychiatry represent attempts to improve on chlorpromazine, none has been shown definitely to be an all-round improvement. Their effects are similar to those of chlorpromazine although they differ in emphasis.

Dimethylaminopropyl side-chain. This group is relatively sedative. Promazine is less hepatotoxic and hypotensive than is chlorpromazine and so is safer in the old; but it is probably also less effective in schizophrenia. Other members are fluopromazine (Vespral), methotrimeprazine (Veractil).

Piperazine side-chain. This group is relatively stimulant and may be useful in apathetic and withdrawn patients. It is also less hepatotoxic than chlorpromazine but is more prone to cause serious central nervous system effects; the dystonic effect can be so severe as to mimic tetanus. Members

SOME PHENOTHIAZINE TRANQUILLISERS

Classification by side chain	Proprietary name and tablet size in mg.	Total oral daily dose in mg (2 to 4 doses)*
Dimethylaminopropyl		
chlorpromazine	Largactil (10, 25, 50, 100)	50–1500*
promazine	Sparine (25, 50, 100)	50–600*
Piperazine		
trifluoperazine	Stelazine (1, 5)	3–45*
perphenazine	Fentazin (2, 4, 8)	6–48*
Piperidine		
thioridazine	Melleril (10, 25)	60–600*

* Milder cases treated as out-patients generally receive dosage at the lower end of this range.

include fluphenazine (Moditen), prochlorperazine (Stemetil), perphenazine (Fentazin), trifluoperazine (Stelazine), thiopropazate (Dartalan).

Piperidine side-chain. This group has relatively strong atropine-like action. Thioridazine (Melleril) in high dosage can cause retinal damage.

Choice of phenothiazine tranquilliser

If chlorpromazine proves unsatisfactory, then promazine or trifluoperazine may be tried, but the choice is not critical. The absence of adequate data on which to judge these drugs is partly due to the fact that new drugs are appearing faster than they are being properly compared.

Long-acting neuroleptics

Since about 40% of schizophrenics do not take tablets prescribed and even in hospital 20% of patients may not actually swallow the tablet given to them, it is useful to have neuroleptics that can be given i.m. at long intervals (1 to 5 weeks) for maintenance therapy.

Extrapyramidal syndromes are common and can be controlled by anticholinergic antiparkinsonian drugs (e.g. benzhexol, orphenadrine) which are often given routinely. Severe depression can occur.

Preparations include the decanoate of fluphenazine (Modecate) and the enanthate (Moditen Enanthate); flupenthixol decanoate (Depixol).

Butyrophenones, e.g. haloperidol (Serenace), trifluperidol (Triperidol), can control acute mania and may be useful in severe schizophrenia. Extrapyramidal syndromes commonly occur. They are worth trying in severe dyskinesias. Benperidol (Anquil) may be considered for severe socially disabling sexual behaviour.

Miscellaneous

Thioxanthenes, e.g. chlorprothixene (Taractan) are similar pharmacologically and therapeutically to the phenothiazines.

Rauwolfia alkaloids (reserpine, etc.). The alkaloids of rauwolfia have two principal effects, hypotensive (central and peripheral effect) and tranquillising (central). As tranquillisers they are inferior to the phenothiazines and may cause severe depression.

Tetrabenazine (Nitoman) is a synthetic drug the actions of which resemble reserpine. It is worth trying in severe dyskinesias.

Pimozide (Orap) is an alternative neuroleptic.

Anxiolytic Sedatives

Benzodiazepines are sedatives with a marked taming effect in vicious animals; they suppress induced aggression. In contrast to barbiturates which are general CNS depressants, benzodiazepines are relatively selective for the limbic system (hippocampus, amygdala, hypothalamus) which is concerned with control of emotion. They also have anticonvulsant and central muscle-relaxant effects. They do not induce hepatic microsomal enzymes to an important extent and so are drugs of choice where this needs to be avoided, e.g. during anticoagulant therapy.

Chlordiazepoxide (Librium) (5, 10, 25 mg) has a plasma half-life of about 24 hrs. It is used for anxiety in doses of about 10 mg 8-hrly.

Diazepam (Valium) (2, 5, 10 mg) is similar with a half-life of about 8 hrs. It is used orally in anxiety (6 to 40 mg daily in about 3 doses) and as a centrally acting muscle relaxant. Given i.v. (or i.m., painfully) it is useful in status epilepticus and for minor surgical procedures (which see).

Nitrazepam (Mogadon) (5 mg) has a half-life of about 24 hrs. It is used chiefly as a hypnotic (see index). *Medazepam*, *oxazepam*, *flurazepam*, *clorazepate* are alternatives.

Unwanted effects are usually trivial and are extensions of the therapeutic sedative effects; hangover may be prolonged.

Overdose. Even with severe overdose patients remain rousable. For this reason, wherever there is a possibility of self-poisoning the benzodiazepines are the sedatives and hypnotics of choice. But respiratory depression can occur.

Meprobamate (400 mg) was introduced as a tranquilliser following research into substances derived from mephenesin. Under the name Miltown (after the town in the U.S.A. where it was made) it became, in 1957, the most prescribed drug in that country. Since then evidence has accumulated to suggest that as a sedative or hypnotic it does not differ from the barbiturates in any clinically important respect. It may sometimes help Parkinsonian tremor and myoclonic epilepsy. It can cause rashes and other allergic effects. The oral dose is 400 mg as a hypnotic or 8-hrly as a sedative.

Antidepressants

Tricyclic antidepressants or dibenzazepines, e.g. imipramine (Tofranil) are structurally related to the phenothiazines and were synthesised during a search for new tranquillisers. They prevent the active reuptake into cellular stores of released noradrenaline. This action probably contributes to their potentiating effect on injected adrenaline and noradrenaline (negligible with isoprenaline) and to their antagonism of antihypertensives. They also have anticholinergic and anti-5HT effects.

Imipramine (10, 25 mg) is well absorbed from the gut and is largely metabolised in the liver. It is converted into an active metabolite desmethylimipramine (which is also available as a drug, desipramine, Pertofran). Neuroleptics inhibit metabolism of tricyclics but this does not lead to noticeable clinical effects, perhaps due to the sedative action of the neuroleptic.

Unwanted effects include those characteristic of its anticholinergic action, dry mouth, etc., and there is a risk to glaucomatous and prostatic patients. There also occur postural hypotension, tremors, hallucinations, excitement and jaundice, and there may be some hazard in using tricyclics in patients liable to cardiac arrhythmia. *Poisoning* causes cardiac arrhyth-

mias, hypertension and convulsions which are treated by antiarrhythmic drugs, α-adrenoceptor block and anticonvulsants (e.g. diazepam), respectively.

Abuse is not a problem with tricyclics since their immediate effects are not noticeably pleasant, but some dependence does occur and sudden withdrawal may be followed by unpleasantly increased dreaming.

Interactions. Catecholamines and other sympathomimetics are potentiated. This is important and even the amounts of adrenaline or noradrenaline in dental local anæsthetics may produce a serious rise in blood pressure. Severe toxicity, resembling atropine overdose, can occur if full doses are combined with an MAO inhibitor. Such combination is sometimes used clinically, but great caution is needed.

Tricyclics antagonise adrenergic neurone blocking antihypertensives by preventing their uptake into the adrenergic nerve ending which is their site of action.

Choice of tricyclic. There are clinically important differences in the relative sedative and stimulant effects of tricyclics and these may determine choice in treating depressed patients: amitriptyline and trimipramine are relatively sedative, but desipramine and protriptyline are relatively stimulant and so less suitable for agitated depression.

It is reasonable to use impramine as first choice for depression, substituting amitriptyline where sedative effect is also wanted.

Clinical use. Clinical response of *depression* occurs in about 10 days. If a patient has not responded to proper dosage in 3 weeks it may be assumed he will not do so at all. See also under *choice of drugs*.

Nocturnal enuresis may be relieved, but relapse usually occurs on withdrawal of the drug. Its use may be best confined to special occasions, e.g. when the child is away from home. The dose is as for depression and the onset of effect is delayed for about 2 days.

Pain. An antidepressant is sometimes useful in addition to analgesics in chronic pain, even in the absence of recognisable depression.

Dose of imipramine orally 25 mg, 8-hrly, increasing gradually weekly to 75 mg.

Monoamine oxidase (MAO) inhibitors

In 1951 iproniazid (related to isoniazid) was tested for clinical antituberculosis activity and it was noticed that it stimulated the central nervous system. Early trials in psychiatry proved negative, but in 1958 a favourable report of its effect in chronically regressed and withdrawn patients precipitated a flood of therapeutic trials that has only abated recently. In the three years 1959–62 over 1,300 reports were published on this group of drugs.

Iproniazid inhibits monoamine oxidase, an enzyme present in the central nervous system, in adrenergic nerve endings, in the liver and gut wall, and which is concerned in the breakdown of serotonin (5-hydroxytryptamine, 5-HT) and catecholamines (adrenaline, noradrenaline). Many

compounds with this effect and less toxicity have since been made; the chemical structure of some resembles that of amphetamine.

Actions. Drugs of this group have been found to have, to varying degrees, the following actions:

1. MAO inhibition (other enzymes too)
2. Sympathomimetic effect (some only, see below)
3. Sympathetic blocking effect (one MAO inhibitor, pargyline, is used as an antihypertensive).

Their actions and interactions are as complicated as is to be expected from these facts.

When monoamine oxidase is inhibited, there is an increase of 5-HT and catecholamines in the central nervous system. In man, chemicals which inhibit the enzyme have powerful mental effects ranging from feelings of well-being and increased energy, to frank psychosis. Imipramine has similar effects. It may be, that MAO inhibitors allow the build-up of catecholamines in the brain by preventing destruction and that imipramine does the same by blocking uptake into tissue stores.

There is also an increase in noradrenaline stores in adrenergic nerve endings. It is evident that there will be *potentiation of sympathomimetics* that act indirectly (i.e. by releasing stored noradrenaline) and of sympathomimetics that are substrates for MAO (present in the gut wall and liver). But important potentiation of administered adrenaline, noradrenaline and isoprenaline is not to be expected since these substances are chiefly destroyed by catechol-O-methyltransferase in the blood, and in any case MAO is not the chief factor in terminating effects of these substances at receptors. This is done by diffusion away from the area and by tissue uptake. In this respect adrenergic endings differ from cholinergic endings.

Detailed discussion will not be pursued here since the use of MAO inhibitors is declining but it is plain, both from experimental pharmacological studies and from fatal accidents during therapy, that sympathomimetics can be highly dangerous to patients taking MAO inhibitors.

Some MAO inhibitors (phenelzine, tranylcypromine) also have direct sympathomimetic activity similar to that of amphetamine, i.e. releasing stored noradrenaline, unrelated to enzyme inhibition. Thus, hypertensive attacks are to be expected; when they occur, they resemble the hypertensive attacks of phæochromocytoma.

MAO inhibitors can, by themselves, also cause hypotension and it is uncertain whether this is related to MAO inhibition. There is probably a direct blocking action on the peripheral sympathetic system, partly on ganglia and partly due to reduced release of the transmitter (noradrenaline) at postganglionic endings. The hypertensive interactions mentioned above will still take place in the presence of hypotensive effect, so that a patient might suffer from postural hypotension, eat a meal of cheese (see below) and die in a hypertensive crisis.

Symptoms of hypertensive crises are severe throbbing headache with slow palpitation. If headache occurs without hypertension it may be due to histamine release.

Treatment of hypertensive crisis. The mechanism is excessive stimulation of α-adrenoceptors as in a phæochromocytoma. The rational and effective treatment is an α-adrenoceptor blocker (phentolamine, 5mg, i.v.). Should excessive tachycardia occur after the phentolamine, a β-adrenoceptor blocker may be added. Other kinds of antihypertensive are irrational and some can even potentiate sympathomimetics.

Unwanted effects also include irritability, apathy, sadness, insomnia, fatigue, ataxis, tremulousness, restlessness, impotence, difficult micturition, sweating, hyperpyrexia, gastro-intestinal disturbances, leucopenia, rashes, convulsions, jaundice. Optic nerve damage occurs with some.

Interactions with sympathomimetics are discussed above. Patients must be warned not to indulge in *self-medication* of any kind, for many trivial remedies sold direct to the public, e.g. for coughs and colds, contain sympathomimetics. Unfortunately some *foods* contain substantial amounts of sympathomimetics, largely tyramine, which acts by releasing tissue-stored noradrenaline. These substances are normally inactivated by MAO in the intestine wall and liver, where large amounts of enzyme occur. Patients are therefore deprived of this protection, so that, as well as having larger stores in nerve endings (waiting to be released), they absorb more of the sympathomimetics.

The first food interaction with MAO inhibitors was reported in 1963 and concerned cheese. It might be thought that, as cheese has been known to contain tyramine for at least 60 years, the danger might have been predicted, but it was not, and the association of hypertensive headache with evening meals of cheese was made by clinical acumen.

Responses are variable, but *any food subjected to bacterial decomposition* during preparation may contain pressor amines due to decarboxylation of aminoacids.

The following foods either can produce, or may be expected to be capable of producing, dangerous hypertensive effects: cheese, especially if well matured (the amines are produced from the aminoacids of casein by bacteria, e.g. tyramine from tyrosine) (*18*); yogurt; some pickled herrings; broad beans (contain dopa, a precursor of adrenaline); yeast extracts (Marmite); meat extracts (Bovril); wines, beers. This list may be incomplete. It is plain that patients must receive detailed instructions about their diet. They may cautiously try some of the above items to discover whether they are safe for themselves, and, if they are, they should not assume that the same food from different sources is harmless.

Interactions with drugs other than sympathomimetics. The following substances that are not metabolised by MAO may be potentiated (*20*):

Other antidepressants: excitement and hyperpyrexia with tricyclics.

Narcotic analgesics: if *pethidine* is given to a patient taking an MAO inhibitor there is liable to be respiratory depression, restlessness, even coma, and hypotension. This is probably due to inhibition of the hepatic enzyme that demethylates pethidine. Interaction with other opiates is less certain.

Central nervous system depressants, barbiturates, tranquillisers, antihistamines, alcohol (probably), antiparkinsonian drugs, but not inhalation anæsthetics.

Antihypertensives (but hypertension and excitement may occur with methyldopa).

Insulin and tolbutamide.

Bee venom (perhaps).

The mechanisms of many are obscure, perhaps they are due to inhibition of other drug-destroying enzymes. Reactions can be very severe and even fatal.

Use of MAO inhibitors. It is plain that patients taking these drugs are at risk in a number of ways and that, in the absence of specific indications for them, as well as of any evidence that they are superior to imipramine-like drugs, they are not drugs of first choice, though they may be found to suit some patients best. They are more effective in reactive than in endogenous depression. So numerous are the necessary precautions, and so important is it that it be known, in the event of accident, that the patient is taking a MAO inhibitor, that patients should be supplied with a printed card with appropriate warnings.

The *therapeutic effects* of MAO inhibitors come on in from a day or two, to 2 weeks, and may persist for as long as 2 to 3 weeks after stopping treatment, both because the drugs are slowly excreted and because they inhibit MAO irreversibly so that enzyme activity can only be restored by synthesis of fresh enzyme.

Anxiety and agitation may be made worse and depressed patients may even become hypomanic. Chlorpromazine can reduce this, given cautiously.

Other antidepressant drugs should not generally be commenced until 1 to 2 weeks after stopping the MAO inhibitor, because of the slow resynthesis of MAO.

This group of drugs includes:

Hydrazine group: phenelzine (Nardil); isocarboxazid (Marplan); mebanazine (Actomol); iproniazid (Marsilid); nialamide (Niamid). Jaundice is more common than with non-hydrazines.

Non-hydrazine group: tranylcypromine (Parnate); pargyline (Eutonyl).

Lithium

Lithium first achieved prominence in medicine in the 1940's when it was used as a salt substitute for patients needing a low sodium diet (cardiac

failure, hypertension). Some patients died of lithium poisoning. Lithium, like bromide, is treated by the body somewhat like sodium, i.e. it is retained if sodium intake is low and is excreted (though slowly) along with sodium if sodium intake is high. The half-life of a single dose is about 24 hrs with normal sodium intake.

Lithium was observed to be sedative to animals and was tried in clinical mania, which may be controlled in 5 to 10 days. It is also effective as a prophylactic to attenuate both the manic and the depressive phases of manic-depressive psychosis and against recurrent depression. Schizophrenics do not respond.

Because of its pharmacokinetics in relation to sodium, the fact that the therapeutic range of plasma concentration is narrow and because lithium is toxic, plasma concentrations must be monitored during therapy. This also provides a check on whether the patient is taking the drug; in one study 10% of patients had no lithium in their blood.

Effects of too high a plasma lithium concentration include: anorexia, vomiting, diarrhœa, dry mouth, muscle weakness, ataxia, coma, hypotension; with prolonged use goitre may occur, and diabetes insipidus. Paradoxically, diuretics may raise plasma lithium concentration.

Psychostimulants

Amphetamines

Amphetamine (racemic) and dexamphetamine (dextro-: the lævo-form is relatively inactive) are the principal drugs of this group used as psychostimulants; their use in depression is controversial. Their mode of action on the brain is unknown. Their *peripheral actions* are similar to those of ephedrine (which see). Amphetamine will be described, and its allies only in the ways in which they differ. As with all drugs acting on the central nervous system the psychological effects vary with mood, personality and environment as well as with dose. The difference in response between children and adults is well illustrated by amphetamine and ephedrine, for in *children* these drugs are generally sedative, not excitant. The following description can thus only be approximate.

The subject becomes both mentally and physically more active and fatigue is postponed. He may be more confident and show more initiative. He is better satisfied with a performance which has, in fact, deteriorated in accuracy as well as being more speedily accomplished. On the other hand there may be anxiety and a feeling of nervous and physical tension, especially with large doses, and the subject may show tremors and confusion, and feel dizzy. Time seems to pass with greater rapidity. The sympathomimetic effect of the heart, causing palpitations, may intensify the patient's discomfort or alarm.

Amphetamine increases peripheral oxygen consumption, and this, together with vasoconstriction and restlessness leads to hyperpyrexia in overdose.

Acute poisoning is manifested by excitement and sympathomimetic effects; convulsions may occur, also, in acute or chronic overuse, a state

resembling hyperactive paranoid schizophrenia with hallucinations. Hyperpyrexia occurs (see above) especially if the subject exercises, with cardiac arrhythmias, vascular collapse and death.* Athletes should not take amphetamine. Treatment may require use of α and β adrenoceptor blocking agents and sedation. As in any case of convulsant drug poisoning environmental stimuli should be reduced to a minimum. Excretion is greater in an acid urine. The $t_{\frac{1}{2}}$ is about 12 hours.

It is of interest that in mice the lethal dose of amphetamine is higher if the mice are caged separately than if they are caged in groups, probably due to a higher environmental temperature in the latter case.

Dependence on amphetamine and similar sympathomimetics occurs; it is chiefly emotional, but there is an abstinence syndrome, suggesting physical dependence; tolerance occurs.

Mild dependence on prescribed amphetamines has long been common, particularly amongst people with unstable personalities, depressives, and tired, lonely housewives. In the 1960's adolescents began to turn to amphetamines for occasional use to keep awake to have "fun" and then as an aid to the challenges normal to that period of life. Unfortunately, drugs provide only a temporary solution of avoidance and postponement of these challenges and so retard rather than assist the progress to maturity.

As well as oral use, i.v. administration (with the pleasurable "flush" as with opiates) is employed. Severe dependence induces behaviour disorders, hallucinations and even florid psychosis. Withdrawal is accompanied by lethargy, sleep, EEG changes, desire for food and sometimes severe depression which leads to a desire to resume the drug.

Appetite suppression. It was noticed casually in 1937 that patients receiving amphetamine tended to lose weight. This was investigated in animals and man and found to be due to a reduction in voluntary food intake (*48*). Dogs would starve in the presence of food when given amphetamine, although they still showed interest in being fed and jealousy of the dog being fed before them. It was only when the food was actually placed in their cage that enthusiasm abated. Tolerance to the anorexiant effect occurs.

Amphetamine is absorbed from the gut and is largely **excreted** unchanged in the urine, and this is substantially greater if the urine is acid. Urinary acidification should be useful in treatment of acute poisoning and to obtain evidence in cases of suspected dependence.

Amphetamine has had multifarious **uses,** but its potential for abuse is such that it should now only be used where essential, and this is rare:

1. *Narcolepsy:* patients pass directly into REM sleep (which see); amphetamine delays onset of REM sleep.
2. In some *hyperactive children* with abnormal EEG.

* *Brit. med. J.* (1960). **2,** 590, 844.
Arch. intern. Med. (1963). **112,** 822.

3. As an *analeptic* in poisoning by hypnotics if facilities for controlled respiration are not available.
4. *Miscellaneous:* in some cases of Parkinsonism and epilepsy (curiously, amphetamine has some anticonvulsant effect in electro-shock in animals); against fatigue (seldom justified); appetite suppression (alternatives are preferable).

Dexamphetamine is similar to amphetamine.

Methylamphetamine (Methedrine) is similar to amphetamine but CNS effects are relatively greater.

Phenmetrazine (Preludin) is similar to amphetamine and is chiefly used to reduce appetite. Dependence occurs. **Phentermine** (Duromine) is similar as is diethylpropion (Tenuate) and there are others. There is, of course, a lot more to the treatment of obesity than merely giving drugs (*47*).

Methylphenidate (Ritalin) (10 mg) has effects similar to amphetamine. It is sometimes useful in Parkinsonism. The oral dose is 20 to 60 mg total/day in divided doses.

Pemoline (Kethamed) and meclofenoxate (Lucidril) see under *intellectual function.*

Barbiturate–amphetamine combinations

For many years clinicians had thought such mixtures useful in depression and pharmacologists vaguely disapproved of what they considered a rather naive approach. Eventually the mixture was investigated scientifically, and it is now known that such combinations can produce effects that cannot be got with either drug alone. For instance, the mixtures enhance the spontaneous exploratory behaviour of rats when placed in new environments that ordinarily inhibit such activity. It is possible that this is because amphetamine increases activity, and the barbiturate reduces fear (*24*).

In normal man the mixtures induce elation and sociability, and the exercise of simple skills is impaired less than with the barbiturate alone.

The therapeutic values of these mixtures is questionable, but their potential for abuse is not and they should only be prescribed after this risk has been carefully considered.

Tablets of one such combination, because of their distinctive triangular shape and colour, became known as "purple hearts", and an extensive illicit trade developed, particularly amongst adolescents. In 1964 one manufacturer changed the tablet to an inconspicuous round blue tablet in an attempt to discourage misuse.

A typical combination contains dexamphetamine 5 mg plus amylobarbitone 30 mg (Drinamyl); there are others.

Appetite suppression and obesity

It is convenient to deal with this here. Sympathomimetics with pronounced CNS effects suppress appetite (see above) but the effect is

transient (2 or 3 weeks) and dependence occurs. They should only be used briefly, if at all, as an aid to dietary re-education.

Fenfluramine (Ponderax) (20 mg) is structurally related to amphetamine, but its effects differ. It is sedative rather than stimulant to the CNS, though there may be some elevation of mood at the outset of therapy. For immediate "pep" effect drug abusers prefer amphetamine, but some physical dependence to fenfluramine does occur and sudden withdrawal is followed by depression, especially marked after 4 days; it is best to withdraw the drug gradually.

Fenfluramine also has some peripheral effects on carbohydrate and lipid metabolism and it is uncertain whether these promote weight reduction.

Fenfluramine does not antagonise hypotensive therapy as do the amphetamines, indeed there may be some potentiation.

Unwanted effects are common and include sleepiness, depression, diarrhœa and impotence. Tolerance probably occurs.

Heavy overdose can cause CNS stimulation and cardiac arrhythmias.

Fenfluramine is probably the drug of choice for obesity (where a drug is needed), and certainly so in hypertensives. It may be given for 3 months and slowly withdrawn. It should not be necessary to give drug therapy indefinitely for obesity, and indeed it is ineffective.

The oral dose of fenfluramine is: for mild obesity 20 mg twice daily; for severe cases increase this gradually over 4 weeks to 120 mg total/day in three doses.

Biguanide antidiabetics reduce intestinal carbohydrate absorption and may induce weight loss without reducing blood glucose concentration. But their use is probably best confined to diabetics.

Bulk preparations, e.g. methylcellulose, are used to fill the stomach with non-nutrient material and induce a feeling of satiety. Their use is probably based on a wrong physiological concept. Animals eat for calories, not bulk; it is possible to feel hungry in the absence of a stomach.

Appetite stimulation sometimes occurs with cyproheptadine (Periactin) and with benzodiazepine anxiolytic sedatives (e.g. diazepam, chlordiazepoxide). Insulin increases appetite by lowering blood dextrose concentration. There is little, if anything, to be gained by using drugs to stimulate appetite, though they may be tried as adjuvants in anorexia nervosa.

Cannabis may induce hunger.

THE XANTHINES

(Caffeine, Theophylline, Theobromine)

These three compounds are obtained from plants. They are qualitatively similar but differ markedly in potency. Tea contains caffeine and theophylline. Coffee contains caffeine, and cocoa contains caffeine and theobromine. The cola nut ("cola" drinks) contains caffeine. Theo-

bromine is weak and is of no clinical importance. Theophylline is generally used in the form of *aminophylline*, a combination with ethylenediamine.

The effects of *caffeine* and *theophylline* are largely due to their capacity to increase cyclic AMP (by decreasing breakdown) in muscle and CNS; catecholamines increase formation of cyclic AMP and the two groups potentiate each other.

Central nervous system stimulation. Caffeine is more powerful than theophylline, but both drugs stimulate mental activity; thought is more rapid and fatigue is removed or its onset delayed. The effects on mental and physical performance vary according to the state and personality of the subject. Reaction-time is decreased. Performance that is inferior because of excessive anxiety may become worse.

The effects of caffeine and amphetamine on performance and mood have been compared (59).

There is no doubt that both amphetamine and caffeine can improve **physical performance** both in tasks requiring more physical effort than skill (athletics) and in tasks requiring more skill than physical effort (monitoring instruments and taking corrective action in a mock aeroplane cockpit). These tasks are affected by both physical ability and mental attitude. It is uncertain whether the improvement consists only of restoring to normal performance that is impaired by fatigue or boredom, or whether the drugs can also enable the subject to improve on his normal maximum performance. The drugs may produce their effects by altering both physical capacity and mental attitude. There are various differences between them, perhaps the most obvious being their effect on hand steadiness; this is decreased by caffeine and increased by amphetamine. Large doses of amphetamine before athletic effort can be dangerous.

There is insufficient information on the effects on **learning** to be able to give any useful advice to students preparing for examinations. But **intellectual performance** may be improved where it has been reduced by fatigue or boredom.

Effects on **mood** vary greatly amongst individuals and according to the environment and the task in hand. In general, caffeine and amphetamine induce feelings of alertness and well-being, euphoria or exhilaration. Onset of boredom, fatigue, inattentiveness and sleepiness is postponed. Overdose can cause anxiety, tension and tremors and will certainly reduce performance. The regular, frequent use of caffeine-containing drinks to obtain these effects is part of normal social life; ill-effects are rare and seldom serious when they occur (see below). However, the use of amphetamine in the way that caffeine is generally used carries the danger of serious dependence and, eventually, of psychotic states.

That the effects of caffeine are generally desired is shown by the remarkable popularity of caffeine-containing drinks throughout the world. Habitual tea and coffee drinkers are seldom willing to recognise that they have an emotional drug dependence, however.

Excessive prolonged consumption of caffeine causes anxiety, restless-

ness, tremors, insomnia, headache and confusion. The existence of a physical abstinence syndrome is doubtful. Both caffeine and theophylline are effective respiratory stimulants and will abolish Cheyne-Stokes respiration. In huge doses they cause convulsions.

Skeletal muscle. Metabolism is increased, and this may play a part in the enhanced athletic performance mentioned above.

Cardio-vascular system. Both drugs directly stimulate the myocardium and cause increased cardiac output, tachycardia and sometimes ectopic beats and palpitations. This effect occurs almost at once after i.v. injection and lasts half an hour. Theophylline effectively relieves acute left ventricular failure. There is peripheral vasodilatation due to a direct action of the drugs on the blood vessels, but stimulation of the vasomotor centre tends to counter this. Changes in the blood pressure are therefore somewhat unpredictable. The cerebral circulation responds differently; the vessels constrict, with consequent reduction of blood flow. Increased coronary artery blood flow may occur. The utility of these drugs in angina pectoris is still debatable despite the fact that they were first advocated in 1895. Slow intravenous injection of caffeine or theophylline is essential because they are liable to cause an initial brisk hypotension, the cause of which is uncertain; sudden death can occur.

Smooth muscle (other than vascular muscle which is discussed above) is relaxed. The only important clinical use for this action is in resistant cases of asthma (theophylline). Therapeutic effect is unpredictable but can be excellent.

Kidney. Diuresis occurs in normals chiefly due to reduced tubular reabsorption. The drugs are not used for this purpose as superior agents are available.

Miscellaneous effects. Gastric secretion is increased and the basal metabolic rate may increase slightly (see skeletal muscle, above).

Slight tolerance occurs. Caffeine and theophylline are readily absorbed from the alimentary tract including the rectum. They are metabolised in the body.

Unwanted effects are described above.

Preparations and Uses of Caffeine and Theophylline

Caffeine alone is not used in therapeutics. It is included in analgesic tablets, where it is thought to potentiate non-narcotic analgesics, and it is used in migraine (enhances ergotamine absorption). Theophylline is valuable clinically.

The most generally useful preparation is **aminophylline** (100 mg) which is a salt of theophylline with ethylenediamine. Aminophylline is irritant and because of this is often given i.v. (5 to 6 mg/kg over 15 to 30 min) (see *status asthmaticus*), although sudden death may occur if it is given fast: a special formulation is available for i.m. use. Its plasma half-life is 180 to 600 min (the longer time occurs with high plasma concentrations). Patients are liable to vomit if given more than 300 mg orally three times

a day. Aminophylline suppositories B.P.C. are more effective than tablets, but can cause proctitis, especially if used more than twice a day. When given i.v. some of the observed respiratory stimulation is due to the ethylenediamine.

Attempts to make non-irritant orally effective preparations of theophylline have resulted in **choline theophyllinate** (oxtriphylline, Choledyl) (200 mg), which is reasonably effective. The dose is 100 to 400 mg orally 6-hrly. It is used to relieve bronchospasm, and with dubious effect in angina pectoris. Numerous theophylline variants are available, e.g. bamifylline (Trentadil), diprophylline (Silbelphylline), proxyphylline (Brontyl).

The principal uses of aminophylline are:

In paroxysmal nocturnal dyspnœa it is given i.v. for its immediate effect on the heart. Its effect is brief but is often enough to terminate an attack. Morphine or pethidine may be given too, to prevent excessive respiratory stimulation.

When diuretics fail in heart failure aminophylline may, chiefly by improving renal blood flow, enable a diuresis to be established; it is given i.v. 2 hrs after the diuretic.

When digoxin given i.v. fails to improve severe heart failure in 1 hr aminophylline may be given i.v. for its cardiac effect, which is synergic with digoxin. But a potent diuretic may be preferred.

In asthma aminophylline is often used when sympathomimetic drugs fail.

In the dying patient aminophylline i.v. may cause brief and unrepeatable, but socially useful, recovery of consciousness and coherence.

In angina pectoris the value of aminophylline or its allies is doubtful.

Xanthine-containing Drinks

Cocoa never hurt anybody, probably because nobody has ever drunk enough of it, but tea and coffee in excess can make people tense and anxious as well as cause exacerbation of peptic ulcer. Small children are not usually given tea and coffee because they are less tolerant of the CNS stimulant effect, but cola drinks irrationally escape this prohibition. At different times coffee has incurred disapproval of the Mohammedan religion and of at least one Christian sect.

There is no evidence that these xanthines, although related chemically to uric acid, are harmful in gout. They are not converted to uric acid in the body. It is possible, on theoretical grounds, to make an imposing list of diseases which may be made worse by caffeine-containing drinks, but there is no conclusive evidence to warrant any general prohibitions.

Decaffeinated coffee, from which the caffeine has been extracted with trichlotoethylene, is available for those who are kept awake by after-dinner coffee, but unfortunately it is expensive and extraction is only partial. There is great individual variation in this effect of coffee both between individuals and sometimes in the same individual at different times of life.

Choice of Drugs in Mental Disorders

In **psychotic states** (severe manic depressive illness and schizophrenia) both neuroleptics and antidepressants (tricyclic) are given in rapidly increasing doses at first, with longer intervals between increases later.

Withdrawal should be gradual to avoid sudden and dangerous relapse. Duration of treatment is impossible to predict; no attempt at withdrawal should be made until 6 to 8 weeks after apparent recovery, and permanent treatment may be necessary, in which case a long-acting i.m. formulation may be preferred.

Severe intercurrent illness may reduce drug requirement.

In general, as with all potentially toxic drugs, the lowest effective doses should be used, especially in patients living at home. Resistant cases may be admitted to hospital to receive high dosage.

Manic states. An injection of morphine and hyoscine is still valuable in controlling acute mania; a neuroleptic is an alternative and is also suitable for continued control, e.g. chlorpromazine in rapidly increasing doses to 600–800 mg/day, sometimes with haloperidol. If the patient is in a single room, accompanied by a suitable nurse, smaller doses of depressant drugs will be needed, for excitement tends to subside sooner under these circumstances than it does in the presence of other patients, or if the patient is left entirely alone. Some maniacal patients are not quietened even by large doses of depressants, until they suddenly collapse with respiratory depression. Lithium can be used in milder cases where there is no haste.

The schizophrenias. Neuroleptics are the most important drugs and they can greatly reduce aggression, hyperactivity, delusions and hallucinations. It is sometimes necessary to use another drug, e.g. an antidepressant (tricyclic), or ECT.

Depression. The place of drugs in treatment remains controversial. Most cases eventually recover spontaneously and most drugs take a week or two to act, so that careful controls are needed if credit for recovery is to be correctly allotted. Antidepressants can precipitate epilepsy in those with a family history of epilepsy, who have had previous ECT, or organic brain damage. Treatment should generally last about 6 mths.

The following notes attempt to summarise some of the more widely accepted opinions held at present. They give no more than general guidance.

Reactive (exogenous) depression: see under psychoneuroses below.

Endogenous depression: the tricyclic group are the first choice, but ECT may be needed if depression is severe or if a quick effect is needed. A combination of imipramine and ECT may be ideal in severe cases, and the drug may reduce the number of shocks needed.

It is important not to withhold ECT where imipramine fails. In one trial (*21*) half the patients who failed to respond to imipramine in 4 weeks benefited from ECT. At the first sign of overdose of antidepressant, the drug should be withdrawn and chlorpromazine given.

Prophylaxis: in cases with less than three recurrences, six months treatment with a tricyclic may be sufficient, but with more relapses, long-term lithium may be preferable.

Sympathomimetics, such as amphetamine, can make endogenous depression worse by increasing tension and restlessness.

Senile and arteriosclerotic conditions in which patients are un-co-operative and disturbed are sometimes helped by promazine or one of the anxiolytic sedatives. These patients are commonly intolerant of drugs; nocturnal delirium may be made worse by barbiturates and helped by caffeine taken as strong tea. No doubt the familiar tea-ritual also plays its part in helping the British patient to keep a normal relationship with the environment.

Toxic confusional states, e.g. delirium tremens, post-operative confusion, may be benefited by diazepam or chlorpromazine. Paraldehyde is also often satisfactory. Correction of any accessible biochemical, toxic or anoxic abnormality is of the first importance.

Psychoneuroses. In general drugs are less useful than in psychotic states, as the environment is relatively more important. Drugs are best confined to short periods, to help a patient over a bad phase of his illness. Prolonged drug therapy is seldom as rewarding as in psychoses. It must be admitted that this view is not unanimously held, some physicians believing that drug therapy is of great value in the routine treatment of psychoneuroses. Only the collection of scientific data in carefully designed and conducted therapeutic experiments can resolve this difference.

Reactive depression is best treated by a phenothiazine, an anxiolytic sedative or a tricyclic antidepressant. A MAO inhibitor may be used if these fail.

For **anxiety and tension** a benzodiazepine or other anxiolytic sedative may be used. Neuroleptics are best avoided in milder cases. Alcohol is, of course, highly effective, as the many neurotics who have become addicted testify. *Obsessional* and *hysterical* states are helped little, if at all, by drugs, but anxiolytic sedatives and antidepressants may be tried.

Severe chronic phobic anxiety that has resisted other treatment sometimes responds to imipramine or MAOI despite the absence of depression.

Drugs may also be used to remove peripheral effects of anxiety or tension that add to it by causing distress, e.g. a centrally acting muscle relaxant for excessive voluntary muscle tone or a β-adrenoceptor blocker for tachycardia. Relief of anxiety may occur in the absence of complaint of these effects.

Aggressive psychopaths are sometimes improved by œstrogens; the aggression need not necessarily take a sexual form to be benefited by œstrogens.

Aids to psychotherapy. Apart from the above uses, i.v. drugs are occasionally given for *narcoanalysis* or *abreaction* and *psychodysleptics* are experimental.

Anorexia nervosa: chlorpromazine is useful, and cyproheptadine (Periactin) may be tried as an appetite stimulant.

Narcolepsy. Amphetamine or dexamphetamine should be tried first; large doses may be needed. Methylphenidate (Ritalin) sometimes helps.

Naturally, if the above conditions are worsened by *insomnia* then hypnotics may help, without themselves acting on the main symptom. The early waking of depressed patients may be helped by tricyclic antidepressants.

Behaviour control. The fact that drugs can be used to quell inconvenient behaviour of mental defectives, the demented or psychotics and as a cheap substitute for skilled staff, is a matter for concern. Similar use on persons deemed by authority to be social or political deviants is also something to be feared. Control of socially unacceptable sexual behaviour by a butyrophenone (benperidol) also presents ethical problems.

The foregoing account of the use of drugs in mental disease is so absurdly inadequate in relation to the dominating importance of the subject that it is worth pointing out that knowledge is in its infancy. In relation to drug therapy, virtually nothing is known about the causes of mental disease or about how many drugs may work to relieve symptoms. In addition, there is a dearth of well-designed therapeutic trials such as are essential to determine what drugs can do. It would have been possible to have expanded this chapter with a complicated disquisition on psychopharmacology, but of the immense body of facts, little is of practical clinical relevance at present.

Suicide and Drugs

It is not uncommon to have to prescribe sedative drugs for potentially suicidal patients living at home. In such cases it is usual to prescribe minimal doses for short periods and, when the danger seems serious, to hand over the supply of drugs to a responsible person rather than to the patient.

Benzodiazepines are the sedatives and hypnotics of choice in such patients as heavy overdose is most unlikely to kill the patient.

Intellectual Function and Drugs

There are some clinical reports that meclofenaxate (Lucidril) can improve senile intellectual function, and that pemoline (Kethamed) may improve senile memory. Both are psychostimulants. Similar claims have been made for various vasodilators: cyclandelate (Cyclospasmol), naftidrofuryl (Praxilene). All are questionable, though recent work suggests that pessimism need not be as complete as hitherto.

Learning capacity in certain experimental situations can be both impaired and enhanced by drugs.

No drug has yet been shown reliably, usefully and over substantial periods to restore impaired, or to enhance normal intellectual functions.

PSYCHODYSLEPTICS or HALLUCINOGENS (see also ch. 13)

These substances produce mental changes which resemble those of some psychotic states. They are chiefly used by seekers after experience.

But psychiatrists also use these drugs in supervised therapeutic sessions to encourage the release and reliving of unconscious material in the hope that, assisted by appropriate psychotherapy, the patient may gain insight and an improved ability to cope with his environment. Such use is experimental and potentially dangerous (suicide, prolonged psychosis), and should only be investigated by responsible and sane psychiatrists.

Experiences with these drugs vary greatly with the subject's expectations and personality and environment. Subjects can be prepared so that they have a good "trip" and not a bad "trip". It is therefore impossible to describe the pharmacological effects of psychodysleptics in the fashion that can be adopted for most of the drugs in this book.

The following brief account of **experiences with LSD in normals** will serve as a model. Experiences with mescaline and psilocybin are similar:

Vision may become blurred and there may be hallucinations; these generally do not occur in the blind and are less if the subject is blindfolded. Objects appear distorted, and trivial things, e.g. a mark on a wall, may change shape and gain a special significance for the subject.

Auditory acuity increases, but hallucinations are uncommon. Subjects who do not appreciate music may suddenly come to do so.

Foods may feel coarse and gritty in the mouth.

Limbs may be left in uncomfortable positions.

Time may seem to stop or to pass slowly, but usually it gets faster and thousands of years may suddenly seem to go by.

Mental problem-solving becomes difficult.

The subject may feel relaxed and supremely happy, or may become fearful or depressed. Feelings of depersonalisation and dreamy states occur.

The experience lasts a few hours, depending on the dose; intervals of normality then occur and become progressively longer.

Somatic symptoms include nausea, dizziness, paræsthesia, weakness, drowsiness, tremors, dilated pupils, ataxia. Effects on the cardiovascular system and respiration vary and probably reflect fluctuating anxiety.

So disrupting to the individual are some of these drugs, particularly in respect of thought processes, that special legal control is needed, perhaps especially in view of the possibility of their use in a "person in a position of high authority when faced with decisions of great importance".*

There is no shortage of accounts of experience with psychodysleptics, because there has been a vogue amongst intellectuals, begun by Mr.

* HOFFER, A. (1965). *Clin. Pharmacol. Therap.*, 6, 183.

Aldous Huxley (5), for publishing their experiences. Subsequent accounts are tedious to most except their authors and to those who would do the same; they have little pharmacological importance, revealing more about the author's egocentricity than about the pharmacology of the drug. The same applies to published accounts of what it is like to be a drug addict.

Lysergic acid diethylamide (LSD). Lysergic acid provides the nucleus of the ergot alkaloids and it was during a study of derivatives of this in a search for an analeptic that in 1943 a Swiss research worker investigating LSD (which structurally resembles nikethamide) felt queer and had visual hallucinations. This led him to take a dose of the substance and so to discover its remarkable potency, an effective oral dose being about 30 mcg. The plasma $t_{\frac{1}{2}}$ is about 3 hrs.

Tachyphylaxis occurs to LSD. Psychological dependence may occur, physical dependence does not.

Amphetamine potentiates LSD.

LSD has been used in the dying; it induced analgesia and indifference.

Its effect on the brain may partly be due to antagonism of 5-HT and to anticholinesterase effect.

Serious adverse effects include: psychotic reaction (which can be delayed in onset) with suicide; teratogenic and mutagenic effects are uncertain.

LSD causes curious effects to occur in animals: green sunfish become aggressive, Siamese fighting fish float nose up, tail down, and goats walk in stereotyped patterns. The elephant exhibits episodically a form of delinquent behaviour known as "musth". LSD 100 mcg/kg i.m. was given to an animal (the usual dose for man is up to about 2 mcg/kg) to test whether this induced a similar state. The animal developed laryngospasm and status epilepticus and died.* Not every experiment can have a successful outcome.

Mescaline is an alkaloid from a Mexican cactus, the top of which is cut off and dried and used as "peyote buttons" in religious ceremonies. Mescaline does not induce serious dependence and the drug has little importance except to members of some North and Central American societies and to psychiatrists and biochemists who are interested in the mechanism of induced psychotic states.

Adrenochrome is an oxidation product of adrenaline. It can produce effects similar to those of mescaline and LSD, a fact that has led to speculation as to the possibility of its playing role in mental disease.

Phencyclidine was made in a search for a better intravenous anæsthetic. It is related to pethidine. It was found to induce analgesia without unconsciousness, but with amnesia, in man. However, the postoperative course was complicated by psychiatric disturbance (agitation, abreactions, hallucinations). As the interest of anæsthetists waned, so that of psychiatrists grew, and the drug is now used in experimental therapy. Ketamine (which see) originates from this work.

* COHEN, S. (1967). *Ann. Rev. Pharmacol.*, **7**, 301.

Psilocybin is derived from a Mexican fungus. It is chemically related to LSD and there is cross-tolerance.

Cannabis is obtained from the annual plant *cannabis sativa* (hemp) and its varieties *c. indica* and *c. americana*. The preparations which are smoked are called marihuana (grass, pot, weed, etc.) and consist of crushed leaves and flowers. There is a wide variety of regional names, e.g. ganja (India), kif (Morocco), dagga (Africa). The resin scraped off the plant is known as hashish (hash). The term cannabis is used to include all the above preparations. Since most preparations are illegally prepared it is not surprising that they are impure and of variable potency. The plant grows wild in the Americas, Africa and Asia, and although it will also grow in Britain, the yield of active principles is low due to insufficient sunlight, so that it is only during an exceptional summer that the optimistic sowers of cage-bird seed are rewarded by a saleable crop and the ensuing attention of the law.

Prof. W. D. M. Paton* (and the editor of *Drugs and Society*) have generously allowed this account to be reprinted here.

"*Active principles*. Of the scores of chemical compounds that the resin contains, the most important are the oily cannabinoids, including tetrahydrocannabinol (THC), which is the chief cause of the psychic action. Samples of resin vary greatly in the amounts and proportions of these cannabinoids according to their country of origin; and as the sample ages, its THC content declines. As a result, the THC content of samples can vary from almost zero to eight per cent. Pure THC is unstable unless kept in the dark under nitrogen, but is better preserved in the undamaged plant. One result of these facts is that the dose of THC taken, unless under laboratory control, is far more uncertain than with other drugs.

In addition to the cannabinoids are certain water-soluble substances, including a small amount of an atropine-like substance (which may contribute to the dry mouth), and some acetylcholine-like substances (which may contribute to the irritant effect of the smoke).

Little is known about the composition of the smoke from a cannabis cigarette, save that about twenty five to fifty per cent of the THC content is delivered to the respiratory tract.

THC and other cannabinoids are now fairly easily detectable in small amounts by gas-liquid chromatography. But once THC enters the body, it is hard to trace, unless it has been labelled for research purposes with a radioactive atom—partly because it is taken up by the tissues, partly because it undergoes a series of still incompletely understood conversions. The products of these conversions are found in the urine, but a urine or blood test suitable for forensic or research use is still not available. This is a serious handicap to clinical investigation and means, that there is no way of establishing how much (if any) cannabis a subject has taken.

The cannabinoids are extremely fat-soluble, and correspondingly insoluble in water. They and their metabolites therefore persist in the

* PATON, W. D. M. (1972). *Drugs and Society*, **1**, No. 9, p. 17.

body; thus twenty four hours after a dose of labelled THC, a rat has eliminated, as metabolites in urine and fæces, about ten per cent of the dose, a rabbit about forty five per cent, and a man about twenty five per cent.

"*Psychopharmacology*. Reactions are very varied, and they are much influenced by the behaviour of the group. Euphoria is common, though not invariable, with giggling or laughter which can seem pointless to an observer. Sensations become more vivid, especially visual, and contrast and intensity of colour can increase, although no change in acuity occurs. Size of objects and distance are distorted. Time as experienced becomes longer than clock time; thus a subject asked to say when sixty seconds has elapsed responds too early, but if asked to say how long some period of time was, overstates it: sense of time can disappear altogether, leaving a sometimes distressing sense of timelessness. Recent memory and selective attention are impaired; the beginning of a sentence may be forgotten before it is finished, and the subject is very suggestible and easily distracted. Psychological tests such as mental arithmetic, digit-symbol substitution, and pursuit meter tests show impairment, the effect being greater as the task becomes more complex. The vividness of sensory impressions and distractability gives rise to imagery and fantasy; this can progress with increasing dose from mere fanciful interpretation of actual sensations to hallucination in the sense of vivid sensory impressions lacking an external basis. These effects may be accompanied by feelings of deep insight and truth. They are similar in type, though often more intense, to those experienced in hypnagogic imagery or while recovering from an anæsthetic.

It seems likely that these effects of cannabis can be explained if it removes a restraining 'gate' on the inflow of sensory information. Normally, considerable selection takes place, and familiar stimuli or those judged irrelevant are ignored. A dis-inhibitory action of cannabis, lifting this gate, would allow the 'flood of sensation' so often reported. Further, it is believed that time sense depends on the frequency of sensory impressions; an increased flow would therefore give the feeling that more time had elapsed. Finally, it is known that the process of memory involves at least three processes: entry into a sensory 'register' and passage into a short-term 'store'; rehearsal of information either consciously or unconsciously, leading to consolidation and transfer to a longer-term store; and retrieval. It appears that retrieval is not impaired by cannabis (longstanding memories often form the basis of the imagery), and entry seems normal; but conversion of short-term to long-term memory is known to be interfered with by a flow of additional sensory impressions, just as a telephone number is likely to be forgotten if someone speaks to you just after you have heard it. It is likely that the flow of sensory impressions under cannabis interferes with the consolidation of recent information in a similar way. Once memory is impaired, concentration becomes less effective, since the object of attention is less well remembered.

With this may go an insensitivity to danger or the consequences of actions.

A striking phenomenon is the intermittent wave-like nature of these effects—a subject may return towards normal, or bring himself 'down' for a period. This intermittence effects mood, visual impressions, time sense, spatial sense, and other functions; it represents, incidentally, one of the many experimental difficulties in analysing cannabis action. The effect of a single dose usually ends with drowsiness or actual sleep.

The effects can also be unpleasant, especially by inexperienced subjects, particularly timelessness and the feeling of loss of control of mental processes. Feelings of unease, sometimes amounting to anguish, occur, and may well have some physical basis—perhaps associated with the acceleration of the heart rate. There is also, especially in the habitual user, a tendency to paranoid thinking. High or habitual use can be followed by a psychotic state; this is usually reversible, quickly with brief periods of cannabis use, but more slowly after sustained exposures.

"*Other pharmacology*. Cannabis smoked or taken by mouth produces reddening of the eyeballs (probably the forerunner of the general dilation of blood vessels and fall of blood pressure with higher doses), unsteadiness (particularly for precise movements), and acceleration of heart rate. The latter effect can be substantial, and although the insolubility of the cannabinoids in water makes intravenous abuse difficult, cardiac failure would be a serious risk with such use. The smoke produces the usual smoker's cough, and the tar from reefer cigarettes is as carcinogenic in animal experiments as cigarette tobacco tar. Although increase in appetite is commonly experienced, no explanation for it exists, and cannabis use does not have any striking effect on the blood sugar. In animals, with chronic administration of substantial doses, food intake is reduced and weight loss occurs.

An important finding in animals is that cannabis prolongs sleeping time after a dose of a barbiturate such as pentobarbitone (Nembutal). This has been shown to be due to an impairment of the ability of the liver to break down (metabolise) the barbiturate, as a result of inhibition of the microsomal enzymes. The importance lies in the fact that many drugs used in medicine are also dealt with by these enzymes; and it is to be expected that their function will be impaired in the liver of any recent or habitual cannabis user. The effect is not due to THC itself, but mainly to another constituent of the resin, cannabidiol. One hopes that cannabis users seeking medical treatment would inform their doctors accordingly; the main danger would be of overdosage or of overprolonged action.

A recent report (*68*) has concerned the loss of brain substance, as measured by the technique of air encephalography, in a group of ten young heavy cannabis users. The enlargement of the ventricles of the brain is of the type that occurs in old age, or in middle years with chronic alcoholics. The work needs confirmation, since although the subjects

had taken hundreds of doses of cannabis, they had also had a number of doses of LSD or amphetamines, and occasionally heroin. One is, however, bound to take it seriously, since cannabis, the main drug used by the patients, is cumulative, with a very high affinity for fat, and able to impair cell division by lymphocytes in tissue culture.

Cannabis has been found to produce fetal deformities and fetal resorption in animals (rats, rabbits and hamsters) in doses (per unit weight) ranging down to that used in man. The effect has been shown to be dose-related, and (unlike the teratogenic effect in animals of many drugs, but like thalidomide and other known human teratogens) is exerted at a small fraction of the dose liable to kill the mother. It is not clear what the effect in the human is, and it is to be hoped that it is the human equivalent of fetal resorption (miscarriage) rather than teratogenicity. Tests for chromosome damage have been negative, so that there is no evidence for a heritable genetic defect; but the same tests showed an impairment of cell division, and it may well be this, applied to the developing fetus, which causes the reduction deformities. The teratogenic effects appear to be due to some factor other than THC in the resin.

"*Cannabis and crime.* There is much debate about the connection between cannabis and criminality. A reasonable view, covering other aspects of behaviour, is that cannabis may accentuate a particular mood or facilitate a train of action and such a process could well explain the cases of violence described. A similar position could hold about the connection with sexual behaviour. But here two other contrasting factors enter: the alteration in time sense would change the apparent duration of sexual intercourse; and the predisposition to fantasy may replace sexual activity with images of it. There is, too, the unexplored possibility that the circulatory effects of cannabis include a mild genital engorgement.

More important, however, is likely to be the effect of repeated use described as the 'amotivational syndrome'. This term dignifies a still imprecisely characterised state, ranging from a feeling of unease and sense of not being fully effective, up to a gross lethargy, with social passivity and deterioration. It is difficult to assess, when personal traits and intellectual rejection of technological civilisation are also taken into account. Yet the reversibility of the state, its association with cannabis use, and its recognition by cannabis users make it impossible to ignore.

"*Escalation theory.* Attention has mainly concentrated on progression from cannabis to heroin or other opiates. Although only a very small proportion of casual users progress, it is much commoner with heavy users, and the vast majority of opiate users have prior experience of cannabis. Although it is often said that there is no pharmacological basis for such progression, this in fact exists, since cannabis increases suggestibility and shares with heroin (though in milder form) the ability to produce euphoria and analgesia.

But the situation is a more general one. It seems probable that amphetamine use also predisposes to heroin use; and the overlap in

actions between cannabis and LSD makes intelligible the observed progression to LSD. The role of prior use of 'soft' drugs, or use of drugs by 'soft' techniques in predisposing to more serious abuse needs much more study, particularly by methods which can establish objectively the actual amount of drug used. Although it can only be one of many factors, it could be important in the prevention of serious abuse.

"*Tolerance and dependence.* Tolerance to the behavioural effects of cannabis and of THC in animals has now been repeatedly demonstrated. As with the fat-soluble barbiturates, the first few doses may cumulate, masking the underlying development of insensitivity to the drug's effects. It is not clear whether the tolerance results from increased destruction of the drug or a resistance at the cellular level.

In man, the evidence is largely anecdotal and uncontrolled . . . There is limited evidence that THC disappears somewhat faster from the blood of users as compared with naive subjects. Perhaps the best evidence is still that in the Laguardia report,* where it was found that a three times higher dose was required to produce a given degree of ataxia in users than in non-users. Withdrawal symptoms of morphine or barbiturate type do not occur: but after heavy use, depression, anxiety, sleep disturbance, tremor and other symptoms develop, and many users find it very difficult to abandon cannabis use. In studies on self-administration by monkeys, spontaneous use did not occur, but once use as initiated, drug-seeking behaviour developed. Subjects who have become tolerant to LSD or opiates as a result of repeated dosage respond normally to cannabis but there appears to be cross-tolerance between cannabis and alcohol. . . .

"*Finally*, cannabis occupies a fascinating position in the debate of what society should tolerate, and the outcome of the debate will be important. Despite the damage done in later life by alcoholism, it is possible to draw a line between it and cannabis: there seems no rational basis for drawing a line between cannabis on the one hand and LSD, the amphetamines or the less potent opiates on the other."

The desired effects of cannabis, as with other psychodysleptics, depend not only on the expectation of the user and the dose, but also on his environmental situation and personality. Thus genial or revelatory experiences cannot be relied on to occur, despite optimistic reports, e.g. "Haschich Fudge† (which anyone can whip up on a rainy day). This is the food of Paradise . . . euphoria and brilliant storms of laughter, ecstatic reveries and extension of one's personality on several simultaneous planes are to be complacently expected. Almost anything St. Teresa‡ did, you can do better . . .".

* *Mayor's Committee on Marihuana: the marihuana problem in the City of New York: sociological, medical, psychological and pharmacological studies.* (1944). Lancaster, Penn.: J. Cattell Press.

† From *The Alice B. Toklas Cook Book.* (1954). London: M. Joseph. The author was companion to Gertrude (a rose is a rose is a rose) Stein (1874–1946).

‡ St. Teresa of Avila (1515–1582).

Reality is more prosaic. Acute panic can occur as well as "flashbacks" of previously experienced hallucinations on LSD. Acute overdose causes sleep; it is claimed that death has not occurred.

Cannabis and skilled tasks (e.g. car driving). In general performance in both motor and psychological tests deteriorates, more in naive than in experienced subjects. Effects may be similar to alcohol, but experiments in which the subject is unaware that he is being tested (and so does not compensate voluntarily) are difficult to do, as with alcohol. Some scientists claim the effects are negligible but this view has been "put in proper perspective" by a commentator* who asked how these scientists "would feel if told that the pilot of their international jet taking them to a Psychologists' conference, was just having a reefer or two before opening up the controls".

Legalisation of cannabis. The potential hazards of cannabis are still largely undefined; any long-term social effects will be particularly difficult to discover. Experience with medicines and with other social drugs (tobacco, alcohol) suggests that it would be unwise to assume that because hazards are not obvious they do not exist. The general problem of drugs for social use is discussed in ch. 13.

Treatment of "bad trips" due to psychodysleptics

Milder episodes may be managed by reassuring talk ("talking the patient down"), but more severe cases are helped by sedation with diazepam, a barbiturate or chlorpromazine. With their aid the "premorbid ego" may rapidly be re-established. If the reaction is due to abuse of an anticholinergic drug, natural or synthetic, then diazepam is preferred since chlorpromazine also has anticholinergic effects; a dose of an anticholinesterase that penetrates the CNS (eserine 2 to 4 mg i.m.) is useful in severe reaction to an anticholinergic.

Guide to Further Reading

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Chapter 15

COUGH, RESPIRATORY STIMULANTS AND VOMITING

COUGH

There are two sorts of cough, the useful and the useless. Cough is useful when it effectively expels secretions, exudates, transudates or extraneous material from the respiratory tract, i.e. when it is *productive*; it is useless when it is *unproductive.* Useful cough should be allowed to serve its purpose and only suppressed when it is exhausting the patient or is dangerous, e.g. after eye surgery. Useless cough should be stopped, or, if it is due to thick secretions that cannot be expelled, made useful if possible.

Clinical assessment of the cough of disease by objective recording via a microphone of its frequency and intensity allows assessment of antitussives despite the great spontaneous fluctuations. Such recording has shown patients' own reports of their cough to be too unreliable for drug comparisons.

Experimental cough, induced by inhalation of an irritant, e.g. citric acid, does not correlate well with cough of disease so that it is unreliable for detecting antitussive effect, but it can be used to delineate the time-course of action of drugs.

Placebo effects are great in cough.

Sites of action of useful antitussives are:

1. **Peripheral sites.** (a) on the *afferent side of the cough reflex* by reducing input of stimuli from throat, larynx, trachea, e.g. warm moist atmosphere, demulcents in the pharynx, or by depressing pulmonary receptors (perhaps benzonatate).

(b) on the *efferent side of the cough reflex:* measures to render secretions more easily removable (expectorants, mucolytics, postural drainage) will reduce the amount of coughing needed, by increasing its efficiency. The best antitussive is removal of the cause of the cough by, for example, chemotherapy or surgery.

2. **Central nervous system,** where they may act on the cough centre (opiates), on the cerebral cortex and on the sub-cortical paths (opiates and all sedatives).

If it is true that cough can result from summation of sub-threshold stimuli from mechano- and chemo-receptors from many parts of the respiratory tract, and outside it, e.g. diaphragm, pleura, it is not surprising that it may be reduced by drugs apparently acting at sites far removed

from the site of disease, e.g. demulcents in bronchitis, though it has not been shown that any such relief is other than a placebo effect. Also, there is no doubt that cough can be induced by psychogenic factors such as by anxiety not to cough when it is socially disadvantageous to do so, e.g. when in hiding or during the quiet parts of a musical concert, and reduced by a placebo.

Cough is also under substantial voluntary control, as witness the increase during the louder parts of a London winter concert. A good woman with a cough may sleep better alone and free from fear of depriving her exhausted spouse of sleep, whilst a child may cough less if in reassuring company in his parents' room. Considerations such as these are relevant to practical therapeutics.

Cough Suppression

Antitussives acting peripherally

The patient should stop smoking.

Where the cough arises *above the larynx* then syrups and lozenges that glutinously coat the pharynx (demulcents) may be used, e.g. Liquorice Lozenges, B.P.C. Small children are prone to swallow lozenges and so a confection on a stick may be preferred.

Linctuses are demulcent preparations that can be used alone and as vehicles of other antitussives. That their exact constitution is not critical was known and taught to medical students in 1896.* "Many of you know that this (simple) linctus used to be very much thicker than it is now, and very likely the thicker linctus was more efficacious. The reason why it was made thinner was this. It was discovered that a large number of children came to the surgery complaining of cough, and they were given the linctus, but, instead of their using it as a medicine, they took it to an old woman out in Smithfield, who gave them each a penny, took their linctus, and made jam tarts of it."

When cough arises *below the larynx* water aerosol inhalations and a warm environment often give relief. If it is wished to make the inhalation smell therapeutic, Benzoin Inhalation, B.P.C.† may be added to the hot water. Benzoin inhalation may also promote secretion of dilute mucus and so help to give a protective coating to inflamed mucous membrane, but its effects are more probably solely psychological.

Benzonatate (Tessalon) is a local anæsthetic, related to amethocaine, that may reduce cough by depressing pulmonary stretch receptors and so moderating the response to the lung inflation that is the first stage of the act of cough. Its effect comes on after 5 to 7 days administration so that occasional single doses are useless. It is more interesting as a novel approach than it is useful.

* BRUNTON, L. (1897). Lectures on the action of medicines. Macmillan. London.
† Cpd. Benzoin Tinct. (Friar's Balsam) is similar.

Antitussives acting on the central nervous system

In general when it is desired to suppress cough, drugs acting on the medullary cough "centre" are used. Where these drugs are opiates then part of the effect may result from their actions on higher nervous centres. The morphine-group drugs principally used are relatively non-addicting and have little depressant effect on the respiratory centre, though they may dry the mucosa and thicken the sputum. They include codeine, pholcodine (Ethnine), noscapine (narcotine, Coscopin), dextromethorphan (Romilar). It is possible that as good results can be obtained with these as with the more addicting substances, morphine, heroin and methadone which are powerful respiratory depressants. Linctuses of codeine, pholcodine and methadone are often used. Codeine needs to be given in high doses, say 60 mg, and a tablet is satisfactory. A great many synthetic centrally acting non-opiate antitussives have come and gone; patients will not suffer if the physician ignores them.

Expectorants and Mucolytics

Patients with chest disease can have difficulty in clearing their chest of viscous sputum by cough and because the bronchial cilia are ineffective. They can be assisted in two ways by drugs; by inducing secretion of less viscous fluid, or by liquefying what is already present.

1. **Expectorants** which act by a reflex from the stomach stimulate cough and may also cause a reflex increase in watery bronchial secretion. Some also have a direct effect on bronchial secretory cells. This group includes iodide, chlorides, bicarbonates, acetates, squill, ipecacuanha, creosotes, volatile oils, guaiacols. Some antihistamines are included in cough mixtures; they may stimulate the stomach as above and also reduce unnecessary cough by their sedative effect. Simply hydrating a dehydrated patient can have a beneficial effect in lowering sputum viscosity.

2. **Mucolytics**

(a) *Bromhexine* (Bisolvon) (8 mg) is a synthetic derivative of a plant alkaloid (vasicine) which has been used as an expectorant in the East for many years. Taken orally, it can reduce viscosity of bronchial secretion by depolymerization of the mucopolysaccharide-protein fibres. With a lesser viscosity, larger volumes of sputum are expectorated, but ventilatory function is not necessarily improved. Bromhexine is worth trying in bronchitics with slight to moderate airway obstruction. The oral dose is 8 to 16 mg, 6 to 8-hrly.

(b) *Acetylcysteine* (Airbron) and methylcysteine (Visclair) have free sulphydryl groups that open disulphide bonds in mucus. They must be given by inhalation (or instillation) and may be chiefly useful where particularly viscous secretion is a problem (cystic fibrosis, care of tracheostomies). Carboxymethylcysteine (Mucodyne) is an alternative.

(c) *Detergents* given as aerosols, e.g. superinone (Alevaire) are probably not significantly superior to the above.

(d) *Enzymes*, trypsin, chymotrypsin are probably inferior to (a) and (b) above; they attack living mucous membranes.

(e) *Iodide*, as well as being an expectorant by gastric reflex, stimulates bronchial secretion by direct effect on secretory cells and potentiates the effect of proteolytic enzymes in the sputum. It generally is necessary to give it to the limits of tolerance and so it is not popular. It interferes with measurement of thyroid function.

(f) *Ascoxal*, a mixture of sodium perborate, ascorbic acid and copper sulphate has mucolytic effect given by aerosol.

(g) *Water inhalation* as an aerosol (*not* steam), though cheap, is not to be despised.

Cough Mixtures

There are innumerable mixtures of antitussives, expectorants, mucolytics, bronchodilators and sedatives. Every formulary is replete with them. A selection is mentioned below. Choice is not critical.

Choice of Drug Therapy in Cough

Choice of drug therapy in cough depends on numerous factors. For example, cough due to invasion of a bronchus by a neoplasm requires different treatment from that due to chronic bronchitis with bronchospasm. As always, it is necessary to have a clear idea of what it is intended to achieve before starting to use drugs.

The following are general recommendations only; there is usually a wide choice of agents of approximately equal efficacy for any one case.

For simple suppression of useless cough: codeine, pholcodine, methadone (in that order of potency) in large infrequent doses. In children, cough is nearly always useful and sedation at night is more effective to give rest than is codeine. Pertussis is an exception, sedation, codeine and atropine methonitrate may be tried.

To increase bronchial secretion slightly and to liquefy what is there: water inhalations with or without Benzoin Inhalation, B.P.C., and Sodium Chloride Compound Mixture, B.P.C., or Ammonia and Ipecacuanha Mixture, B.P.C. The irritant expectorants can cause gastric pain if used in effective dose for a long time. If a brisk increase in secretion is desired, large doses of iodide, 10 to 15 ml of 6% potassium iodide 4 to 6-hrly and increased after 2 or 3 days for up to 3 weeks is probably the best way to get it, but unwanted effects may be unavoidable.

Bromhexine orally may be useful.

For cough originating in the pharyngeal region, glutinous sweets or lozenges (demulcents), incorporating a cough suppressant or not, as appropriate, are used.

All drug formularies include numerous remedies for cough, some of which contain both an expectorant and a suppressive, e.g. Squill Opiate

Linctus B.P.C. The rationale of this apparent therapeutic incompatibility is to make coughing more effective whilst also controlling it. Such mixtures have not been scientifically evaluated.

If bronchostriction complicates cough then bronchodilator drugs can be used, e.g. orciprenaline (Alupent), perhaps with bromhexine (Alupent Expectorant). Atropine is undesirable as it thickens bronchial secretion. Oxygen inhalation also thickens secretion and patients having oxygen may need expectorants. The oxygen must be bubbled through water to avoid drying the secretions and so rendering them even more viscous.

Respiratory Stimulants (Analeptics)

Respiratory stimulants are little used, but may have some place in some cases of:

1. **Acute respiratory failure** due to:

(a) depression of respiratory centre by poisons, e.g. barbiturates, as an emergency measure only, until mechanical respiration is available.

(b) pulmonary failure with hypercapnia, drowsiness and inability to cough, to stimulate respiration and coughing, as a short term measure only, e.g. to "buy time" for chemotherapy to control infection.

2. **Chronic ventilatory failure** with hypercapnia; this is a dubious use, for although alveolar ventilation may increase, so does the muscular work of breathing. Thus increased CO_2 production may balance the CO_2 eliminated by increased ventilation; the pCO_2 may remain unchanged. In some patients the pCO_2 falls, but this is transient only and the patient may be no better for it since he has chronic ventilatory failure, the cause of which remains unaffected.

Drugs used are general CNS stimulants and for most the effective respiratory stimulant dose is close to that causing convulsions, preceded by restlessness and twitching (at first round the mouth), itching, vomiting and flushing; convulsions may occur though the patient remains unconscious. The margin of CNS safety is probably greater with doxapram but it causes hypertension and other cardiovascular effects. Aminophylline may be infused slowly i.v. (500 mg in 6 hrs).

Available drugs include nikethamide (Coramine), doxapram (Dopram), crotethamide plus cropropamide (prethcamide, Micoren), amiphenazole (Daptazole), ethamivan (Vandid), leptazol, bemegride (Megimide). They are generally given i.v. Oral use is probably therapeutically worthless, though pharmacological effects have been demonstrated. Theophylline (e.g. aminophylline) (which see) is also a respiratory stimulant.

In an emergency nikethamide 2 to 10 ml (25% soln) may be given i.v.

Picrotoxin is a powerful convulsant from an Asian plant. Its use in medicine is now as obsolete as is its use as a bitter in beer (for which it was used until its pharmacology was clarified).

Strychnine and *lobeline* are also obsolete. *Menthol* is a convulsant. Occasionally cases of poisoning occur as it is included in proprietary inhalations and "cold" remedies to make them smell therapeutic.

Thujone is a convulsant which used to be an ingredient of absinthe.

Irritant vapours, to be inhaled, have an analeptic effect in fainting, e.g. Aromatic Solution of Ammonia, B.P.C. (Sal Volatile). No doubt they sometimes "recall the exorbitant and deserting spirits to their proper stations" (Thomas Sydenham).

VOMITING, ANTIEMETICS AND EMETICS

If the cause of vomiting cannot be removed it may de desirable to attempt to prevent or to suppress it by drugs. The pharmacology of vomiting was little studied until the 1939 war, when motion sickness attained military importance because "when a landing has to be made in the face of resistance it is easy to see that seasickness might on occasion become a handicap". The British military authorities and the Medical Research Council therefore organised an investigation which has provided a type for many subsequent drug trials (*4*).

The aim was to find what drugs in what dose would prevent seasickness without interfering with physical and mental efficiency. The only guide to choice of drugs for the trial was the numerous claims based on uncontrolled observations in the past, which, however, made it clear that anticholinergic drugs (atropine and hyoscine) were likely to be important. Attempts to use swing sickness in the hope of being able to avoid "the disadvantage which the inconstancy of the sea imposed" were not satisfactory, as those who were sick on a swing were not necessarily sick at sea. Reluctantly the workers turned to the sea for their experiments, observing that "dependence on so fickle an element for experimental conditions imposed a considerable strain on the patience of the investigator. Chronic sufferers from seasickness may be astonished to learn that on most days throughout the year an obstinate and baffling calm haunts the waters round this island."

Whenever there was a prospect of sufficiently rough weather about 70 soldiers were sent to sea in small ships, again and again, after being dosed with a drug or a dummy tablet and having had their mouths inspected to detect avoidance. The ships returned to land when up to 40% of the soldiers vomited. "On the whole the men enjoyed the trips", some of them, however, being soldiers, thought the pills were given in order to make them vomit and some "believed firmly in the efficacy of the dummy tablets". It was concluded that, of the remedies tested, hyoscine (0·6 mg or 1·2 mg) was the most effective.

This study has been followed by very many others on the physiology and pharmacology of nausea and vomiting due to motion, drugs and disease.

Site of action. Vomiting results from stimulation of the emetic centre via afferents from the gut or cerebral cortex or from the nearby chemo-

receptor trigger zone (CTZ) which is the site of action of some emetic drugs and diseases. Antiemetics acting on the emetic centre (atropine, some antihistamines) will therefore affect vomiting from any cause but drugs acting on the CTZ (phenothiazines, metoclopramide) will only affect vomiting mediated by the chemoreceptors (morphine, digoxin, uræmia).

Antiemetic effect on the emetic centre is probably due to anticholinergic action and that on the CTZ is unknown. That many antihistamines are useful antiemetics is due to the fact that they also have anticholinergic actions.

Motion Sickness

There was a young lady of Spain
Who was dreadfully sick in a train,
Not once, but again,
And again and again,
And again and again and again.*

Motion sickness is more easily prevented than cured. It is chiefly due to overstimulation of the vestibular apparatus; it does not occur if the labyrinth is destroyed. Other factors also contribute; visually, a moving horizon can be most disturbing, as can the sensations induced by the gravitational inertia of a full stomach when the body is in vertical movement. That the environment, whether close and smelly or open and vivifying, is important, is a matter of common experience amongst all who have passed between Dover and Calais by sea on a rough day. Psychological factors and the fate of one's companions are also important. Tolerance to the motion occurs, generally over a period of days.

Once motion sickness has started oral administration of drugs may fail, not only because they are vomited, but because the pylorus may be closed so that they cannot reach their site of absorption in the small intestine. Injections or suppositories are then to be preferred. It is as well to remember that prevention of motion sickness may only be possible at the expense of troublesome unwanted effects; sleepiness, dry mouth, blurred vision. A holidaymaker travelling for 1½ hours or less from Dover to Calais by sea or from London to Paris by air may not be grateful for prophylaxis at such cost, especially if drugs as long-acting as meclozine or promethazine are used; also, if he is going to drive a car, the unwanted effects are dangerous, and he must be warned of this, as well as being told to take no alcohol. The duration of exposure is relevant to the choice of drugs: *hyoscine* may be as good as other drugs for brief, but not for prolonged, exposure.

It is usual to take antiemetics prophylactically 30 to 60 mins before exposure to the motion, but longer-acting drugs may be begun 12 to 24 hrs before.

* Anonymous limerick.

Choice of drugs. Many drugs are effective, and details of those most commonly used are given in the table. A suitable choice would be meclozine or cyclizine (repeated) for prolonged and hyoscine or cyclizine for brief prophylaxis.

Protection rates are clearly likely to vary a lot with the conditions of the trial, but about 70% protection may be expected by the right doses given at the right time. Confident prediction of what will happen to any one subject about to take a drug of this kind for the first time may be unwise, but much may be gained by an assured air on the part of the prescriber. A sedative, e.g. diazepam can be a useful adjunct if the patient is anxious or distressed. Much may be done to prevent motion sickness by simple commonsense behaviour over meals and environment.

Vomiting due to drugs. Emetic drugs may act in the central nervous system on the chemoreceptor trigger zone (morphine, apomorphine, digoxin), or in the gastro-intestinal tract. Digitalis and ipecacuanha probably act both in the central nervous system and in the gastro-intestinal tract. In general there is paucity of evidence as to how most drugs cause vomiting.

SOME DRUGS EFFECTIVE AGAINST MOTION SICKNESS

Non-proprietary name	*Proprietary names (Tablet size in mg)*	*Oral dose (no. of doses per day)*	*Remarks*
meclozine	Ancolan Bonamine (25) Sea-legs	50 mg (1)	Low incidence of side effects. May cause sleepiness; good for prolonged prophylaxis.
promethazine HCl	Phenergan (25)	25 mg (1–3)	Best taken in evening as sleepiness fairly common.
promethazine theoclate	Avomine (25)	25 mg (1–3)	Probably not superior to promethazine.
diphenhydramine	Benadryl (25)	50–100 mg (3)	May cause sleepiness.
dimenhydrinate	Dramamine (50)	100 mg (3)	The chlorotheophyllinate of diphenhydramine, to which in equiv. dose it is probably not superior. May cause sleepiness.
cyclizine	Marzine (50) Marezine	50 mg (3)	Low incidence of side-effects. May cause sleepiness. Good for prolonged prophylaxis.
hyoscine	Kwells (0·3) Sereen tablets	0·6 mg (3)	Useful in single dose for short journeys. Side-effects too troublesome for prolonged use. Atropine is probably equally effective.

These drugs all have anticholinergic effects and most happen to be antihistamines.

The best treatment of drug-induced vomiting is to withdraw or reduce the dose of the drug, but if this cannot be done an attempt, often unsatisfactory, may be made to oppose it by another drug. In general, chlorpromazine or another phenothiazine or metoclopramide, which are ineffective against motion sickness, are the best drugs to try. However, in the case of vomiting due to morphine-like drugs diphenhydramine, dimenhydrinate and cyclizine might be better. There is a combined preparation, Cyclimorph. Cerebral depressant effects of morphine and the anti-emetics are additive, and chlorpromazine potentiates morphine, so that caution is needed.

A usual dose of chlorpromazine is 25 to 50 mg orally 8-hrly, but if vomiting has already begun the first dose at least may be given i.m. Bigger doses can be used.

Post-anæsthetic vomiting can be reduced by chlorpromazine, metoclopramide, meclozine and cyclizine which may be given before or after the operation. Chlorpromazine potentiates anæsthetic agents and analgesics and hypnotics, and this must be taken into account when it is used, for waking may be delayed. The sedative effects of meclozine and cyclizine are additive with those of other drugs.

Vomiting of pregnancy. All drugs should be avoided in early pregnancy as far as possible, and much can be done by other approaches. Clinical evaluation is difficult because "many women are so pleased to have their troubles taken seriously and discussed in detail that they are unwilling to declare the new treatment to be a failure" (*6*). A start may be made with psychotherapy and magnesium trisilicate. Meclozine may be the best systemic antiemetic: chlorpromazine is effective but side-effects are more common. There is no reason to think meclozine dangerous to the fetus when used in ordinary dose, but phenothiazines are perhaps best avoided where possible. Although pyridoxine deficiency has not been shown to occur in simple pregnancy vomiting, it may occur in hyperemesis gravidarum. Pyridoxine has been widely used in pregnancy vomiting, alone and with meclozine. It is probably not useful (*6*), but has the advantage of being almost certainly harmless. It can be considered as a suitable placebo to support psychotherapy if the prescription of a tablet will itself provide useful reassurance that something definite, i.e. not just talk, is being done.

Vomiting of disease. When removal of the cause is not possible this may be helped by chlorpromazine, metoclopramide, cyclizine or meclozine.

Radiation sickness is treated similarly to vomiting of pregnancy and with metoclopramide.

Vertigo. A great range of drugs has been recommended for vertigo. There is not yet enough knowledge of the physiology of the symptom for drug therapy to be on a scientific basis. All the antiemetic drugs are used, also a hodge-potch of remedies whose variety indicates the absence of scientific evidence of their value, vasoconstrictors, vasodilators, central nervous system stimulants and depressants and, inevitably, vitamins.

Perhaps sedation and an antiemetic (promethazine, cyclizine) are most likely to help. Betahistine may be useful in Menière's syndrome.

Metoclopramide (Maxolon) (10 mg) is structurally related to procainamide. It acts on the chemoreceptor trigger zone. It also has a peripheral action which alters upper gut motility, increasing gastric peristalsis and emptying, and relaxing the pyloric antrum and duodenal cap. These effects may contribute to the antiemetic effect and are also made use of to facilitate intubation procedures, radiological examination of the gut and to empty the stomach before emergency anæsthesia and in labour. The direct effects on the gut are antagonised by atropine and other anticholinergics. The site of action is in the gut wall, so it is not prevented by surgical vagotomy. Gastric secretion is unaffected. The dose of metoclopramide is, oral, 10 mg 8-hrly: i.m. or i.v. 10 mg when oral use is impracticable. Adverse reactions include extrapyramidal dystonia such as occurs with phenothiazines, so they are best not used together. Anticholinergic antiparkinsonian drugs are effective if it is essential to continue the metoclopramide.

Therapeutic Emesis (*8*)

Except in cases of poisoning (which see), therapeutic emesis is rarely required. Mechanical stimulation of the throat by the patient's *own* fingers or by nauseous draughts of saline or mustard often fail, and the substantial fluid volume needed with the latter may promote passage of a poison through the pylorus. The best emergency emetic may be a single dose of Ipecacuanha Syrup USP* (15 ml orally followed by 200 ml water and repeated in 20 mins if vomiting has not occurred). It acts both peripherally (stomach) and centrally (CTZ). It has the advantage that it can be used safely by non-medical people in emergency. The principal active ingredient of ipecacuanha is emetine, a useful amœbicide, which illustrates the undesirability of naming drugs after their pharmacological properties.

Apomorphine is a semisynthetic morphine-like alkaloid with the emetic action of morphine greatly enhanced. It also has the other central actions of morphine and can cause coma, especially if given to a patient whose central nervous system is already depressed. A second dose should never be given if the first fails, as it may. The drug is deservedly obsolescent. Innumerable other substances cause vomiting.

A crude treatment of alcoholism is to give alcohol followed by an emetic to "condition" the patient against it. This is named "aversion therapy".

Of course, no emetic should ever be administered to an unconscious patient. The relative usefulness of emesis and of gastric lavage in acute poisoning is discussed later (see index).

* *Not* Liq. Extr. Ipecac. (B.P.) which is stronger.

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On Cough

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Chapter 16

CHOLINERGIC AND ANTICHOLINERGIC DRUGS

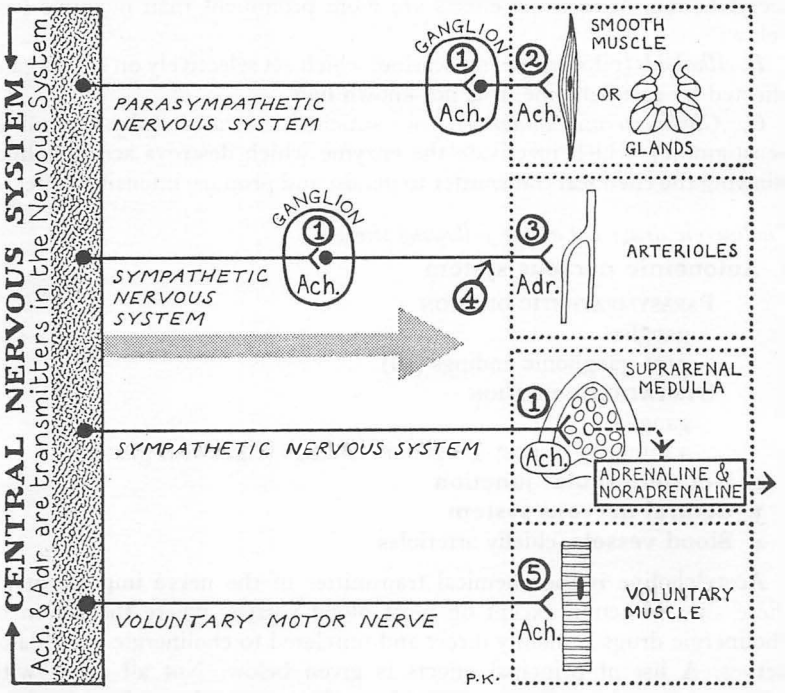

FIG. 19. Diagram showing sites of chemical transmitters of nerve impulse.

Ach. = acetylcholine
Adr. = noradrenaline or adrenaline

Site 1 is blocked by ganglion-blocking agents and stimulated by nicotine and big doses of some choline esters and anticholinesterases.

Site 2 is blocked by atropine and stimulated by some choline esters, anticholinesterases and pilocarpine.

Site 3 is blocked by adrenoceptor blocking agents and function is interfered with by drugs that deplete noradrenaline stores in nerve-endings and end-organs (reserpine).

Sympathomimetic amines stimulate here.

Site 4 is blocked by adrenergic neurone-blocking agents (guanethidine).

Site 5 is blocked by neuromuscular blocking agents and stimulated by choline esters and anticholinesterases.

CHOLINERGIC DRUGS

THESE substances act at all the sites in the body where acetylcholine is the chemical transmitter of the nerve impulse. They may stimulate and later paralyse. In addition, like acetylcholine, they act directly on peripheral blood vessels to dilate them.

Cholinergic drugs may be:

A. Choline esters (carbachol, methacholine) which act at all sites like acetylcholine. Muscarinic effects are more prominent than nicotinic (see below).

B. Alkaloids (pilocarpine, muscarine) which act selectively on end-organs affected by acetylcholine, it is not known how.

C. Cholinesterase inhibitors, or anticholinesterases (physostigmine, neostigmine), which inactivate the enzyme which destroys acetylcholine, allowing the chemical transmitter to persist and produce intensified effects.

Cholinergic drugs act at the following sites:

1. **Autonomic nervous system**
   - PARASYMPATHETIC DIVISION
     - ganglia
     - post-ganglionic endings (all)
   - SYMPATHETIC DIVISION
     - ganglia
     - a minority of post-ganglionic endings (e.g. sweat glands)
2. **Neuromuscular junction**
3. **Central nervous system**
4. **Blood vessels,** chiefly arterioles

Acetylcholine is the chemical transmitter of the nerve impulse at all these sites of action except on most blood vessels, where the action of cholinergic drugs is mainly direct and unrelated to cholinergic vasodilator nerves. A list of principal effects is given below. Not all occur with every drug and not all are noticeable at therapeutic doses. For example, methacholine does not stimulate autonomic ganglia and central nervous system effects of cholinergic drugs are best seen in cases of anti-cholinesterase poisoning. *Atropine antagonises all the effects of cholinergic drugs except those at autonomic ganglia and the neuromuscular junction.*

Autonomic nervous system

Parasympathetic division. Stimulation of both the cholinergic synapses in ganglia and the post-ganglionic endings affects chiefly the following organs:

Eye: miosis and spasm of the ciliary muscle occur so that the eye is accommodated for near vision. Intra-ocular pressure falls due, perhaps, to vasodilatation of vessels at the point where intra-ocular fluids pass into the blood.

Exocrine glands: there is increased secretion, most noticeably of the salivary, lachrymal, bronchial and sweat glands. The last are mostly cholinergic although anatomically part of the sympathetic system; some sweat glands may be adrenergic.

Heart: bradycardia occurs, with atrio-ventricular block and eventually cardiac arrest. The stroke volume is decreased.

Bronchi: bronchoconstriction occurs, also increased secretion, these effects may be serious in asthmatic or other allergic subjects, in whom cholinergic drugs should be used with caution.

Alimentary tract: there is increased movement and secretion and colicky pain may occur. The patient may defæcate embarrassingly.

Bladder and ureters contract and the drugs promote micturition.

Sympathetic division. *The ganglia* only are stimulated, also the cholinergic nerve to the adrenal medulla. These effects are overshadowed by effects of the drugs on the parasympathetic system and are commonly only evident if atropine has been given to block the latter, when tachycardia, vasoconstriction and hypertension occur.

Neuromuscular junction

The neuromuscular junction has a cholinergic nerve ending and so is stimulated, causing muscle fasciculation followed, if excess is given, by a depolarisation neuromuscular block.

Central nervous system

There is usually stimulation followed by depression, but variation between drugs is great, possibly due to differences in penetration into the nervous system. Mental excitement occurs, with confusion and restlessness, insomnia (with nightmares when sleep does come), tremors and dysarthria, and sometimes even convulsions and coma.

Blood vessels

There is stimulation of cholinergic vasodilator nerve endings in addition to the more important direct dilating action on arterioles and capillaries. Anticholinesterases potentiate acetylcholine which exists in the vessel walls independently of nerves.

Nicotinic and muscarinic effects

The actions of acetylcholine and substances acting like it at autonomic ganglia and the neuromuscular junction (i.e. at the end of cholinergic nerve fibres which arise in the central nervous system) are described as **nicotinic** because they are like the stimulant effects of nicotine. The actions at post-ganglionic cholinergic ends (parasympathetic endings plus the cholinergic sympathetic nerves to the sweat glands) and those directly on blood vessels are described as **muscarinic** because they resemble those of the alkaloid muscarine. The central nervous system actions are not included in this categorisation. The terms are useful

because it is more concise to say, that atropine blocks the muscarinic but not the nicotinic effects of neostigmine than it is to describe this antagonism in any other way. But these terms seem to be unacceptable to clinicians who, although they were nearly all brought up on them, decline to apply them when discussing the clinical use of drugs, perhaps because they find them unnecessary as well as confusing, despite the fact that they were introduced to avoid confusion.

Acetylcholine

Since acetylcholine has such great importance in the body it is not surprising that attempts have been made to use it in therapeutics. But a substance with such a huge variety of effects and so rapidly destroyed in the body is unlikely to be useful in therapy.

The use of acetylcholine in psychiatry illustrates some facets of the introduction of new remedies as well as providing interesting clinical pharmacological data. It was first injected intravenously as a therapeutic convulsant in 1939, in the justified expectation that the fits would be less liable to cause fractures than those following therapeutic leptazol convulsions. Recovery rates of up to 80% were claimed in various psychotic conditions. Enthusiasm began to wane however when it was shown that the fits were due to anoxia resulting from cardiac arrest and not to pharmacological effects in the brain (*1*).

The following composite description of the effects of i.v. injection on many patients shows a mixture of direct effects of acetylcholine and of anoxia due to acetylcholine-induced cardiac arrest: A few seconds after the injection (which was given as rapidly as possible to avoid total destruction in the blood) the patient sat up "with the knees drawn up to the chest, the arms flexed and the head bent forward. There were repeated violent coughs, sometimes with flushing. Forced swallowing and loud peristaltic rumblings could be heard." Respiration was laboured and irregular. "The coughing abated as the patient sank back in the bed. Forty seconds after injection the radial and apical pulse were zero and the patient became comatose." The pupils dilated, and deep reflexes were hyperactive. In 45 seconds the patient went into opisthotonos with brief apnœa. Lachrymation, sweating and borborygmi were prominent. The deep reflexes became diminished. The patient then relaxed and "lay quickly in bed—cold moist and gray. In about 90 seconds flushing of the face marked the return of the pulse." The respiratory rate rose and consciousness returned in about 125 seconds. The patients sometimes micturated but did not defæcate. They "tended to lie quietly in bed after the treatment". "Most of the patients were reluctant to be treated" (*2*).

The investigators who did this series obtained bad therapeutic results except in one schizophrenic who nearly died. In this patient the pulse first disappeared for 50 seconds, returned for 20 seconds and disappeared again for 140 seconds. It then reappeared for 5 and disappeared for the following 50 seconds, after which the patient "recovered". The authors

considered that the brain had suffered such extensive anoxic damage "that obvious schizophrenic symptoms, at least for the time being, (were) impossible."

These and other results were sufficiently intimidating for therapy to be modified to non-convulsant doses for neurotics. After several favourable reports a careful study was done in which it was shown that acetylcholine was not a therapeutic agent because the same rate of improvement occurred in control groups, the use of control groups having been neglected by those who popularised the treatment. The authors of this series commented on the necessity for a placebo or dummy in controlled therapeutic trials as being "nowhere more true than where psychiatric practice is concerned, because a substantial proportion of emotionally disturbed patients show favourable responses to any therapeutic effort which combines enthusiasm, impressiveness and benevolence" (*3c*).

As it would clearly be useful to the physician to be able to produce some of the effects of acetylcholine without all the others, related substances have been investigated and there is now a variety of drugs available with longer action and varying degrees of selectivity; but none confine their effects to one organ alone. The principal drugs are described below.

Other Choline Esters

Methacholine is destroyed by cholinesterase less rapidly than acetylcholine. It is potentiated by anticholinesterase drugs. The effects are predominantly cardiovascular and last up to 30 minutes after 10 to 30 mg . s.c. It is unreliable when swallowed, being largely destroyed in the intestine. Methacholine can be used to stop supraventricular tachycardias, and to stimulate bowel and bladder, although carbachol may be preferable for this. When it is used atropine (0·5 to 2 mg. i.v. or s.c.) should be available to stop dangerous cardiac effects (bradycardia and arrest).

Carbachol is a choline ester which is not destroyed by cholinesterase, so that its effects summate with anticholinesterases; there is not potentiation as with methacholine. Carbachol is both more potent and longer acting than methacholine and its actions are more pronounced on the bladder and bowels, so that it is usual in clinical practice to use methacholine for cardiac effects and carbachol for bowel and bladder stimulation.

Carbachol (1 mg.) is given s.c. (0·2 to 0·5 mg.) or orally (1 to 4 mg.); unlike methacholine it is stable in the alimentary tract. Both carbachol and methacholine are extremely dangerous if given i.v.

Bethanechol (Urecholine, Mechothane) (5 mg.) is related to methacholine but it is not destroyed by cholinesterase. It acts chiefly on the bowel and bladder The dose is 2 to 5 mg., s.c., or 5 to 30 mg. orally

Alkaloids with Cholinergic Effects

Pilocarpine is an alkaloid from an American plant. It acts directly on end-organs innervated by post-ganglionic cholinergic nerves (parasympathetic system plus sweat glands); it also stimulates and then depresses the central nervous system. Its action at the neuromuscular junction and autonomic ganglia is very slight. Its chief clinical use is in the eye as a miotic (1%

solution). It has an undeserved reputation as a hair restorer but is very occasionally useful as a sialogogue in Parkinsonian patients taking large doses of atropine. Objectionable effects, such as sweating, often more than counterbalance the benefits. Overdose is liable to cause respiratory symptoms due to bronchospasm and profuse bronchial secretion.

Arecoline is an alkaloid in the betel nut which is chewed in the East. It induces a mild dependence, for like other parasympathomimetic drugs it stimulates the brain. It has no place in therapeutics.

Muscarine is of no therapeutic importance, but cases of poisoning occur when the fungus (Amanita muscaria, fly agaric, so called because it was used to poison the common fly, Musca domestica) which contains it, is eaten. The effects are those of stimulation of all end-organs innervated by post-ganglionic cholinergic nerves. In addition it causes vasodilatation and stimulates the central nervous system. All these effects are antagonised by atropine.

The lengths to which man is prepared to go in taking "chemical vacations" from life, if conditions are hard, are shown by the inhabitants of Eastern Siberia who used the fungus habitually for its cerebral stimulant effects. They were apparently prepared to put up with the autonomic actions to escape briefly from reality. The fungus was scarce in winter when, no doubt, the greatest need for it was felt and the frugal devotees discovered that by drinking their own urine they could recover some of the alkaloid. Unfortunately cheap alcohol has supplanted most of these interesting practices.

It is convenient to deal here with the effects of eating poisonous fungi. They are usually described as "mushroom" poisoning although mushrooms are not poisonous, merely somewhat indigestible.

"Mushroom" Poisoning

There are three principal clinical pictures:

EARLY ONSET. Cholinergic ("muscarinic") effects occur in less than 2 hrs. This is typical of Amanita muscaria poisoning. The treatment is on general principles and with large doses of atropine.

LATE ONSET. Abdominal pain, vomiting and diarrhœa occur more than 5 hrs after ingestion. This is typical of Amanita phalloides poisoning. Later there are signs of acute liver and renal damage. There may be severe hypoglycæmia and electrolyte disturbances. Death is common. Treatment is on general principles.

NON-SPECIFIC GASTRO-ENTERITIS.

It is evident that it may not be easy to distinguish the three kinds early on.

Anticholinesterases

In the region of cholinergic nerve-endings and in erythrocytes there is an enzyme specific for the destruction of acetylcholine, "true" cholinesterase or acetylcholinesterase. In various tissues, especially blood plasma, there are other esterases which are not specific for acetylcholine but which also destroy other esters, e.g. procaine. These are called "non-specific" or "pseudo" cholinesterases. Chemicals which inactivate these esterases (anticholinesterases) are used in medicine, and in agriculture as insecticides. They act by allowing naturally formed acetylcholine to accumulate instead of being destroyed and their effects are almost entirely due

to this accumulation in the central nervous system, at the neuromuscular junction, autonomic ganglia, post-ganglionic cholinergic nerve endings (which are principally in the parasympathetic nervous system) and in the walls of blood vessels, where acetylcholine is not necessarily associated with nerve endings. Some of these effects oppose each other, for instance the effect of an anticholinesterase on the heart will be the resultant of stimulation at sympathetic ganglia and the opposing effect of stimulation at parasympathetic (vagal) ganglia and post-ganglionic nerve endings. Therefore the clinical effects of anticholinesterases are not entirely predictable. Anticholinesterases, of course, increase the effect of all cholinergic drugs.

Anticholinesterase poisoning (*6*, *7*). The anticholinesterases used in therapeutics are generally those which reversibly inactivate cholinesterase for a few hours. Those (organophosphates) which inactivate it almost or completely irreversibly, so that recovery depends on formation of fresh enzyme, which takes weeks, have been found suitable for use as agricultural insecticides and have been studied for use in war ("nerve gas"). Cases of poisoning are therefore likely to be met outside therapeutic practice. Diagnosis depends on observing a substantial part of the list of actions below. The prominence of individual effects varies with different drugs, e.g. sweating and salivation are not usual with dyflos poisoning.

Death is due to a combination of the actions in the central nervous system, to paralysis of the respiratory muscles by peripheral neuromuscular block, and to pulmonary œdema and bronchial obstruction due to circulatory and bronchial secretory changes; these together may culminate in respiratory failure. The central effects, and those due to stimulation at post-ganglionic cholinergic nerve endings and vasodilatation, are antagonised by atropine. The neuromuscular block is not, for atropine does not antagonise acetylcholine at the endings of nerve fibres which arise in the central nervous system (nicotinic effects).

Poisoning by reversible inhibitors may be treated with atropine in large doses and by artificial respiration if necessary.

Whilst atropine is important, it merely antagonises some (the muscarinic) anticholinesterase effects; it does not antagonise neuromuscular block (nicotinic effect) and it does not reactivate cholinesterase.

Fortunately there are selective antagonists that reactivate cholinesterase (see below) and these are specially active against irreversible inhibitors of cholinesterase. The antagonists are more effective against neuromuscular block (nicotinic effect) than against the muscarinic effects, and therefore complement the effects of atropine.

The principal cholinesterase reactivators are oximes, **pralidoxime** (Protopam, PAM) and its close relatives, DAM and P_2S, which are substances developed since it was discovered that the organophosphate compounds inactivate cholinesterase by phosphorylating the active centre of the enzyme. The reactivators are either phosphorylated very easily so that they compete for the poison in the body, diverting it from cholinesterase, or they may dephosphorylate the enzyme. One dose is often

enough, but especially in the case of parathion, which is slowly converted into an active form after it enters the body, further doses may be required. Early administration is important because poison and enzyme become irreversibly linked over several hours.

A typical case of poisoning will first develop anorexia and nausea with mental confusion and a sense of unreality. Vomiting, cramp-like abdominal pain, cold, sweating and salivation follow. The patient is often giddy, apprehensive and restless. Miosis may occur, but is not invariable; nor is it an index of severity, for it may be due to a local effect of the poison entering by the conjunctivæ.

Next, muscle twitching begins, in the eyelids and tongue, then the face, neck and the rest of the body, accompanied by severe weakness. Convulsions may occur. Other signs include diarrhœa, tenesmus, incontinence of fæces, pulmonary œdema and bronchoconstriction, ataxia, tremor, drowsiness, respiratory depression and coma. At autopsy, ileal intussusceptions are commonly found.

Treatment. The most common route of entry in accidental poisoning is by the skin, so treatment may begin with removal of contaminated clothes and washing of exposed skin with sodium bicarbonate solution or alcohol.

Atropine (2 mg.) is given i.m. or i.v. at once and repeated every 10 to 30 minutes as indicated by clinical progress. It should be continued until signs of atropinisation appear (mydriasis, tachycardia, dry mouth); 20 mg. or more may be needed.

A specific cholinesterase reactivator pralidoxime (1·0 g) should be given i.v., i.m. or orally and repeated as indicated by the patient's condition. It is highly effective against organic phosphorus anticholinesterases (parathion is commonest), but is less effective in carbamate anticholinesterase poisoning (neostigmine, pyridostigmine).

The patient should be kept fully atropinised for at least 24 hrs. and may need as much as 100 mg. atropine total.

Artificial respiration (preferably by a positive pressure device) may be needed. Attention to the airway is vital because of the bronchoconstriction and excessive mucus secretion, and endotracheal intubation or tracheostomy with suction may be required. Blood cholinesterase content should be measured if possible, both for diagnosis, and to determine when a poisoned worker may return to his task in the event of his being willing to do so. This should not be allowed until his blood cholinesterase exceeds 70% of normal, which may take several weeks.

Barbiturates are potentiated, but may be needed for convulsions. The following drugs may be dangerously potentiated: morphine, aminophylline, reserpine, phenothiazines, depolarising neuromuscular blockers.

Physostigmine (eserine) is an alkaloid, obtained from seeds of a West African plant, which has long been used both as a weapon and as an ordeal poison. It acts for a few hours. It is used in the eye (miosis, spasm of the ciliary muscle and reduced intraocular pressure) and i.v. to control CNS

manifestations of anticholinergic drug poisoning (for it enters the CNS which neostigmine does not).

Neostigmine (15 mg.) is a synthetic anticholinesterase whose actions are more prominent on the neuromuscular junction and the alimentary tract than on the cardiovascular system and eye. It is therefore principally used in myasthenia gravis and to stimulate the bowels and bladder after surgery, and as an antidote to neuromuscular blocking agents acting by competition. In addition it has a direct stimulating action of its own, unrelated to inhibition of cholinesterase, which may be of importance in myasthenia gravis. Neostigmine is effective orally (15 to 30 mg., three or four times a day), and by injection (usually s.c.) 0·25 to 1 mg. But higher doses may be used, often combined with atropine, in myasthenia gravis.

Pyridostigmine (Mestinon) (60 mg.) is similar to neostigmine but has a slower onset and slightly longer duration of action and perhaps fewer visceral effects. It is often used for myasthenia gravis, 4 mg. of the bromide are equivalent to 1 mg. neostigmine bromide.

Distigmine (Ubretid) is a variant of pyridostigmine (two linked molecules as its name implies).

Ambenonium (Mytelase) is similar.

Edrophonium (Tensilon) is related to neostigmine. It is a very short-acting anticholinesterase, with, in addition, direct stimulant effects at the neuromuscular junction, for which site it is comparatively selective. Autonomic effects are minimal and are usually only marked at high doses. Overdose causes neuromuscular block. Its action (after 3 mg. i.v.) is finished within five minutes and so is too brief to make it a useful antidote to competitive neuromuscular blocking agents, though anæsthetists sometimes use it to elucidate dual block (which see). It is useful in the diagnosis of myasthenia gravis.

Dyflos (DFP or diisopropyl fluorophosphate) is one of the many organophosphates which are powerful and long-acting anticholinesterases, the duration of whose effects is limited more by synthesis of new cholinesterase than by freeing of inactivated enzyme. The effects in man may last for two weeks or more, so that it is unsuitable for systemic use, though it has been used in the eye as a miotic.

Ecothiopate (Phospholine) and **demecarium** (Tosmilen) are used as long lasting miotics. Enough can be absorbed to potentiate cholinergic drugs and suxamethonium given systemically for weeks after cessation of use. Spasm of the ciliary muscle may be intense and cause headache. These would qualify as suitable for chemical warfare if even more noxious anticholinesterases had not been discovered: TEPP (tetraethyl pyrophosphate), HETP (hexaethyl tetraphosphate), OMPA (octamethyl pyrophosphoramide), parathion, amiton, demeton, demeton-methyl, dimefox, Gusathion, masidox, mipafox, Phosdrin, phosphamidon, schradan, sulfotep and sarin, some of which are used as pesticides in agriculture.

Myasthenia Gravis

In myasthenia gravis there is defective synthesis and storage of acetylcholine at the motor nerve ending. Ordinarily the disease is treated by neostigmine.

Neostigmine was introduced in 1931 for its stimulant effects on intestinal activity. In 1934 it occurred to Dr. Mary Walker that since the paralysis of myasthenia had been attributed to a curare-like substance in the blood, physostigmine (eserine), an anticholinesterase drug known to antagonise curare, might be beneficial. It was, and she reported this important observation in a short letter.* Soon after this she used neostigmine by mouth with greater benefit.

The sudden appearance of an effective treatment for a hitherto untreatable chronic disease must always be a dramatic event for its victims. The impact of the discovery of the action of neostigmine has been described by one patient.

"My myasthenia started in 1925, when I was 18. For several months it consisted of double-vision and fatigue. . . . An ophthalmic surgeon . . . prescribed glasses with a prism. Soon, however, more alarming symptoms began." Her limbs became weak and she "was sent to an eminent neurologist. This was a horrible experience. He . . . could find no physical signs . . . declared me to be suffering from hysteria and asked me what was on my mind. When I answered, truthfully, that nothing was except anxiety over my symptoms, he replied, 'My dear child, I am not a perfect fool . . .' and showed me out." She became worse, and at times she was unable to turn over in bed. Eating and even speaking were difficult. Eventually her fiancé, a medical student, read about myasthenia gravis and she was correctly diagnosed in 1927. "*There was at that time no known treatment and therefore many things to try.*" She had gold injections, thyroid, suprarenal extract, lecithin, glycine and ephedrine. The last had a slight effect. "Then in February 1935, came the day that I shall always remember. I was living alone with a nurse. . . . It was one of my better days, and I was lying on the sofa after tea. . . . My fiancé came in rather late saying that he had something new for me to try. My first thought was, 'Oh bother! Another injection, and another false hope.' I submitted to the injection with complete indifference, and within a few minutes began to feel very strange . . . when I lifted my arms, exerting the effort to which I had become accustomed, they shot into the air . . . every movement I attempted was grotesquely magnified until I learnt to make less effort . . . it was strange, wonderful, and at first very frightening . . . we danced twice round the carpet. That was my first meeting with neostigmine, and we have never since been separated."†

Anticholinesterase drugs are also used in the **diagnosis** of myasthenia gravis. If the weakness and fatiguability are dramatically relieved then the diagnosis is confirmed although occasionally some response may occur in other muscle disease, e.g. dystrophies. 1 to 3 mg. neostigmine may be injected s.c. It is best to give 0·5 mg. atropine for each 1 mg. neostigmine to avoid unpleasant visceral effects, e.g. colic, vomiting, defæcation, due to stimulation of the parasympathetic autonomic system. The atropine does

* WALKER, M. B. (1934). *Lancet*, **1**, 1200.
† *Disabilities and How to Live with Them* (1952). London: Lancet.

not interfere with the effect of neostigmine at the neuromuscular junction, i.e. it antagonises the muscarinic but not the nicotinic effect of acetylcholine. A failure to improve dramatically does not prove the patient has not myasthenia gravis, as a few cases respond poorly. Edrophonium (Tensilon) has fewer autonomic side-effects and a much briefer action than neostigmine. A syringe is loaded with 10 mg; 2 mg are given i.v. and if there is no reaction in 30 sec the rest is injected. An hour later 15 or 20 mg can be given if there was no response to the first injection.

Treatment is usually by neostigmine, 15 to 75 mg a day, or by pyridostigmine, 60 to 300 mg a day, in three or four doses, orally; but more may be needed. Pyridostigmine may give a more even effect. Individual variation in response is substantial and care in adjusting doses and intervals is rewarding.

Ephedrine enhances neuromuscular conduction and may be useful.

Too high a dose of anticholinesterase drugs may make the weakness worse (**cholinergic crisis**) and it is important to distinguish this from an exacerbation of the disease (**myasthenic crisis**). There is no simple means of making this distinction, but if the total daily dose of anticholinesterase is less than 15 tablets and the pupil diameter exceeds 3 mm the weakness is unlikely to be cholinergic. The pattern of relief of weakness may also help; if it increases more than 2 hrs after a dose and is relieved by the next dose, this suggests myasthenic weakness; if it is marked 1 hr after a dose and is not significantly improved by the next dose it is likely to be cholinergic.* A consideration of the mechanism of action and of the time-course of drug effect shows why this should be so. A dose of edrophonium will make the diagnosis; a myastenic crisis gets better and a cholinergic crisis gets dangerously worse.

The habitual use of atropine to abolish parasympathetic effects is undesirable because it may mask excessive therapy, and so make the differentiation between myasthenic and cholinergic crisis more difficult, for parasympathomimetic effects (miosis, salivation, abdominal cramps, bradycardia) act as a warning that overdose is being approached.

The patient should learn to recognise the symptoms of both over and underdosage, and should be warned of the risks of the former for "overdose of drugs in myasthenia gravis is probably one of the major causes of death in the disease"†. At high doses accumulation may occur over several weeks so that onset of a cholinergic crisis may be delayed. Eye muscles are relatively resistant to therapy so that forcing the dose to correct diplopia may cause a cholinergic crisis.

A cholinergic crisis should be treated by withdrawing all anticholinesterase medication, mechanical respiration if required, and atropine i.v. for muscarinic effects of the overdose. The neuromuscular block is a nicotinic effect and will be unchanged by atropine. Pralidoxime may be tried (500 mg i.v. repeated as necessary) though it may be ineffective.

* Simpson, J. A. (1971). *Prescr. J.*, **11**, 9.
† Schwab, R. S. (1963). *New Engl. J. Med.*, **268**, 596, 717.

A resistant **myasthenic crisis** may be treated by withdrawal of drugs and artificial respiration for a few days.

Recovery from myasthenic crisis has followed paralysis with tubocurarine and artificial respiration, to "rest" the motor endplate, in a few cases, but this is an experimental remedy for a desperate situation.

It has long been known that potassium is capable of enhancing synaptic transmission and this has led to the trial of large doses of potassium chloride orally in resistant cases, with little benefit.

The use of spironolactone, which reduces the excretion of potassium, has been claimed to give benefit and it is theoretically justified, but confirmation is needed.

Streptomycin and other antibiotics that can cause neuromuscular block, as well as quinidine and respiratory depressants, are potentially dangerous in this and in other muscle diseases.

Immunosuppression. Adrenal steroid therapy has been tried on the hypothesis that myasthenia may be an autoimmune disease. Large doses of prednisone or corticotrophin have been reported effective though improvement may not be maintained. There is sometimes an initial exacerbation of the weakness. Immunosuppressive drugs, e.g. azathioprine have also been reported successful. But such treatments carry hazards.

The principal uses of cholinergic drugs may be summarised:

1. To stimulate a reluctant bowel or bladder, e.g. after surgery. Postoperative ileus may respond to carbachol or neostigmine; but the stimulation is hazardous to surgical gut anastomoses, which may leak.

Neostigmine sometimes helps the gaseous distention, constipation and diarrhœa which result from loss of smooth muscle in the gut in scleroderma and systemic sclerosis.

2. In the eye, to constrict the pupil, to make the ciliary muscle contract and to reduce intra-ocular pressure (physostigmine, pilocarpine, ecothiopate).

3. Anticholinesterases (neostigmine) as antidotes to those neuromuscular blocking agents (e.g. curare, gallamine), which act by competition, and in myasthenia gravis.

4. Rarely in tachycardias (methacholine).

DRUGS WHICH OPPOSE ACETYLCHOLINE

These drugs may be divided into three groups:

1. *Anticholinergic* drugs which act principally at post-ganglionic cholinergic (parasympathetic) nerve endings—atropine and related drugs. Site 2 in Fig. 18 (p. 16.1).
2. *Ganglion-blocking* agents. Site 1 in the diagram.
3. *Neuromuscular blocking* agents. Site 5 in the diagram.

It is not known why drugs oppose acetylcholine more at some sites than at others. The above groups are not perfectly separate, for both curare and atropine have weak ganglion-blocking effects.

Atropine and related drugs block the effect of acetylcholine principally at post-ganglionic cholinergic (parasympathetic) endings, site 2 on the diagram 16.1; they also block the direct vasodilator effect of acetylcholine on the blood vessels (i.e. antimuscarinic) and in the central nervous system. Some drugs of this group have a blocking effect at autonomic ganglia also, but none blocks the neuromuscular junction.

The actions of atropine will first be described. Other drugs will be dealt with chiefly in how they differ from atropine. Many anticholinergic drugs have a variety of other actions, e.g. antihistamine, but find a place in therapeutics as anticholinergic agents.

Atropine

Atropine is an alkaloid from the plant Atropa belladonna, the first name of which commemorates its success as a homicidal poison, for it is derived from the senior of the three legendary Fates, Atropos, who cuts with shears the web of life spun and woven by her sisters Clotho and Lachesis (there is a minor synthetic atropine-like drug called lachesine). The term belladonna refers to the once fashionable female practice of using an extract of the plant to dilate the pupils (and incidentally to block ocular accommodation) as part of the process of "making myself attractive."

Atropine acts by competing for the same drug receptors as acetylcholine, occupying them, and thus rendering the acetylcholine ineffectual, i.e. it has the same affinity as acetylcholine but a different intrinsic activity.

In general the peripheral effects of atropine are inhibitory but there is commonly a transient phase of stimulation before the inhibition occurs and in the case of the heart this can have clinical importance. Atropine also blocks the effects of injected cholinergic drugs both peripherally and on the central nervous system. The clinically important actions of atropine are listed below; they are mostly the opposite of the stimulant effects on the parasympathetic system produced by cholinergic drugs.

Actions at parasympathetic post-ganglionic nerve endings

Exocrine glands. All secretions except milk are diminished, and dry mouth is common.

On **gastric secretion:** anticholinergic drugs are capable of reducing the total number of mEq. of HCl secreted to as little as one tenth of the original quantity. But the H^+ concentration (pH) is unaltered. Therefore, in an empty stomach and duodenum there is no change of pH. If food is present, the H^+ concentration can be reduced to about one tenth of what it was, i.e. pH will rise by 1·0 unit, which is unlikely to have much useful clinical effect. Even a 99% reduction of H^+ concentration would alter pH by only 2 units. This probably accounts for the fact that anticholinergic drugs are of little use in treatment of peptic ulcer. Sweating

(sympathetic nerve supply, but cholinergic) is inhibited. Bronchial secretions are reduced and may become viscid, which can be a disadvantage, as removal of secretion by cough and ciliary action is rendered less effective.

Smooth muscle is relaxed. In the gastro-intestinal tract there is reduction of tone and peristalsis. Muscle spasm of the intestinal tract induced by morphine is reduced, but such spasm in the biliary tract is not. Atropine relaxes bronchial muscle and slows micturition, although seldom enough for the patient to notice any change, but urinary retention can occur.

In the eye mydriasis occurs, with a rise in intra-ocular pressure in an eye predisposed to narrow-angle glaucoma (but only rarely in chronic open-angle glaucoma). This is due to the dilated iris blocking drainage of the intra-ocular fluids from the angle of the anterior chamber. An attack of glaucoma may be induced. There is no significant effect on pressure in normal eyes. The ciliary muscle is relaxed and so the eye is accommodated for distant vision. After atropinisation normal pupillary reflexes may not be regained for two weeks, or even more. Atropine is a cause of unequal sized pupils.

Cardiovascular system. Atropine reduces vagal tone, thus increasing the heart rate, and enhancing conduction in the bundle of His, effects which are less marked in the elderly in whom vagal tone is low. Transient initial vagal stimulation, probably in the central nervous system, may be of clinical importance when atropine is given with neostigmine, as when the latter is used to antagonise curare-like drugs. This does not occur in Negroes, a genetic difference. High doses cause ECG changes.

It is generally advised that the atropine be given a few minutes before the negostigmine to avoid the transient summation of the two drugs on the vagus. Atropine has no significant effect on peripheral blood vessels in therapeutic doses, but in poisoning there is marked vasodilatation.

Central nervous system is stimulated by atropine. Restlessness and mental excitement occur with large doses and even mania, delirium and hallucinations. Hyperthermia occurs, made worse by the concurrent prevention of sweating.

Atropine is useful against both tremor and rigidity of Parkinsonism (which see). It prevents or abates motion sickness.

Antagonism to cholinergic drugs. Atropine opposes the effects of all cholinergic drugs on the central nervous system, at post-ganglionic cholinergic synapses and on the peripheral blood vessels. It does not oppose cholinergic effects at the neuromuscular junction or significantly at the autonomic ganglia (i.e. atropine opposes the muscarine-like but not the nicotine-like effects of acetylcholine).

Pharmacokinetics. Atropine is readily absorbed from the alimentary tract and may also be injected by the usual routes. It is little absorbed from mucous membranes, and the occasional cases of atropine poisoning following use of eye drops are due to the solution running down the

lacrimal ducts into the nose and being swallowed, a mishap that occurs especially in children whose parents are liable to use too many drops.

Atropine is mostly destroyed in the liver but some is excreted unchanged by the kidney. Some tolerance occurs. For prolonged use it is usually given three times a day.

The usual **dose** of the sulphate is 0·5 to 1 mg s.c., i.v. or by mouth. For chronic use in Parkinsonism or peptic ulcer it is usually necessary to find the maximum tolerated dose (by increasing the dose until undesirable effects occur and then reducing it slightly) to obtain useful therapeutic result.

Atropine poisoning presents with the more obvious peripheral effects, dry mouth (with dysphagia), mydriasis, blurred vision, hot dry skin, and, in addition, hyperpyrexia, restlessness, anxiety, excitement, hallucinations, delirium, mania and later cerebral depression and coma, or, as it has been described with characteristic American verbal felicity, "hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hen" (*2*). It may occur in children who have eaten berries of solanaceous plants, e.g. deadly nightshade and henbane. When the diagnosis is doubtful it is said to be worth putting a drop of the patient's urine in *one* eye of a cat (the rabbit is less sensitive). Mydriasis, if it results, confirms the diagnosis, but absence of effect proves nothing. The **treatment** of atropine poisoning is on general lines, e.g. a sedative (diazepam, barbiturate) for excitement. But there is evidence that an anticholinesterase drug that enters the CNS may be useful in reversing both the CNS and the peripheral effects. Physostigmine 1 to 4 mg i.v. or i.m. is effective, though it may need repeating as its action (1 to 2 hrs) is shorter than atropine. Neostigmine does not enter the CNS and so is useless.

Other Anticholinergic Drugs

In the accounts which follow, the principal peripheral atropine-like effects of the drugs may be assumed. The points in which they differ from atropine are the main topics.

Hyoscyamine is less active in the central nervous system. Atropine is racemic hyoscyamine, "hyoscyamine" is the lævo form; the dextro form is only feebly active. Atropine is more stable chemically and so is preferred.

Hyoscine (scopolamine) is chemically related to atropine. It differs chiefly in being a central nervous system depressant, although it may sometimes cause excitement. The old are often confused by hyoscine and so it is avoided in their anæsthetic premedication. Mydriasis is briefer than with atropine. The dose is 0·3 to 0·6 mg. s.c. Genoscopolamine is similar to hyoscine.

Atropine methonitrate (Eumydrin) blocks autonomic ganglia as well as having strong peripheral effects, especially on the intestinal tract and salivary secretion. It has been used in the conservative treatment of congenital hypertrophic pyloric stenosis, combined with dietary control, but this tedious treatment has been superseded by surgery. Atropine methonitrate is also advocated as an antitussive in whooping cough on slender evidence.

Hyoscyamus, stramonium and belladonna are crude plant preparations containing hyoscyamine, hyoscine and atropine in varying proportions. At one time Bulgarian belladonna had a high reputation as a remedy in Parkinsonism. It was taken in white wine "after the first sleep" and was part of a system of "cure" which included bathing in water warmed by the sun and sleeping only on the right side. This routine naturally had a marked, but only temporary, success. Bulgarian belladonna was soon shown not to be superior to other forms.

Hyoscine methobromide (Pamine) is longer acting than hyoscine and has negligible central nervous system effects.

Hyoscine butylbromide (Buscopan) also blocks ganglia. It is ineffective orally (unabsorbed) but given i.m. or i.v. it is a potent relaxant of smooth muscle, including the cardia in achalasia, the pyloric antral region and the colon. Radiologists use it for this. It may sometimes be useful for colic.

Homatropine is used for its ocular effects (2% solution as eye drops). Its action is shorter than atropine and therefore less likely to cause serious rise of intra-ocular pressure. Its effects wear off in a day or two. Complete cycloplegia cannot always be obtained unless repeated instillations are made every 15 minutes for 1 to 2 hrs. It is especially unreliable in children, in whom atropine is preferred. The pupillary dilatation may be reversed by physostigmine eye-drops. Derivatives are available for systemic use but offer no important advantages.

Tropicamide (Mydriacyl) and **cyclopentolate** (Mydrilate) are useful (as 0·5 or 1% solutions) for mydriasis and cycloplegia. They are quicker and shorter acting than homatropine. The differences between them are trivial. Mydriasis occurs in 10 to 20 minutes and cycloplegia shortly after. The duration of action is 6 to 12 hrs.

Deptropine (Brontina) (1 mg.) is chemically related to diphenhydramine. It has anticholinergic, antihistamine and antiserotonin effects. It is used in asthma, 1 mg orally, 12-hrly.

Propantheline (Pro-Banthine) is perhaps the best known of a large number of synthetic anticholinergic drugs which have achieved a largely undeserved popularity, especially in the treatment of peptic ulcer. It has marked peripheral atropine-like and weak ganglion-blocking actions, so that, although it can interfere with all autonomic functions its effects are most marked on the parasympathetic division. At *very* high doses it has a curare-like effect at the neuromuscular junction, so it has been shown to be capable of antagonising acetylcholine at all peripheral cholinergic nerve endings. The unwanted effects are what might be expected, dry mouth, blurred vision, constipation and difficult micturition. Postural hypotension and impotence may occur.

Maximum tolerated doses are given. It may be useful in colonic diverticulitis and in irritable bowel syndrome. Any effect on gastric motor activity will be to reduce gastric mixing and to delay emptying, which is theoretically a bad thing in gastric ulcer. On the other hand, since an antacid is emptied at the same rate as the other contents (about half every 20 minutes), propantheline may possibly increase the effectiveness of antacids and prolong the buffering action of food.

Antisecretory activity is discussed in Ch. 21.

Emepronium (Cetiprin) is similar to propantheline. It has been found

useful in reducing bladder motility and increasing bladder capacity in cases of urinary frequency, tenesmus and urgency incontinence.

Many drugs similar to propantheline have been marketed because any really effective and selective parasympathetic-blocking agent might theoretically have some use in treatment of peptic ulcer, but in general they are ineffective under conditions of clinical use. It would be profitless as well as tedious to describe each drug and to enumerate the claims made for it, and so only some of the names will be given here for identification of the type of drug: dicyclomine (Merbentyl), diphemanil (Diphenatil), methanthelinium (Banthine), oxyphenonium (Antrenyl), penthienate (Monodral), tricyclamol (Lergine, Elorine), poldine (Nacton), oxyphencyclimine (Daricon), glycopyrronium (Robinul), isopropamide (Tyrimide).

Other drugs with anticholinergic effects are described under the drug therapy of Parkinsonism. For **poisoning** see under atropine.

Uses of Anticholinergic Drugs

The clinical uses of anticholinergic drugs are legion. For their actions in the central nervous system some (atropine, hyoscine, and numerous synthetic drugs) are used against the rigidity and tremor of *Parkinsonism* in which disease doses higher than the usual therapeutic amounts are often needed and tolerated. They are used as *anti-emetics* (principally hyoscine) and as *sedatives* (hyoscine) in delirium or mania, in obstetrics and in anæsthetic premedication. For their peripheral action they (atropine, homatropine, cyclopentolate) are used in ophthalmology to *dilate the pupil and to paralyse ocular accommodation.* If it is desired only to dilate the pupil, a sympathomimetic (e.g. phenylephrine) is useful. In the *respiratory tract* they (atropine, belladonna, stramonium) are used as bronchodilators, though they are not particularly effective; they also reduce and thicken secretions.

For their actions on the *alimentary tract* a wide range, but chiefly belladonda, atropine and propantheline, are used against gastric secretion and muscle spasm and hypermotility throughout the tract. They are used in ulcerative colitis, and against colic (pain due to spasm of smooth muscle) and to prevent morphine-induced muscle spasm when that analgesic is used against colic.

In the *urinary tract* the drugs (atropine, belladonna, hyoscyamus) are used against muscle spasm accompanying infection in cystitis and against colic.

Hyperhidrosis may be relieved by propantheline. In disorders of the *cardiovascular system* anticholinergic drugs may be useful in attacks of cardiac arrest due to hyperactive carotid sinus reflexes and occasionally in heart-block and in post myocardial infarction bradycardia (atropine), but the initial vagal stimulation is a disadvantage.

In *cholinergic poisoning* atropine is an important antidote against both central nervous, parasympathomimetic and vasodilator effects though it has no effect at the neuromuscular junction and will not prevent voluntary muscle paralysis. It is also used to block autonomic effects when cholinergic

drugs, such as neostigmine, are used for their effect on the neuromuscular junction in myasthenia gravis. This group of drugs can precipitate narrow-angle glaucoma, or urinary retention in the presence of prostatic hypertrophy. In organic pyloric stenosis these drugs may prevent gastric emptying by reducing peristalsis and they may also make œsophageal achalasia worse, but they are used in *infantile pyloric stenosis* and in infantile *colic* (dicyclomine).

Drug Treatment of Parkinsonism

Drugs do not cure, they benefit only for as long as they are given. Therefore the patient need not be put to the trouble of drug therapy until he has a disability sufficient to justify its inconveniences.

The basal ganglia control movement by two balanced systems, one cholinergic, the other dopaminergic, in which the chemical transmitter is dopamine.

In Parkinsonism the dopaminergic system is defective (basal ganglia dopamine concentration has been shown to be low), so that the cholinergic system is dominant.

There are thus two possibilities for restoring the balance: to reduce cholinergic activity (by anticholinergic drugs) or to enhance dopaminergic activity by levodopa, (L-dihydroxyphenylalanine) a precursor of dopamine, or by amantadine. Both of these approaches are useful in therapy and may usefully be combined.

The main symptoms of Parkinsonism that require alleviation are **tremor, rigidity and hypokinesia.**

Anticholinergics can reduce tremor and rigidity (usually incompletely) but do not affect the hypokinesia which is a major cause of disability.

Levodopa can reduce hypokinesia and rigidity substantially and may sometimes benefit tremor.

The introduction of anticholinergics was due to a chance finding, but the introduction of levodopa was the result of biochemical investigation which revealed dopamine deficiency. Levodopa is the single most useful drug in Parkinsonism. It illustrates the importance of research into the causes of disease as a major factor in developing effective treatment. Animal models of Parkinsonism are unsatisfactory.

Levodopa is a precursor of dopamine. Dopamine cannot itself be used because it is poorly lipid soluble, i.e. it is not only poorly absorbed from the gut, but does not usefully penetrate the CNS.

Much of the administered levodopa is quickly converted into dopamine in peripheral tissue (by decarboxylation) so that only a small amount of the levodopa enters the brain to be converted into dopamine (again by decarboxylation) at the site where it is needed. If this conversion into dopamine in the periphery can be prevented then less levodopa need be given as more would enter the brain. This can be achieved by giving a decarboxylase inhibitor (which must, of course, not enter the brain)

along with the levodopa; potential advantages include less nausea and vomiting and easier dose adjustment.

Drug-induced Parkinsonism, by neuroleptics, is benefited by anticholinergics, but not by levodopa or amantadine, probably because the neuroleptics block the dopaminergic receptors.

Treatment. A hindrance to improvement of therapy has been the great variability of the symptoms in any one patient from day to day, so that accurate measurement of drug effects is difficult. However, by using a battery of tests, grip strength, finger-thumb proximation rate, circle drawing, handwriting, time to walk 10 metres and others, as well as observation of the patient's performance in daily living, e.g. washing, dressing, etc., it has been possible to obtain some quantitative estimate of the value of different drugs.

Treatment for a patient with disability may be begun as follows: titrate to the maximum tolerated dose of levodopa: when the patient is stabilized on this, add an anticholinergic (benzhexol, orphenadrine) if necessary and increase this to the maximum tolerated dose. Amantadine is a drug of third choice. Occasionally a psychostimulant (methylphenidate) or a tricyclic antidepressant is useful.

Sudden withdrawal of effective therapy (levodopa or anticholinergic) may result in rapid relapse (i.m. orphenadrine may be needed in the severest cases). If it is desired to change a partially effective drug for one that might be better, the process must be gradual.

Results of treatment. Benefit to idiopathic Parkinsonism is about 15% with anticholinergics and about 65% with levodopa given alone. Combination of the two groups is useful but not fully additive. Post-encephalitic Parkinsonism responds less and patients are liable to be intolerant of levodopa.

Oculogyric and autonomic crises may not need treatment, but if they do the following may be tried; ethopropazine, 250 mg, i.m., or orphenadrine 20 to 40 mg i.m. If salivation is troublesome an anticholinergic drug will stop it. Excessive dryness of the mouth with these drugs can sometimes be usefully countered by a small dose of pilocarpine or by sucking acid sweets, if the dose of the anticholinergic drug cannot be reduced without loss of benefit.

All drugs having anticholinergic effects may aggravate narrow angle glaucoma or cause urinary retention in the presence of an enlarged prostate. Tremor, exacerbated by anxiety, may be helped by sedation or by β-adrenoceptor block where it is socially embarrassing.

Anticholinergics act by blocking acetylcholine in the CNS. Until 1947 natural alkaloids (hyoscine) were the mainstay of therapy. They have since been replaced by synthetic drugs. Data on a few are given in the table.

Overdose with anticholinergics can occur due to accumulation, especially if more than one is used; it may occur very slowly and cause a toxic confusional state that is sometimes misattributed to the disease, and the

physician who withdraws the drugs is the one who gets the patient's gratitude. It can be reversed by physostigmine i.v. or i.m.

DATA ON SOME SYNTHETIC ANTICHOLINERGIC ANTIPARKINSONIAN DRUGS

Name (Tablet size in mg.)	*Principal type of drug action*	*Each oral dose (doses/day in brackets)*	*Remarks*
benzhexol, trihexyphenidyl (Artane, Pipanol) (2)	anticholinergic	2–8 mg. (3)	May cause excitement and mental confusion if dose increased too rapidly.
orphenadrine (Disipal) (50)	anticholinergic antihistamine	50–100 mg. (4)	Chemically closely related to diphenhydramine (Benadryl) but less soporific.
ethopropazine (Lysivane) (50)	anticholinergic	50–125 mg. (2–5)	Chemically related to chlorpromazine. Occasionally causes muscle cramps.
procyclidine (Kemadrin) (5)	anticholinergic antihistamine	2·5–10 mg. (3–4)	High doses can cause mental confusion.
benztropine (Cogentin) (2)	anticholinergic antihistamine	0·5–2 mg. (1–3)	Recommended that a drug with cerebral-stimulant effect (benzhexol, cycrimine, amphetamine) be combined. Also given i.m.

Others which may suit individual patients very well are diphenhydramine (Benadryl), the belladonna group (atropine, hyoscine), promethazine (Phenergan), chlorphenoxamine (Clorevan), phenindamine (Thephorin), biperiden (Akineton), methixene (Tremonil), benapryzine (Brizin).

Levodopa (250, 500 mg)

The initial oral dose is 500 mg/day in doses after food, increasing by increments of 250 mg/day every third day, e.g. 250 mg three and then four or more times a day, then adding to each dose, until the maximum tolerated dose (usually in the range 3 to 6 g total/day) is reached as evidenced by involuntary movements (general restlessness or head, lip or tongue movements or choreoathetosis). If the dose is increased too rapidly nausea will be the limiting factor; it may be helped by cyclizine 50 mg 30 min before food. Other adverse reactions include postural hypotension, psychiatric disturbances, and rarely cardiac dysrhythmias. Increased sexual activity may occur and may or may not be deemed an adverse effect. It is probably due to improved mobility and resulting enthusiasm rather than to a pharmacodynamic effect of levodopa.

Maximum benefit is often delayed for at least a month but useful effects are often seen within a week. Sadly, benefit may decline after about 2 yrs.

Pharmacokinetics. Levodopa is absorbed from the small intestine by active transport; the plasma half-life is about 30 min; it is largely

decarboxylated (by dopa-decarboxylase) to dopamine, which is a substrate for MAO, and which is also converted to noradrenaline by dopamine β–oxidase; there are other metabolic paths; metabolites appear in the urine where they interfere with tests for phæochromocytoma.

Interactions. MAOI: dangerous hypertension may occur: tricyclic antidepressants are safe: reserpine antagonises. Pyridoxine reverses the therapeutic effect of levodopa perhaps by increasing peripheral decarboxylation to dopamine, which cannot penetrate the brain. This antagonism can occur with the doses in tonics that the patient may obtain for himself. It can be a cause of unexplained failure of therapy.

General anæsthesia seems to present no special hazard.

Levodopa—DOPA—decarboxylase inhibitor combinations (see above) are available, e.g. levodopa and carbidopa (Sinemet). Pyridoxine does not antagonize.

Amantadine (100 mg) is an antiviral drug that, given against influenza to a Parkinsonian patient, was found to be beneficial. It may act by increasing dopamine synthesis. It is given orally, 100 mg once a day for 1 week, then 100 mg twice a day. It is not titrated as with levodopa and anticholinergics. Adverse reactions include CNS disturbances (including insomnia and hallucinations) postural hypotension, and livedo reticularis and ankle œdema which may be due to local effects of the drug.

Other involuntary movements (choreas, tics, dystonias, hemiballismus, etc.) are not consistently improved by any drugs. Occasional success in some may be had with tetrabenazine (Nitoman), thiopropazate (Dartalan), haloperidol, levodopa, methyldopa.

Guide to Further Reading

On cholinergic drugs

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b. Carbon dioxide inhalation therapy in neurosis. A controlled clinical trial, page 52.

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Chapter 17

SYMPATHOMIMETICS, ASTHMA, HYPOTENSIVE STATES

As their name implies, the sympathomimetic drugs mimic the effects of stimulation of the sympathetic division of the autonomic nervous system. They include substances which occur naturally in the body:

1. *Adrenaline* (epinephrine) which is the main hormone of the adrenal medulla.
2. *Noradrenaline* (norepinephrine, levarterenol, arterenol) which is the main transmitter at post-ganglionic sympathetic adrenergic nerve endings, but which is also present in small amounts in the adrenal medulla.
3. *Isoprenaline* (isoproterenol, isopropylnoradrenaline) which does not occur in the body.

A large number of related compounds with sympathomimetic effects have been synthesised, but only a few have earned a place in therapeutics. Ephedrine was originally found in a Chinese plant but is now synthesised. The amphetamines are peripheral sympathomimetics but are also important for their effects on the central nervous system.

History. Sir Henry Dale has told of the discovery of the hypertensive effect of adrenaline: "Dr. Oliver . . . was a physician in practice. . . . He appears to have used his family in his experiments, and a young son was the subject of a series, in which Dr. Oliver measured the diameter of the radial artery and observed the effect upon it of injecting extracts of various animal glands under the skin. We may picture Professor Schafer . . . finishing an experiment . . . in which he was recording the arterial pressure of an anæsthetised dog. To him enters Dr. Oliver, with the story of the experiments, and, in particular, with the statement that injection under the skin of a glycerine extract from the calf's suprarenal gland was followed by a definite narrowing of the radial artery. Professor Schafer is said to have been entirely sceptical, and to have attributed the observation to self-delusion. . . . Dr. Oliver, however, is persistent . . . so Professor Schafer makes the injection, expecting a triumphant demonstration of nothing, and finds himself standing 'like some watcher of the skies, when a new planet swims into his ken', watching the mercury rise in the manometer with amazing rapidity and to an astounding height. . . ."*

This discovery led eventually to the isolation and synthesis of adrenaline in the early 1900s. Many related compounds were examined and, in 1910, Barger and Dale invented the word "sympathomimetic" and also

* DALE, H. (1938). *Edin. med. J.*, **45**, 461.

pointed out that noradrenaline mimicked the action of the sympathetic nervous system more closely than did adrenaline. Nevertheless adrenaline was generally thought to be the sympathetic mediator for the next 35 years, partly because noradrenaline was not known to be present in the body, and partly because many of the preparations of "adrenaline" available did in fact contain a substantial amount of noradrenaline. Clarification of the situation had to wait until accurate methods both of identifying adrenaline and noradrenaline and of estimating them separately were found.

Mode of action of sympathomimetic drugs (*1–4, 22, 23*)

Noradrenaline is synthesised and stored at adrenergic nerve terminals and can be released from these stores by stimulating the nerve or by drugs (reserpine, guanethidine, ephedrine, amphetamine). These noradrenaline stores may be replenished by i.v. infusion of noradrenaline, and abolished by cutting the nerve.

Sympathomimetics may be classified thus: those that act—

(*a*) *directly* on the adrenergic receptor (adrenaline, noradrenaline, isoprenaline entirely, and methoxamine and phenylephrine mainly).

(*b*) *indirectly*, by causing a release of noradrenaline from stores at nerve endings (amphetamine, methamphetamine, mephentermine, tyramine).

(*c*) *by both mechanisms* (*a*) and (*b*) above (metaraminol, ephedrine).

It is evident that tachyphylaxis (diminishing response to frequent doses) is particularly to be expected with drugs in group (*b*), and that they are less suitable for use in maintaining blood pressure than drugs of group (*a*).

The interactions of sympathomimetics with other drugs acting on the vascular system are complex. Some drugs prevent the uptake of noradrenaline from the circulation into stores (this may account for the potentiation of the pressor effect of noradrenaline by some hypotensives and tricyclic antidepressants) and some drugs actively deplete the stores (reserpine) and thus block the action of sympathomimetics that act by releasing noradrenaline from stores. It is now evident that the sympathetic system is a lot more complicated than many had previously supposed, and that some drugs will act differently after acute and after prolonged administration, according to whether the noradrenaline stores are depleted or not.

But this is not all. Recently it has been proposed that the sympathetic nerves are in fact cholinergic and that it is acetycholine that causes the release of noradrenaline from the stores at nerve terminals. This hypothesis opens up interesting pharmacological possibilities, but it cannot yet be regarded as proved and is only mentioned here because it could have practical importance in therapeutics and because it is an example of how an accepted physiological mechanism can suddenly be called in question by clever experimentation (*4*).

Actions of sympathomimetics

Many sympathomimetics are racemic compounds and one form is

commonly much more active: for instance lævo-noradrenaline is at least 50 times as active as the dextro form.

For 46 years, until 1958, it was known that the peripheral motor (vasoconstriction) effects of adrenaline were preventable and that the peripheral inhibitory (vasodilatation) and the cardiac stimulant actions were not preventable by the available antagonists (ergot alkaloids, phenoxybenzamine).

In 1948 Ahlquist introduced a hypothesis to account for this. He proposed two different adrenergic receptors (α-and β). For a further ten years, only antagonists of α-receptor effects (α-adrenoceptor block) were known, but in 1958 the first substance to selectively and competitively prevent β-receptor effects (β-adrenoceptor blocker), dichloroisoprenaline, was discovered. However, it was unsuitable for clinical use and it was not until 1962 that the first reasonably satisfactory β-adrenoceptor blocker (pronethalol) was introduced to medicine. Unfortunately it proved to be carcinogenic in mice (but not in rats) and was soon replaced by propranolol (Inderal).

The clinically important aspects of this classification are as follows:

α-**Effects** (α-**Receptor**)	β-**Effects** ($\beta_1 + \beta_2$ **Receptors**)
	Heart (β_1 receptor) *increased:* 1. *contractility* (muscle) 2. *rate* (S-A node) 3. *conduction velocity* 4. *decreased refractory period*
Vasoconstriction chiefly in skin, viscera	**Vasodilatation** (β_2 receptor) chiefly in muscles
Mydriasis	**Bronchial relaxation** (β_2 receptor) **Uterine relaxation** (β_2 receptor)

In the intestine both α-and β-receptors mediate relaxation. Metabolic effects (hyperglycæmia, lacticacidæmia, increase in blood free fatty acids) also do not fall clearly into a simple α-and β classification; but it seems that glycogenolysis in liver is an α-effect and in muscle it is a β-effect. Diabetics treated with a β-adrenoceptor blocker have become hypoglycæmic unaware, for the symptoms of hypoglycæmia (which are largely due to sympathetic discharge) are also suppressed, e.g. palpitations.

The principal clinically useful antagonists (see ch 18) are:

α-adrenoceptor blocking drugs—phentolamine, phenoxybenzamine, thymoxamine.

β-adrenoceptor blocking drugs—propranolol, practolol, alprenolol, oxprenolol.

The principal agonists are adrenaline, noradrenaline and isoprenaline etc. Their effects differ according to their selectivity for α- or β-receptors.

Comparison of Noradrenaline, Adrenaline and Isoprenaline

Effect on	*Noradrenaline*	*Adrenaline*	*Isoprenaline*
Heart:			
(*a*) rate	*slowed* (reflexly due to B.P. rise)	*increased* (direct action)	*increased* (direct action)
(*b*) force of mycardial contraction	little effect	increased (direct action) "palpitations" due to *a* + *b*	increased (direct action) "palpitations" due to *a* + *b*
(*c*) cardiac output (stroke)	insignificant or reduced	increased	increased
(*d*) excitability, conductivity	increased	much increased	much increased
Blood pressure:			
(*a*) systolic	rises	rises (due to *b* and *c* above)	little change, or may fall
(*b*) diastolic	rises	falls (due to *a* below)	falls
Vascular beds in:			
(*a*) muscle	Usually constricted	dilated	dilated
(*b*) skin & viscera	constricted	constricted	dilated
(*c*) heart	? dilated	dilated	dilated
Total peripheral resistance	*increased*	*decreased*	*decreased*
Metabolism: O_2 consumption, liberation of glucose	insignificant	increased	none
Central nervous system	insignificant	stimulation: feelings of fear and anxiety, respiration increased, tremor	stimulation
Smooth muscle:			
(*a*) bronchi	little effect	relaxed	relaxed
(*b*) intestine and bladder	relaxed	relaxed	relaxed
(*c*) sphincters	constricted	constricted	constricted
(*d*) uterus (pregnant)	stimulated	usually inhibited	inhibited
Capillary permeability	little effect	reduced	?

The above are approximations. Responses are much influenced by dose and by ratios of α-and β-receptors in tissues.

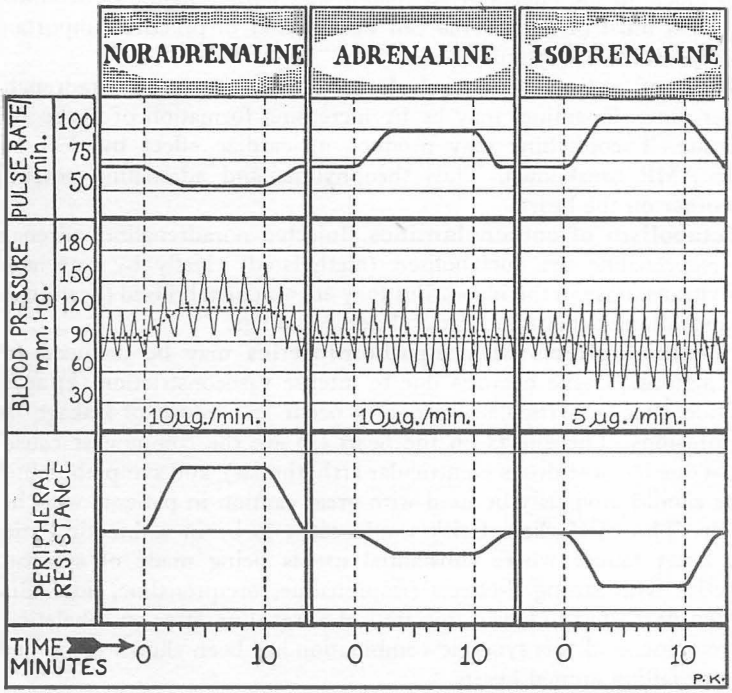

FIG. 20. Cardiovascular effects of noradrenaline, adrenaline and isoprenaline; pulse rate/min., blood pressure in mm. Hg. (dotted line is mean pressure), peripheral resistance in arbitrary units. *By permission after Ginsburg, J., and Cobbold, A. F., Adrenergic Mechanisms, ed. Vane, J. R., et al. London: Churchill,* 1960.

Adrenaline has both α- and β-effects and is useful in asthma (β-effect on bronchi) and in anaphylactic shock (β-effect on heart; α- and β- on peripheral vessels; β-effect on bronchi).

Noradrenaline has predominantly α-effects and is used to raise the blood pressure (α-effect on arterioles; slight β-effect on heart).

Isoprenaline has predominantly β-effects and is useful in asthma (β-effect on bronchi) and, rarely, for its powerful effect on the heart, in heart block (β-effect on conducting tissue).

The overall effect also depends on the dose, for instance adrenaline ordinarily dilates muscle blood vessels (β) (mainly arterioles, but veins also) but in very large doses constricts them (α). The actions described in the table are those of doses used in therapeutics or of amounts ordinarily liberated in the body. The end results are often complex and unpredictable, partly because of the variability of homeostatic reflex responses and partly because what is observed (e.g. a change in blood pressure) is the result of many factors [e.g. vasodilatation (β) in some areas, vasoconstriction (α) in others, and cardiac stimulation (β)].

To block all the effects of adrenaline and noradrenaline both kinds of antagonist must be used. This can be a matter of practical importance, e.g. in phæochromocytoma.

Mode of action of catecholamines* (adrenaline, noradrenaline, isoprenaline, dopamine) may be by increasing formation of cyclic AMP in tissue. Theophylline may produce its cardiac effect by decreasing cyclic AMP breakdown. Thus theophylline and adrenaline potentiate each other on the heart.

Metabolism of catecholamines. Injected noradrenaline, adrenaline and isoprenaline are metabolised (methylated) chiefly by catechol-O-methyltransferase in the blood. But they are also metabolised (deaminated) by monoamine oxidase in liver and nerve endings.

Unwanted effects of sympathomimetics may be deduced from their actions. Tissue necrosis due to intense vasoconstriction (α) around injection sites is particularly prone to occur as a result of leakage from i.v. infusions. The effects on the heart (β) are the commonest cause of deaths due to these drugs (ventricular arrhythmias), and sympathomimetic drugs should obviously be used with great caution in patients with heart disease. The chief clinical risk would seem to be in asthmatic patients with heart failure where substantial use is being made of sympathomimetics with strong β-effects (isoprenaline, orciprenaline, adrenaline). Sudden death has followed injection of adrenaline after an inhalation of isoprenaline, and this synergic combination has been shown to be highly toxic to failing animal hearts.

Sympathomimetics are particularly likely to cause cardiac arrhythmias (β) in patients under chloroform, trichloroethylene or halothane anæsthesia. The effect of the sympathomimetic drugs on the pregnant uterus is variable and difficult to predict, but serious fetal distress can occur, due to reduced placental blood flow as a result both of contraction of the uterine muscle (α) and arterial constriction (α). β-stimulants are used to relax the uterus in premature labour, but unwanted cardiovascular actions can be troublesome.

Only about 2% of circulating adrenaline or noradrenaline is excreted unchanged in the urine, but this is enough to be useful in the diagnosis of phæchromocytoma. The estimation of the breakdown product, vanilyl mandelic acid (VMA) in the urine is also useful.

Administration (see also under individual drugs). Adrenaline and noradrenaline are not given by mouth because most is destroyed in the alimentary tract and what is absorbed is metabolised by the liver, so that insignificant amounts enter the general circulation. Ephedrine and the amphetamines however are not metabolised so fast by the liver, and are effective orally. Isoprenaline is rapidly metabolised by the liver, but is quite well absorbed from mucous membranes, partly because it does not have the vasoconstrictor effects of other sympathomimetics: it can be given as tablets to be dissolved under the tongue for brief effect. However,

* Catechol = a benzene ring with two hydroxyl groups.

a large dose in a sustained release form, swallowed, can be used for prolonged effect.

Individual sympathomimetics

Adrenaline (both α-and β effects) is mainly used as a bronchodilator and in the treatment of allergic reactions. It stabilises cell membrane and prevents release of active substances. It is not given i.v., except as a last resort, e.g. in anaphylactic shock, because of the risk of cardiac arrhythmias, but is given s.c. or i.m., care being taken that the needle is not in a vein. Local constriction of vessels is produced, which slows absorption and so prolongs and smoothes out the effects. Nevertheless, it is generally given in small, often-repeated doses (0·1 ml of Adrenaline Inj. B.P., a 1 : 1,000 solution). An alternative is to give 0·5 ml s.c. at the outset. Generally, 2 ml in 5 min should be regarded as maximal. It can be exceeded, but palpitations, extra-systoles and hypertension will occur. A depôt preparation in oil can be given i.m. for prolonged action, as in asthma. Rarely, its use has been followed by local gas gangrene, presumably due to introduction of Cl. welchii (a normal inhabitant of buttock skin) into an area of muscle anoxic due to intense local vasoconstriction† (high concentrations of adrenaline do not dilate muscle vessels). It is doubtful whether this preparation is essential in therapeutics. Adrenaline mucate s.c. is an alternative; it acts for 8 hrs.

The vasoconstrictor effect is also used when adrenaline (1 : 80,000 or weaker) is added to local anæsthetics to prolong their effects (noradrenaline at the same strength is less effective). A stronger solution of adrenaline (1%) is often used by oral inhalation in bronchial asthma. Enough can be absorbed to have significant systemic effects. The main action in asthma is to relax the bronchial muscle, but the airway may be slightly improved by vasoconstriction and reduction of capillary permeability which reduce the swelling of the bronchial mucous membranes. Intracardiac injection of adrenaline is used in cardiac arrest; even though ventricular fibrillation may be provoked, for this can often be converted to normal rhythm with an electrical defibrillator. The metabolic effects of adrenaline are not essential in therapeutics, but it can be given in insulin hypoglycæmia to mobilise liver glycogen if an i.v. preparation of glucose is not available. Thyrotoxic patients are intolerant to adrenaline and asthmatic patients sometimes become tolerant to it and develop an emotional dependence. Adrenaline eye drops can lower intraocular pressure in glaucoma.

Accidental overdose with adrenaline occurs occasionally. It is rationally treated by propranolol to block the cardiac β-effects (cardiac arrhythmia) and phentolamine to control the α-effects on the peripheral circulation that will be prominent when the β-effects are abolished. Antihypertensives of other kinds are plainly irrational and may even potentiate the adrenaline.

Noradrenaline (chiefly α-effects). The main effect of noradrenaline is to raise the blood pressure by constricting the arterioles and so raising

† Editorial (1961). *Brit. med. J.*, **1**, 730.

the total peripheral resistance, though it does have slight cardiac stimulant (β) effect. This is its principal use in therapeutics. Noradrenaline is always given by i.v. infusion to obtain a gradual sustained response; the effect of a single i.v. injection would last only a minute or so.

It is available in ampoules of solution containing 1 mg./ml. of base and these are diluted (usually 4 ml./litre) in whatever fluid for i.v. infusion seems suitable, the usual dose range is 2 to 4 mcg/minute (approximately 15 to 30 drops/minute) but the rate is always adjusted according to the response. After a few hours the solution will have significantly lost potency (0·5 g. ascorbic acid/litre will delay this). Blood pressure must be taken at 5-minute intervals, and more frequently at the beginning of the infusion. Gangrene of the extremities may follow prolonged infusions and necrotic ulceration of large areas round the infusion vein can occur, for even if the needle does not slip out of the vein, some will leak out. The risk of gangrene can be minimised by using a large vein and rapid flow of dilute solution for the shortest possible time. If an extravasation is detected, the α-adrenoceptor blocking agent phentolamine (5 mg. diluted), should be injected into the area. If an infusion of noradrenaline is given for many hours some blood vessels may cease to respond, and the blood pressure may fall, so that the dose has to be increased even though some vessels at the periphery may be so constricted that gangrene begins.

Noradrenaline infusions should be stopped gradually because their sudden cessation may be followed by a catastrophic fall in the blood pressure. Many explanations have been put forward both for this and for the development of tolerance, but none is established. However, it does seem that, if it is necessary to oppose this fall with a drug, it would be wise to choose neither noradrenaline nor a drug which acts like it (phenylephrine), but a drug which acts at least partly by discharging stored noradrenaline (ephedrine, mephentermine) (*23*). The difficulties and dangers, including cardiac arrhythmias, of noradrenaline infusions are undoubted, and the benefits obtained from them in, for instance, hypotensive states may be questioned: they should be avoided whenever possible. It is not known whether the transient rise of serum potassium that occurs at the beginning of an infusion has practical importance. Noradrenaline is used with injected local anæsthetics (1 : 80,000 or weaker).

Isoprenaline (isoproterenol, isopropylnoradrenaline) (10 mg) (chiefly β-effects) relaxes smooth muscle, including that of the blood vessels, has negligible metabolic or vasoconstrictor effects, but has a vigorous stimulant (β) effect on the heart. This latter is its main disadvantage in the treatment of bronchial asthma and virtually precludes injection except in complete heart block. It is given as tablets, to be dissolved under the tongue (10 to 20 mg), and repeated as necessary, or as a sustained release preparation (Saventrine), to be swallowed. In asthma an oral spray (1%) or aerosol is often used and is more effective than sublingual tablets. Benefit begins in 30 seconds, is maximal in 5 min and disappears in about 1 hr. *Unwanted effects* to be expected of a β-adrenoceptor stimulant include tachycardia, palpitations and tremor. See also *isoxsuprine*.

Orciprenaline, salbutamol, isoetharine and terbutaline are β-adrenoceptor stimulants that are longer acting than isoprenaline probably because they are not substrates for catechol-O-methyltransferase which methylates catecholamines. Orciprenaline stimulates β_1 and β_2 receptors about equally, like isoprenaline, but *salbutamol, isoetharine and terbutaline are relatively selective for* β_2*-adrenoceptors* so that unwanted cardiac effects are less likely to occur, though they can still be serious.

Orciprenaline (Alupent) (20 mg) is active when swallowed (20 mg 6-hrly) and also by inhalation.

Salbutamol (Ventolin) (2 mg) is taken orally 2 to 4 mg up to 4 times/day. It is also useful by inhalation.

Isoetharine (Numotac) (10 mg) is formulated in a plastic slow release matrix and is effective orally 10 to 20 mg up to four times/day.

Terbutaline (Bricanyl) (5 mg) is taken orally 2·5 to 5 mg up to 3 times/day; it may also be injected s.c. or used as an ærosol.

Ephedrine (30 mg.) is chemically similar to adrenaline and has many similar pharmacological effects, but it has a relatively greater stimulant effect on the central nervous system in adults, producing alertness, anxiety, insomnia, tremor and nausea. Children may be sleepy when taking it. In practice central effects limit its use as a sympathomimetic.

Ephedrine is well absorbed when given by mouth and unlike most other sympathomimetics is not much destroyed by the liver; it is largely excreted unchanged by the kidney. It is usually given by mouth but can be injected. It differs from adrenaline principally in that its effects come on more slowly and last longer. Tachyphylaxis occurs, probably because it acts by discharging noradrenaline from stores, which it exhausts.

Ephedrine can be used as a bronchodilator, in heart block, as a mydriatic and as a mucosal vasoconstrictor, but it is being displaced by newer drugs which are often better for these purposes. It sometimes is useful in myasthenia gravis (which see).

Amphetamine (Benzedrine) (5 mg) (see also index) is seldom used for its peripheral effects, which are similar to those of ephedrine, but usually for its effects on the central nervous system on which it is relatively more active, producing cortical arousal. The solid is volatile and used to be available, as the Benzedrine Inhaler, for nasal congestion, but seekers after illicit drugs found this such a useful source (*8*) that the manufacturers substituted instead prophylhexedrine (Benzedrex) which is as good a decongestant (vasoconstrictor) but which has virtually no central nervous system effects.

Excretion is enhanced in an acid urine.

Severe amphetamine poisoning may be treated by chlorpromazine which antagonises both central and peripheral stimulant effects.

Methylamphetamine (Methedrine) is sometimes used to raise the blood pressure (10 to 30 mg i.v. or i.m.) but it has as much central stimulating effect as amphetamine and this may be undesirable, though it has been used in psychiatry for abreaction.

Phenylephrine (Neophryn) has actions qualitatively similar to noradrenaline but has a longer duration of action, up to an hour or so, and slow i.v. injections rather than infusions are given. 0·5 mg i.v. is the usual dose to raise the blood pressure, but 5 mg is sometimes given s.c. It can be used as a nasal decongestant (0·25 to 0·5% solution), but sometimes irritates. In the doses usually given, the central nervous effects are minimal, as are the direct effects on the heart. It is also used as a mydriatic and briefly lowers intraocular pressure.

Other members of this group include hydroxyamphetamine (Paredrinex), methoxyphenamine (Orthoxine), naphazoline (Privine), phenylpropanolamine (Propadrin), tuaminoheptane (Tuamine), tetrahydrozoline (Tyzanol), xylometazoline (Otrivine), oxymetazoline (Hazol), isoxsuprine (Duvalidan), cyclopentamine (Clopane).

SOME SYMPATHOMIMETIC DRUGS USED AS MUSCOSAL VASOCONSTRICTORS OR TO RAISE THE BLOOD PRESSURE

Drug	*Uses*	*Dose*	*Remarks*
methoxamine (Vasoxine, Vasylox)	vasopressor nasal decongestant	5–20 mg. 0·25%	like phenylephrine; negligible or no cardiac effect
mephentermine (Mephine, Wyamine)	vasopressor nasal decongestant	10–30 mg. 0·5%	like methylamphetamine, but with less CNS effects
metaraminol (Aramine)	nasal decongestant vasopressor	0·25–0·5% 2–10 mg.	like ephedrine, but more cardiac stimulation

The more important members are described in the text. When these drugs are used to raise the blood pressure the lower dose may be given by slow i.v. injection, repeated as necessary, or the higher doses may be given i.m. There is little to choose between them. The doses given are those of the commonly used salts.

Nasal Decongestants

Nasal decongestants (vasoconstrictors) are widely used in allergic rhinitis, colds and sinusitis, and to prevent otitic barotrauma, as nasal drops or as sprays to be sniffed. The latter reach a greater area of the mucous membrane. All the sympathomimetic vasoconstrictors, i.e. with α-effects, have been used for the purpose, with or without an antihistamine, and there is little to choose between them, see above. If used more often than 3-hrly and for above 3 weeks the mucous membrane is likely to be damaged. The occurrence of rebound congestion or allergic reaction is liable to lead to overuse. The least objectionable drugs are ephedrine 0·5% and xylometazoline 0·1% (Otrivine). Naphazoline and adrenaline should not be used, and nor should blunderbuss mixtures of vasoconstrictor, antihistamine, adrenal steroid and antibiotics. Oily drops and sprays may enter the lungs and eventually cause lipoid pneumonia.

It may sometimes be better to give the drugs orally rather than up the nose.

Drug Treatment of Bronchial Asthma (*10–21, 25–27*)

Drugs comprise only part of the treatment of bronchial asthma. Psychological and immunological factors are very important though difficult to alter; infection may be a precipitating cause or complication and requires appropriate chemotherapy. The responsible antigen-antibody reaction liberates pharmacologically active substances, including histamine, near the bronchial muscle and these make it contract; the mucosa may become œdematous, further reducing the airway, and the bronchial secretion is sticky and hard to dislodge. This results in bronchial plugging which not only prevents access of inhaled drug to the periphery, but is itself an important factor in the ventilatory insufficiency. It is a reason why bronchodilators can fail to give full relief. **Possible lines of treatment** therefore include—

1. *Prevention of the antigen-antibody reaction* either by hyposensitisation (chiefly effective in pollen or house dust mite asthma) or avoidance of the antigen, if this is known.
2. *Non-specific reduction of the response to the antigen-antibody reaction* by the use of sodium cromoglycate or adrenal steroid.
3. *Drugs which specifically antagonise substances liberated in the antigen-antibody reaction.* So far only the antihistamines have been much used and they are ineffective in asthma.
4. *Anticholinergic drugs* which block the parasympathetic motor nerve endings on the bronchial muscle; these are not often useful, and tend to thicken bronchial secretion unduly.
5. *Drugs which act directly on the smooth muscle of the bronchi* to relax it. This is the most important group and includes the sympathomimetics with pronounced β effects, such as adrenaline, isoprenaline, salbutamol, and theophylline derivatives such as aminophylline and choline theophyllinate.
6. *Production of bronchial mucosal vasoconstriction* by oral sprays (adrenaline, not isoprenaline) is probably not important in therapy.

A fine mist, or *aerosol*, is needed if the droplets are to penetrate to the smallest bronchi. *Severe asthma reduces the efficacy of all inhaled drugs*, of cromoglycate as well as of β_2-adrenoceptor stimulants, due to reduced delivery of drug to the bronchi.

Drugs used in asthma have been described, except sodium cromoglycate.

Sodium cromoglycate (Intal) is *not* a sympathomimetic drug. It probably acts on the mast cell membrane, stabilising it and thus preventing the release of bronchoconstrictor substances (histamine, SRS-A) that ordinarily results from the combination of antigen with antibody. It is ineffective unless present before the antigen challenge occurs, so that it is useful to *prevent* asthmatic attacks. But it is not effective in

terminating an existing attack since it does not antagonise the bronchoconstrictor effect of the active substances once they have been released.

Cromoglycate does not interfere with the actual antigen-antibody combination, but only with the tissue consequences of this combination. Hyposensitisation procedures are not blocked by cromoglycate. With this mode of action it is clear that cromoglycate is chiefly of value in extrinsic (allergic) asthma. But it has also been shown to benefit some patients whose asthma is made worse by exercise or hyperventilation. Therefore its effect in stabilising most cells against disruption due to antigen-antibody combination is not its sole action.

Cromoglycate has also been found useful in *allergic rhinitis* and may be worth trying in allergic alveolitis.

Cromoglycate is given as a powder by inhalation and since the inhalation of a powder can itself induce bronchospasm the drug can be had either plain (Intal Spincap) or, for those suffering this effect, formulated with isoprenaline (Intal Compound). A special inhaler (Spinhaler) is required. The dose is one 20 mg capsule (of which only 1 to 2 mg reach the small bronchi) every 3 to 12 hrs. Some patients derive great benefit; most are usefully affected. Sometimes benefit is delayed for several weeks, and it commonly persists for some days after regular treatment is stopped.

Sodium cromoglycate provides an indirect benefit in that it may reduce the necessity to use adrenocortical steroid and so reduce the hazards of prolonged steroid therapy.

A special formulation (Rynacrom) is used for allergic rhinitis.

Sodium cromoglycate does not alter the use of bronchodilator drugs for acute asthmatic episodes.

Assessment of therapy in asthma. It is necessary to use serial measurements by the simpler respiratory function tests such as forced expiratory volume, peak expiratory flow, vital capacity (which can be easily performed on outpatients) if maximum benefit for the patient is to be achieved. Neither the patients' feelings nor ordinary physical examination are sufficient to determine whether there is still room for improvement with drugs.

"The effort that has to be made to force air through small tubes decreases in proportion to the fourth power of their radius. This explains why even a very slight increase in the bore of the bronchioles gives such welcome relief to a distressed patient."*

Treatment naturally varies with the severity and type of asthma, but may be summarised.

For constant and intermittent asthma: a *β_2-adrenoceptor stimulant* orally, adjusted to suit the pattern of the patient's symptoms as necessary. Suitable drugs include salbutamol, and orciprenaline. *Theophylline*

* WADE, O. L. (1964). *Prescr. J.*, **4**, 48.

derivatives orally are generally disappointing but may help some patients; suppositories at night can be useful; a hypnotic may be needed to counter insomnia due to CNS stimulation.

Sodium cromoglycate is useful in extrinsic asthma but may also be helpful in other forms.

To abort exacerbations a β_2-stimulant aerosol, e.g. salbutamol, can be used. Some aerosols contain an anticholinergic to prolong the effect, but this thickens mucus.

For more severe relapses short courses of adrenal steroid may be used thus: days 1 and 2, 20 mg prednisolone a day; days 3 and 4, 15 mg a day; days 5 and 6, 10 mg a day; day 7, 5 mg.

Chest infections increase reversible airways resistance and should be treated vigorously. The requirement of β_2-stimulant may increase.

Long-term *oral* therapy with *adrenal steroids* is used only when all else has failed in patients who relapse repeatedly into status asthmaticus or who are too disabled to lead a reasonably normal working life. Therapy may begin with a substantial dose, say 60 mg prednisolone orally a day total, and reducing it as soon as feasible to a maintenance dose of 10 mg a day, at which dose the complications of steroid therapy are uncommon. If relapses occur, as they may, the dose may be increased to 30 mg for one day, after which it is reduced by 5 mg a day until the maintenance dose is regained.

If adrenal steroid therapy has lasted more than six months, great caution is required during withdrawal because of a risk of catastrophic relapse. Enzyme induction, e.g. by barbiturate can reduce the effect of a steroid by increasing its metabolism.

Sometimes corticotrophin is effective where a steroid fails; it is preferred in children to avoid growth suppression.

Inhalation of a corticosteroid can control asthma by a local effect on the bronchi without using a dose large enough to cause adrenal suppression; *beclomethasone* is used because it is poorly absorbed from the gut and most of an inhaled dose is, in fact, swallowed; where effective it is plainly preferable to an oral steroid. Secondary candidiasis (mouth and throat chiefly) can occur. Relapses of asthma or lung infection may prevent treatment by inhalation just when it is most needed.

In status asthmaticus, a serious medical emergency, early vigorous treatment is important, for the bronchi may become refractory to β-stimulants (refractory to one means refractory to all) after about 36 hrs, perhaps the result of respiratory acidosis. Full doses of inhaled or injected β-stimulants are tried first and if relief does not occur by the time cardiac stimulation is obvious there should be no hesitation in using an adrenal steroid. Hydrocortisone (100 mg) can be given i.v., but benefit is seldom seen before 8 hrs. It therefore offers no advantage, and therapy may be begun with oral prednisolone (20 mg 4-hrly), which should be reduced as soon as the patient's condition permits, see above; but it may need to be continued for 2 or 3 weeks. Aminophylline i.v. (see *interactions* below) may

be tried, but if there has been no response to β-stimulant in ***full*** doses, it is unlikely to do much good. The dose is 5 to 6 mg/kg i.v. over 15 to 30 min followed by 0·9 mg/kg/hr (*37*).

Whilst waiting for the steroid to act, attention may be given to ensuring that the patient is well oxygenated (*humidified* O_2), which will often reduce some of the distress of his dyspnœa. Excessive bronchial mucus secretion adds significantly to the degree of respiratory obstruction; dehydration thickens mucus and should be remedied by i.v. fluid if necessary. Atropine reduces, but thickens secretion. Severe cases may need assisted respiration or bronchial lavage, but these special techniques are beyond the scope of this book.

Sedation in severe asthma. These patients are anoxic whilst exerting maximum respiratory effort so that any diminution of respiratory drive due to depression of the respiratory centre may lead to serious underventilation. Opiates (morphine) are contraindicated, as a small dose may stop breathing altogether, and barbiturates are also risky.

The least dangerous sedatives and hypnotics are probably diazepam, nitrazepam, chloral derivatives and promethazine. But any sedation that will ensure sleep in a severe asthmatic may suppress cough and respiration undesirably. Chlorpromazine may be used and there is some evidence that α-adrenoceptor block (one of its actions) may be useful in asthma.

Asthma may be precipitated by histamine (which now has no use in medicine), and β-adrenoceptor block (since this is competitive it may be overcome with a sufficient dose of a β-stimulant; the heart is protected and the dose can be monitored by its effect on heart rate). Aminophylline is not blocked by a β-blocker.

Interactions. A patient in a severe attack, who has been taking large amounts of β-adrenoceptor stimulants in an effort to stop it may have absorbed enough to cause substantial cardiac stimulation. Further drugs with cardiac effects (adrenaline, aminophylline) may summate dangerously if given in full doses or rapidly i.v.

Deaths from asthma in the young

In the mid-1960's there was an epidemic of sudden deaths in young asthmatics. It was associated with the introduction of high-dose β-stimulant metered aerosols and did not occur in countries where these high concentrations were not marketed.* The epidemic declined in Britain when the profession were warned and the aerosols were restricted to prescription only.

Though the relation between the use of β-stimulants and death is inescapable, the actual mechanism of death is uncertain; overdose causing cardiac arrhythmia is not the sole factor.

*Stolley, P. D. (1972). *Amer., Rev, Resp. Dis.*, **105**, 883.

DRUGS IN HYPOTENSIVE STATES (*28–33*)

The term "shock" is avoided here because there can be shock with normal blood pressure and because the use of vasopressor drugs is not the most important aspect of its treatment, which may be summarised:

1. *Treatment of the cause:* pain, wounds, infections, adrenocortical deficiency
2. *Replacement of any fluid lost* from the circulation; but extra fluid is dangerous when the primary fault is in the heart or pulmonary circulation.
3. *Maintenance of the diastolic blood pressure and perfusion of vital organs* (brain, heart, kidneys).

Hypotensive states may be due to:

1. Reduced cardiac output (damage to heart: reduced venous return).
2. Reduced peripheral resistance.
3. A mixture of 1 and 2.

Blood flow rather than blood pressure is of the greatest immediate importance for the function of vital organs. But a reasonable blood pressure is needed to render the blood flow independent of the effects of gravity and to provide coronary perfusion and pressure for secretion of urine.

Hypotension due to *low peripheral resistance* is of little importance if the patient is horizontal or tilted head down, for venous return to the heart, and so the cardiac output, are then maintained, and blood flow to brain, myocardium and kidneys remains adequate until the diastolic pressure falls below about 40 mm. Hg. But *low cardiac output* is always of serious significance even though compensatory vasoconstriction maintains the arterial pressure, for blood flow is reduced.

The decision how to treat hypotensive states depends on assessment of the pathophysiology, whether cardiac output, and so peripheral blood flow, is inadequate (low pulse volume, cold constricted periphery), or whether cardiac output is normal and peripheral blood flow is adequate (good pulse volume and warm dilated periphery).

In hypnotic drug poisoning, the principal cause of hypotension is low peripheral resistance due to sympathetic block. The cardiac output can be restored by tilting the patient head down and by increasing the venous filling pressure by cautiously expanding the blood volume with plasma.

This is particularly necessary if the patient is on a respirator, due to the circulatory effects of the intermittent increased intrathoracic pressure (similar to Valsalva's manoeuvre), which reduces cardiac filling.

Use of vasopressor drugs is unnecessary and may be harmful. They do not reproduce the pattern of the missing sympathetic (neurogenic) vasoconstriction and are particularly liable to reduce renal blood flow.

In **central circulatory failure** (acute cardiac damage, e.g. myocardial infarction) the cardiac output is low due to loss of pumping power. Venous return (central venous pressure) is normal or high. The low blood pressure

may set in motion the sympathoadrenal mechanisms of peripheral circulatory failure summarised below.

Not surprisingly, the use of drugs in low output failure due to acute myocardial damage is disappointing. Vasoconstriction, by increasing peripheral resistance, may raise the blood pressure, but it can further reduce cardiac output.

But if there is bradycardia (as there sometimes is in myocardial infarction), this factor in reduced minute output can be eliminated by vagal block with atropine.

Digitalis may be used to increase cardiac output. Vasopressor drugs are only used in extreme circumstances.

In the case of **pulmonary artery embolus** there is theoretical benefit to be derived from a vasoconstrictor. The output of the right ventricle, and so the volume of blood going to the left ventricle, is reduced and as a result the coronary blood flow to both ventricles falls. The right ventricle is therefore doing more work, against the obstructed pulmonary artery, with less oxygen supply to its muscle. If the peripheral resistance is raised by giving vasoconstrictors (e.g. noradrenaline) the diastolic pressure in the aorta will rise and with higher perfusion pressure the coronary flow may improve, and may benefit the overworked right ventricle. See also *Fibrinolytic therapy*.

In **mesenteric infarction,** animal experiments suggest that vasoconstrictor drugs may aggravate intestinal ischæmia.

In **peripheral circulatory failure** due to, for example, severe Gram-negative septicæmia, the cardiac output is low due to sequestration of blood in the abdominal viscera and lungs. First there is a peripheral vasodilatation with fall in arterial pressure. This initiates a vigorous sympathetic discharge that causes constriction of arterioles and venules. There is then a progressive peripheral anoxia and acidosis. The arterioles dilate, but the venules do not so that blood is sequestrated in the periphery and *effective* circulatory volume falls.

The immediate aim of treatment is to restore cardiac output by increasing venous return to the heart. This can be done by increasing intravascular volume (plasma transfusion), keeping a close watch on central venous pressure to avoid overloading the heart, and by tilting the patient head down. Oxygen is useful as there is often irregular pulmonary perfusion.

In addition a vasodilator drug may allow the release of the sequestered blood, and α-adrenoceptor blockers (e.g. phenoxybenzamine) have been used for this.

Unfortunately the blood is liable to stay sequestered despite reduction of the obstructive venular constriction. Administration of a vasodilator drug to a patient with a low blood volume is, of course, disastrous.

Drugs that increase peripheral resistance (sympathomimetics with α-effects and angiotensin) are likely only to make matters worse by further reducing blood flow to vital organs, in the event of the resistance vessels

(arterioles) retaining their reactivity and responding to them, which they may not do. Sympathomimetics that both stimulate the heart (β-effect) as well as inducing vasoconstriction (α-effect) e.g. metaraminol, adrenaline, are unlikely to have more than a marginally useful effect and should only be used where there seems to be no alternative.

A pure β-adrenoceptor stimulant (isoprenaline) may both dilate the constricted vessels and stimulate the heart usefully, and it has been used; cardiac arrhythmias are a risk and the ECG should be monitored.

The position has been summed up: "it is possible to find plenty of experimental support for the use of noradrenaline and other vasoconstrictors, but equally good support for adrenergic blocking drugs with a dilator action. It seems impossible for both approaches to be right, but quite possible for both to be wrong."*

There is evidence from animal experiments that very large doses of an adrenal steroid may do good. Probably the least unsatisfactory course is to adjust central venous filling pressure so that cardiac output increases, by infusion of fluid (with continuous central venous pressure measurement) and to give an adrenocortical steroid (e.g. dexamethasone 2 to 6 mg/kg i.v. as a single injection, not a slow infusion); ordinary doses are useless; they must be big. If the peripheral circulatory failure is due to infection, effective antimicrobial therapy is more likely to save the patient than are any other drugs.

Hypotension in patients with atherosclerosis (occlusive vascular disease) is more serious than in others, for they are specially dependent on pressure to perfuse the vital organs because their vessels are less able to dilate.

Choice of vasopressor drug. On present knowledge the best drug would be one that stimulates the myocardium as well as increasing the peripheral resistance; effects are likely to vary with dose and from case to case. Also it should act directly on adrenergic receptors and not solely indirectly by release of noradrenaline stores. Metaraminol (Aramine) i.m. for emergency use and adrenaline or noradrenaline (i.v. infusion) perhaps come nearest to meeting these criteria. Angiotensin does not stimulate the heart. *Prolonged use of these vasoconstrictor drugs reduces blood volume* due to passage of fluid into the extravascular space. Thus cessation of their use may be followed by a drop in cardiac output.

Technique of use. Either continuous infusion i.v. of noradrenaline or intermittent injection i.v. or i.m. of the longer acting metaraminol can be used. The blood pressure should be measured every few minutes. No attempt should be made to raise the pressure to normal; about 80–90 mm Hg. is enough, for the drugs are not restoring normal physiology. In myocardial infarction an excessive rise in peripheral resistance is likely to lower the cardiac output and so to do further harm.

Replacement of fluid: ideally the transfusion should be similar to that which has been lost, blood for hæmorrhage; plasma for burns; saline for

*Dornhorst A. C. (1968) Fourth Symp. Adv. Med.: ed O. Wrong. Pitman, London.

gastrointestinal loss. But in an emergency speed of replacement is more important than its nature. **Note on dextrans** (polysaccharides): dextran 110 or 70 (these are the molecular weights) can be used as plasma substitutes to restore volume; but dextran 40 should not be used for this purpose; it is rapidly (few hrs) excreted by the kidney; it is concentrated in the urine and, especially if there is oliguria, this results in a highly viscous urine that blocks renal tubules. It is also commonly presented in hypertonic form so that its brief effect in increasing plasma volume is by drawing interstitial fluid into the vascular system. Large volumes of all dextrans (above 1·5 l) can interfere with coagulation.

Angiotensin

Angiotensin amide (Hypertensin) is a polypeptide, formed naturally by the action of an enzyme from the kidney (renin) on a substrate in the plasma, whose place in normal or pathological physiology is uncertain. It was synthesised in 1957. Angiotensin infusion i.v. in man raises blood pressure by increasing the total peripheral resistance (vasoconstriction). This is accompanied by reflex bradycardia and reduced cardiac output, the normal homoeostatic responses to a rise in blood pressure due to increased peripheral resistance. This effect is generally undesirable in therapy because blood flow to vital organs, especially to the kidney, will fall, despite the rise in blood pressure. It is probably a powerful cerebral vasoconstrictor and should be used with great care.

Angiotensin is effective when vessels have become refractory to noradrenaline as sometimes happens after removal of a phæochromocytoma, for example. Tachyphylaxis does not occur except at high doses.

Postural hypotension due to disease of the sympathetic system. This condition is not best treated by sympathomimetics since, as might be expected, a dose that prevents postural drop in pressure is liable to cause hypertension when the patient is supine. Expansion of blood volume by a sodium-retaining adrenocortical steroid (fludrocortisone) plus elastic stockings to reduce venous pooling when erect can give better results. An antigravity suit is effective but impracticable for daily life.

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Chapter 18

HYPOTENSIVE AND VASODILATOR DRUGS

THESE drugs may act at any of the following sites (see illustration):

1. **Vessel wall unrelated to nerve endings,** e.g. nitrites, xanthines, cholinergic drugs and numerous drugs used in hypertension and peripheral vascular disease; nitroprusside, diazoxide, methyldopa, hydrallazine. Diuretics may act here as well as by reducing *plasma volume.*

2. **At the sympathetic receptor, blocking the adrenergic transmitter,** (a) α-adrenoceptor blocking drugs (phentolamine, phenoxybenzamine, thymoxamine: (b) β-adrenoceptor block (propranolol etc).

3. **Sympathetic nerve fibres (post-ganglionic)** or **nerve terminals:** adrenergic neurone blocking drugs (guanethidine, bethanidine); methyldopa; reserpine.

4. **Sympathetic autonomic ganglia,** e.g. pempidine, mecamylamine.

5. **Central nervous system,** e.g. reserpine, clonidine, methyldopa.

6. **Afferent nerve endings,** e.g. veratrum.

Group 3, above, includes drugs that act in highly complex and different ways. Some drugs act at more than one site, e.g. reserpine.

Reduction of blood pressure is the result of reduction of peripheral vascular resistance and/or cardiac output by a variety of mechanisms at a variety of sites.

Reduction of *sympathetic arterioconstrictor tone*, or of the capacity of the effector organ (arteriole resistance vessels) to respond to it, reduces peripheral resistance.

Reduction of *sympathetic venoconstrictor tone*, or of capacity of the effector organ (venule capacitance vessels) to respond to it, leads to pooling of the blood in the veins, reduced venous return to the heart, especially in the upright position, and reduced cardiac output.

Reduction of *sympathetic drive to the heart*, or of the capacity of the heart to respond to it, reduces cardiac output, especially its response to stress, e.g. vertical position, exercise.

Postural hypotension and exercise hypotension are limiting factors particularly with antihypertensives that block the sympathetic system, e.g. adrenergic neurone blockers, because these act primarily by blocking the homeostatic reflexes. It is less troublesome with antihypertensives acting elsewhere, e.g. the CNS (5 above) and on the effector organs (1 above, diuretics, diazoxide) which lower the blood pressure with less impairment of reflex responses to stress.

DRUGS ACTING ON THE VESSEL WALL, UNRELATED TO NERVE ENDINGS

Nitrites (Organic and Inorganic) and Nitrates (Organic) (*6–11*)

Both nitrites and organic nitrates were introduced into medicine in the 19th century; they relax smooth muscle. Their chief use is in angina pectoris. Principal effects are:

The vascular system. There is a generalised dilatation of arterioles (resistance vessels), capillaries and venules (capacitance vessels) resulting in a fall of blood pressure which is postural at first. The drugs are used to relieve angina pectoris, and the possible mechanisms of this are discussed below. A severe drop in blood pressure will reduce coronary flow as well as cause fainting due to reduced cerebral blood flow, and so it is vital to ensure that an overdose is not taken. Patients should be instructed on the signs of overdose: palpitations, dizziness, blurred vision, headache and flushing followed by pallor. The optimum dose is probably that which causes slight tachycardia and a feeling of fullness in the head.

The urinary, biliary and alimentary tracts. Transient relief of pain due to spasm of smooth muscle (colic), can sometimes be obtained.

Preparations of Nitrites and Nitrates

Glyceryl trinitrate (1879) (trinitrin, nitroglycerin) (0·5 mg) is an oily, non-inflammable liquid which explodes on concussion with a force greater than that of gunpowder. However, physicians meet it mixed with inert substances and made into a tablet, in which form it is both innocuous and fairly stable. Tablets more than a year old or exposed to heat or air will have lost some or all potency by evaporation.

Glyceryl trinitrate is the drug of choice in the treatment of angina pectoris. The tablets should be bitten up and dissolved under the tongue, where absorption is more rapid and reliable than from the intestine. In addition, the drug then reaches the systemic circulation without first passing through the liver, which metabolises it. Time spent ensuring that patients understand the way to take the tablets and that the feeling of fullness in the head is harmless is time well spent.

The action begins in two minutes and last up to 30 minutes. The initial dose is 0·5 mg, but the amount required for each patient must be found by trial, up to 6 mg a day total. It is taken at the onset of pain, when stopping exercise to find and take the tablet no doubt contributes to the relief, and as a prophylactic immediately before any exertion which experience has taught usually brings on the pain. The drug is occasionally given as a diagnostic test for angina pectoris, but it is unwise to use it if myocardial infarction is seriously suspected. Slow-release preparations (e.g. Sustac) are available for prophylaxis and these are swallowed; they are less reliable and often ineffective.

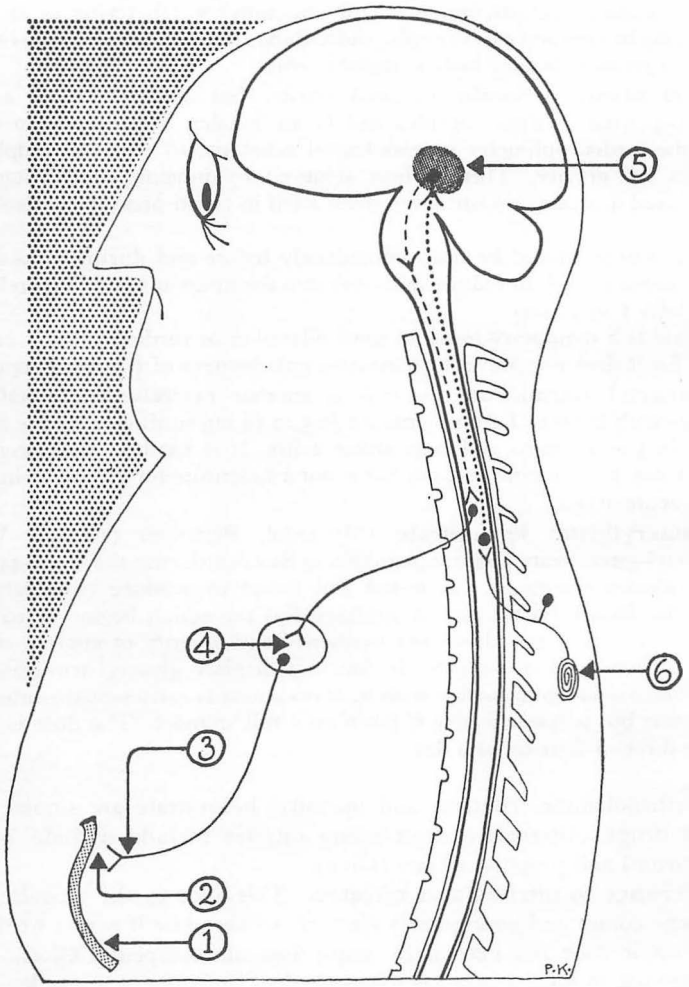

FIG. 21. Sites of action of hypotensive and vasodilator drugs. The numbers correspond with those in the list at the beginning of the chapter.

Amyl nitrite (1867) is an inflammable volatile liquid. It is dispensed in glass capsules (0·2 ml) which are broken between finger and thumb, the gauze covering preserving the patient from injury and also absorbing the liquid, which is then inhaled through the open mouth for absorption via the lungs. Its action begins almost at once and lasts about three minutes. The capsule is best held in the cupped hands or handkerchief to prevent too rapid vaporisation. Its characteristic smell will draw attention to the user even if he has succeeded in breaking the capsule silently. It frequently causes a deep flush and a throbbing headache in the patient and sometimes

in bystanders. These disadvantages have made the drug obsolete in the treatment of angina pectoris, but it is still sometimes worth trying as an antispasmodic in resistant cases of colic and asthma. In cyanide poisoning (which see) it is given to induce methæmoglobinæmia.

Octyl nitrite is similar to amyl nitrite, but slightly longer acting. It is dispensed in glass capsules and in an inhaler. It is chiefly used to relax the cardiac sphincter in œsophageal achalasia, so that the œsophagus empties by gravity. This is best achieved by inhaling whilst standing in a relaxed attitude, a posture in which a fall in blood pressure is also most likely.

Octyl nitrite should be used immediately before and during a meal and before going to bed, to reduce spill-over into the lungs at night. The relaxant effect lasts 1 to 3 mins.

Its use is a temporary measure until dilatation or cardiomyotomy can be done, for it does not prevent progressive enlargement of the œsophagus.

Erythrytyl tetranitrate (15 mg) is another explosive made safe by mixture with lactose. Taken by mouth (7·5 to 15 mg sublingually) the action begins in 5 to 10 mins and lasts about 2 hrs. It is used as a prophylactic against attacks of angina pectoris but is not a substitute for glyceryl trinitrate in the acute attack.

Pentaerythritol tetranitrate (Mycardol, Peritrate) (10 mg). When erythrytyl tetranitrate was unobtainable in Sweden during the 1939–45 war, this explosive substance was tested and found to produce vasodilatation. Taken by mouth (swallowed or sublingually) the action begins in 10 mins and lasts five hrs. It reduces the frequency and severity of anginal attacks in about one-third of patients. It does not displace glyceryl trinitrate and should be used in conjunction with it. It occasionally causes gastro-intestinal symptoms but is less effective if taken on a full stomach. The dose is 20 to 60 mg three or four times a day.

Triethanolamine trinitrate and mannityl hexanitrate are similar long acting drugs. Alternative short-acting nitrates include sorbide nitrate (Vascardin) and propatyl nitrate (Gina).

Tolerance to nitrites and nitrates. Tolerance to the characteristic headache comes and goes quickly (factory workers lose it over a weekend) (*11*), but it does not necessarily imply loss of therapeutic effect. With ordinary use in angina pectoris tolerance does not present a problem.

Unwanted effects of nitrites and nitrates. Collapse due to fall in blood pressure resulting from overdose or allergy may occur. The patient should remain supine, and his legs should be raised above his head to restore venous return to the heart.

These drugs are contra-indicated in myocardial infaction and in angina due to anæmia.

Nitrite headache, which may be severe, is probably due to the stretching of pain-sensitive tissues around the meningeal arteries resulting from the increased pulsation which accompanies the cerebral vasodilatation. If headache is severe the dose should be halved.

Methæmoglobinæmia occurs with heavy dosage.

Other Vasodilators

Dipyridamole (Persantin) relaxes smooth muscle but also may have metabolic effects on the myocardium. Its value in angina is controversial.

Diazoxide (Eudemine) is a thiazide but without diuretic effect; indeed it causes salt and water retention. It is a potent hypotensive acting by reducing peripheral resistance without impairing sympathetic homeostatic reflexes, so that there is generally little postural hypotension except shortly after an i.v. injection.

It is chiefly used i.v. to control severe hypertension; 300 mg (rarely 600 mg) is given in about 30 sec and it produces maximum effect in about 5 min, lasting 2–5 hrs; it should *not* be given by slow infusion; it is strongly alkaline and extravasation should be avoided. Diazoxide relaxes the uterus and may stop labour, which may be restarted by oxytocin.

Diazoxide is used orally for 2 to 3 weeks in hypertension resistant to other drugs, but long-term therapy has been thought undesirable because of salt retention (though this can be overcome by a non-thiazide diuretic), and of hyperglycæmia by inhibiting release of *stored* (but not of newly synthesised) insulin from β-islet cells; the hyperglycæmia can be antagonised by a sulphonylurea. Extrapyramidal syndrome may occur.

Diazoxide is also used to treat pancreatic β-islet-cell tumours. It does not cause permanent diabetes.

Diuretics may partly act to reduce blood pressure by altering sodium balance in the arteriolar wall. They have a short steep dose response curve and in one study it was found that trebling the dose did not increase the antihypertensive effect (*37*). They also reduce plasma volume.

Hydrallazine (Apresoline) has a place in treating milder cases of hypertension in combination with, e.g. a thiazide diuretic. It relaxes arterioles more than veins and so cardiac output may increase, but this does not constitute a significant advantage in renal disease as was once claimed.

Adverse effects include, headache, nasal and conjunctival injection, lacrimation, flushing, palpitations, vomiting. With prolonged heavy doses a syndrome resembling rheumatoid arthritis and proceeding to resemble acute disseminated lupus erythematosus may occur. It can be taken orally or injected.

Sodium nitroprusside by i.v. infusion can be used for immediate control of severe hypertension whilst oral drugs are given time to act. Some cyanide is released in the body and though this seems to be insufficient to harm normals, it could be toxic in the malnourished.

Cholinergic drugs. These produce too many other effects to be clinically useful as vasodilators.

There are numerous other peripheral vasodilators which include inositol nicotinate (Hexopal), nicotinic acid, papaverine, bamethan (Vasculit), buphenine (Perdilatal Forte), xanthinolnicotinate (Complamex), nicotinyl alcohol (Ronicol) etc. Their merits are dubious.

Evaluation of Drugs in Angina Pectoris (*4, 6–9, 12*)

In a study of electrocardiograms of anginal patients before and after measured exercise, it has been found that glyceryl trinitrate prevented E.C.G. changes induced by exercise. Pentaerythritol tetranitrate and erythrytyl tetranitrate may also do this. Ethyl alcohol, taken as whisky, reduced the pain induced by the exercise test but did not modifythe E.C.G. changes, which seems to dismiss the belief that alcohol is a useful coronary vasodilator. It is simply a tranquilliser and analgesic. Theophylline compounds are often recommended in angina pectoris, but 500 mg aminophylline i.v. was found to have slight or insignificant effect. It is therefore unlikely that similar compounds recommended for oral use are really effective in angina pectoris.

Therapeutic trials of the efficacy of drugs in preventing or relieving angina are difficult to perform. The disease is very variable and the pain, having particularly sinister associations, is liable to be much influenced by emotion. Cessation of attacks may be due to the patient changing his physical habits rather than to the drug, e.g. development of angina is related to heart rate and blood pressure rather than to amount of work; regular exercise reduces cardiac effects of a given amount of work. These difficulties show themselves in disputes, sometimes pleasantly acrimonious, about the value of drugs, particularly the longer-acting ones, which are most difficult to assess.

Mode of Action of Drugs in Angina Pectoris

Nitrites and nitrates. About 100 years ago Lauder Brunton suggested that the relief of angina pectoris by amyl nitrite was due to reduction in cardiac work due to lowering of blood pressure. After it was shown that nitrites or nitrates could relax isolated coronary artery muscle and increase coronary blood flow in the isolated hearts of normal animals, it seemed "obvious" that this must be the mechanism of the relief in man and the drugs were even classified as "coronary vasodilators" by pharmacologists.

Now, however, it seems more probable that the first view was correct and that naïve pharmacological studies in animals led to an unwarranted assumption of mechanism of action in diseased man. In any case, anoxia causes coronary vasodilation, and more is unlikely to be achieved once the patient has his pain, though a drug might act as a prophylactic in that way.

Modern studies of myocardial work, oxygen consumption and coronary blood flow* in normal and diseased man suggest that the effects of the short-acting nitrites are as follows. The resting blood pressure is lowered, systolic somewhat more than diastolic, and the pressor response to

* Coronary blood flow is measured by the Fick principle. The subject inhales nitrous oxide, and arterial and coronary venous blood samples are collected. The latter are obtained by passing a catheter into the right side of the heart and manipulating it into the coronary sinus.

exercise is reduced. Blood pressure is an important determinant of myocardial oxygen requirement, and its reduction may make a major contribution to relief of angina.

The duration of cardiac systole is shortened (coronary blood flow occurs chiefly during diastole), and cardiac size is decreased (due to the lowered diastolic filling pressure that results from venous pooling). Though there is a moderate reflex (sympathetic) tachycardia, the end result of these effects is reduced cardiac work. This is perhaps also a major mechanism of relief of angina pectoris. Coronary blood flow may increase in normals, but it does not in anginal subjects.

It is evident that the beneficial effects are only likely to occur with the proper dose of the drugs at the optimal moment, too little is obviously useless, and too much can cause a brisk hypotension with loss of consciousness and seriously reduced coronary perfusion pressure.

The long-acting nitrates given continuously may benefit by reducing the blood pressure rise that is caused by exercise or by anxiety, but this is uncertain; indeed the existence of important beneficial effects is disputed.

The possibility that nitrites and nitrates have a direct useful effect on myocardial metabolism has not been excluded.

β-Adrenoceptor blocking drugs, used continuously, reduce the frequency of anginal attacks. This may be due to reducing the sympathetic cardiac stimulation induced by exercise and by anxiety, i.e. reduction in cardiac work.

Glyceryl trinitrate and **β-adrenoceptor blockers** benefit angina by different mechanisms. They are synergic and may be used together.

Sedatives, e.g. diazepam, also give benefit by reducing the cardiac response to anxiety. There is, of course, a marked placebo response both to medication and to the physician in this disease.

Alcohol reduces the pain, but does not alter the electrocardiograph changes.

Summary of Treatment of Angina Pectoris

1. The cause is treated when possible, e.g. anæmia, syphilis.
2. *Arrangement of life* so as to reduce the number of attacks as far as possible. Weight reduction is very helpful where appropriate.
3. *Glyceryl trinitrate*, taken before exercise that is expected to induce angina. It is also used to relieve the attack.
4. *β-adrenoceptor block*, e.g. propranolol, given continuously (*not* merely when an attack is expected). Dosage is adjusted by results. Some put an arbitrary upper limit to dose, but others recommend that if complete relief is not obtained the dose should be raised to the maximum tolerated, provided the resting heart rate is not reduced below 55/min.
5. The longer acting organic nitrates may be used as prophylactics, erythrytyl tetranitrate sublingually before effort and pentaerythritol tetranitrate swallowed regularly *on an empty stomach.*
6. Sedation may help where anxiety is a factor.

7. Smoking should be discouraged in appropriate cases.
8. In severe cases anticoagulant therapy should be considered.
9. If attacks of angina occur at rest the induction of myxœdema with ^{131}I or antithyroid drugs may be justified occasionally.
10. Surgical attempts to improve the myocardial blood supply are still experimental. Thoracic sympathectomy can be effective, but β-adrenoceptor block should provide the same benefit.

DRUGS ACTING AT THE SYMPATHETIC RECEPTOR BLOCKING THE ADRENERGIC TRANSMITTER

α- and β-Adrenoceptor Blocking Drugs (*1–3*)

Adrenoceptor blocking drugs prevent the response of effector organs to adrenaline and noradrenaline (and other sympathomimetic amines) whether released in the body or injected. Circulating adrenaline and noradrenaline are antagonised more readily than the effects of adrenergic nerve stimulation.

The drugs act by competition with adrenaline and noradrenaline for the α-or β receptors on the effector organs (they neither alter the substances themselves nor affect their production).

Some adrenoceptor blocking drugs have to be altered in the body before they become effective, and this explains the slow onset of action of phenoxybenzamine.

α-Adrenoceptor Blocking Drugs

The principal action of α-adrenoceptor blocking drugs is to produce peripheral vasodilatation.

Unwanted effects of α-adrenoceptor block are postural hypotension, nasal stuffiness and red scleræ. Effects perculiar to each drug are mentioned below.

Tolazoline (Priscol) (25 mg). In addition to its brief and only moderately powerful α-adrenoceptor blocking effects, tolazoline has a direct vasodilator action on peripheral vessels. This makes it suitable for use in peripheral vascular disease, although blood flow is increased more in skin than in muscle. It also causes tachycardia by direct action on the heart and stimulates the gastro-intestinal tract, causing diarrhœa. It is a stimulant of gastric acid secretion and may activate dormant peptic ulcers. Nausea and vomiting result from gastric irritation. As with all drugs having such ill effects, it should be stopped unless it is certainly doing good.

The dose is 25 to 50 mg orally, 4 to 6 hrly.

Phentolamine (Rogitine) is a short-acting drug chemically related to tolazoline. It has similar effects including direct vasodilator action. It is principally used in the diagnosis of, and control of hypertension due to, phæochromocytoma (which see). It is unreliable when given by mouth and it is usually given i.v. or i.m. (5 to 30 mg).

Phenoxybenzamine (Dibenyline, Dibenzyline) (10 mg) is a powerful and specific α-adrenoceptor blocking drug whose effects may last two days or longer. Cumulation may therefore occur at the beginning of treatment

and the dose must be increased slowly. It is usually impossible to reverse the circulatory effects of an overdose by noradrenaline or other sympathomimetic drugs. The full effect of an i.v. dose may take up to an hour to develop.

It is wise to observe the effects of a single test dose closely before starting regular administration.

Indigestion and nausea are common with oral therapy. The oral dose is 10 to 80 mg three or four times a day. By i.v. infusion, 10 to 70 mg, according to the response, may be given over 20 mins.

Thymoxamine (Opilon) is an alternative.

Ergot alkaloids (see index). The naturally occurring alkaloids with effective α-adrenoceptor blocking actions are also powerful vasoconstrictors and this action obscures the vasodilatation which is characteristic of α-adrenoceptor blocking drugs.

Chemical reduction of the natural alkaloids gives derivatives which cause little smooth muscle stimulation and these have been used to produce adrenoceptor block. They are also thought to reduce sympathetic tone by a depressant action on the central nervous system. The principal preparation is Hydergine (a mixture of three dihydrogenated alkaloids). It is liable to cause malaise, nausea and vomiting at effective doses.

Hydergine may increase cerebral blood flow without lowering the blood pressure and its use has been claimed to lead to improvement in some cases of cerebral ischæmia. Similar claims have been made for other vasodilators, but they have not been fully substantiated.

Chlorpromazine has many actions of which α-adrenaceptor block is a minor one, but sufficient to cause hypotension.

Yohimbine is an alkaloid from a West African tree. It is a weak α-adrenoceptor blocking agent. It also stimulates the central nervous system, causing a release of antidiuretic hormone. When given with a barbiturate it causes seminal ejaculation in mice, but despite this it is no longer regarded as an effective aphrodisiac in man.

An **aphrodisiac** would be a drug that would provide a reliable, selective, dose-related increase in sexual desire and performance, lasting, ideally, I suppose, a few hours. There is no such drug. If there were, its social disadvantages might well be found to outweigh any benefits to an occasional individual.

Uses of α-Adrenoceptor Blocking Drugs

These include:

1. **Peripheral vascular disease** (see below).
2. **Hypertension**
   a. phæochromocytoma.
   b. essential: the hypotensive effect tends to wear off. Side-effects are common and these drugs are unsuitable as sole therapy, though they are occasionally combined with an adrenergic neurone blocker.

3. **Miscellaneous:** in *chilblains*, with dubious benefit; in *causalgia* the mechanism of relief, if any, is obscure, but anything is worth trying in this diabolical condition.

Drugs in Peripheral Vascular Disease (5)

The aim is to produce peripheral arteriolar vasodilatation without a concurrent significant drop in blood pressure, so that an increased blood flow in the limbs will result. Drugs are naturally more useful in patients in whom the decreased flow of blood is due to *spasm* of the vessels (Raynaud's phenomenon) than where it is due to *organic obstructive* changes which may make dilatation in response to drugs impossible (arteriosclerosis, Buerger's disease).

α-adrenoceptor blocking agents are widely used in peripheral vascular disease, but they increase skin rather than muscle blood flow (*12*). They have been successfully used in the treatment of superficial ulcers (varicose and traumatic).

Drugs do not remove the cause of the disease, but may delay the onset of gangrene or limit its spread and relieve some of the symptoms. That treatment is unsatisfactory is shown by the wide range of drugs used. Methacholine, ethyl alcohol, aminophylline, neostigmine, papaverine and ganglion-blocking agents have all been recommended at various times. There are very many other peripheral vasodilator drugs, some of which are named above. They are worth trying in troublesome cases, but conclusive therapeutic trials have not been done and so no definite recommendations can be made. Unsubstantiated claims are rife. Muscular cramps, especially at night, are common in patients with peripheral vascular disease. Quinine sometimes relieves them.

Raynaud's phenomenon may be helped by phenoxybenzamine, reserpine and, curiously, griseofulvin which has a vasodilator effect. *Cerebral vascular disease: atherosclerotic*, see *intellectual function and drugs: induced spasm*, e.g. with surgery, phenoxybenzamine and papaverine may be used intravascularly.

β-Adrenoceptor Blocking Drugs*

These drugs block only the β-effects of adrenaline and will convert the characteristic adrenaline effect on blood pressure to that of noradrenaline.

The cardiovascular effects of β-adrenoceptor block depend on the amount of sympathetic tone present. The chief cardiac effects result from diminution of sympathetic drive. They are reduced heart rate (automaticity), reduced myocardial contractility (as measured by rate of rise of pressure in the ventricle) and reduced stroke volume. With reduced rate and stroke volume, the cardiac output/min is reduced and the overall oxygen consumption falls. These effects are more evident on the response to exercise than at rest. Peripheral vascular resistance tends to rise, probably chiefly a reflex response to the reduced cardiac output.

* In 1972 more than 20 pharmaceutical companies were known to be synthesising and testing compounds for β-adrenoceptor block (38).

At first sight the effects might seem likely to be disadvantageous rather than advantageous. Fortunately the heart has substantial functional reserves so that use may be made of the desired properties in the diseases listed below, without inducing heart failure. But heart failure due to the drug does occur in patients with seriously diminished cardiac reserve.

The resting blood pressure is little affected by a single dose, but long term administration generally results in a fall in pressure which may not reach its maximum for 4 weeks or more (with decreased peripheral resistance).

Classification of β-adrenoceptor blockers (*1*)

β-adrenoceptor blockers may be classified into 5 groups based on their, (a) *additional effects* and (b) *selectivity* for receptors in different tissues:

(1) *β-adrenoceptor block only:* sotalol*.

(2) *β-block plus membrane-stabilising* (*local anæsthetic*) *effect:* propranolol (Inderal).

(3) *β-block plus some β-stimulant effect plus membrane-stabilising effect:* oxprenolol (Trasicor), alprenolol (Aptin)*.

(4) *β-block plus β-stimulant effect:* pindolol.*

(5) *selective β-block on different tissues:* practolol (Eraldin) is selective for the heart (less effect on bronchi and blood vessels).

The combination of properties determines to some extent their use in therapeutics, e.g. a drug with membrane-stabilising action will have additional effect in cardiac arrhythmias, like local anæsthetics, in addition to any benefit from β-adrenoceptor block. The clinical importance of membrane-stabilising effect is questionable as practolol (which does not have it) is effective in arrhythmias.

Uses. β-adrenoceptor blockers are likely to be of use in any condition in which sympathetic activity can be disadvantageous to the patient. Such conditions are various; they include increased secretion of catecholamines (phæochromocytoma), hæmodynamic difficulties in congenital cardiac abnormalities, and anxiety.

Uses of β-adrenoceptor blockers may be classified (*1*):

Cardiac

1. Angina pectoris (β-block reduces cardiac work).
2. Cardiac arrhythmias (β-block plus membrane-stabilising effect).
3. Hypertension (β-block, perhaps plus other uncertain effect).
4. Obstruction to ventricular outflow where sympathetic activity occurs in the presence of anatomical abnormalities, e.g. Fallot's tetralogy (R. ventricle: cyanotic attacks): hypertrophic subaortic stenosis (L. ventricle: angina).
5. Mitral stenosis: for tachycardia uncontrolled by digitalis.

* Not marketed in Britain in 1973

Endocrine

1. Thyrotoxicosis, to reduce unpleasant tachycardia).
2. Phæochromocytoma (blocks β-effects of circulating catecholamines).

CNS

1. Parkinsonian tremor is made worse by β-stimulants; may be helped by β-block.
2. Severe anxiety states (reduction of symptoms mediated by sympathetic).

Unwanted effects of β-block include:

Cardiac failure: patients near to cardiac failure need sympathetic drive to give adequate cardiac output/min: a drop in rate may be enough to induce cardiac failure. If the drug cannot be stopped, the failure can be treated with digitalis.

Heart block may be made dangerously worse.

Bronchoconstriction may occur as is to be expected, in asthmatics and some chronic bronchitics.

Intravenous use particularly may cause severe drop in cardiac rate and output and drugs must be given slowly. For excessive bradycardia give an anticholinergic drug (atropine) to block the vagus nerve.

Insulin hypoglycæmia may be prolonged since sympathetic glycogenolysis which occurs as a homœostatic response is a β-effect. This risk dictates special care in diabetics taking the drugs.

EXAMPLES: **Propranolol** (Inderal) (10, 40, 80 mg). The usual oral dose is 10 mg, 3 or 4 times/day increased by 5 or 10 mg/dose, as required, about weekly up to 80 mg/dose or occasionally higher. Unwanted effects (see also above) include nausea, vomiting; occasionally bowel disturbances and depression, but they are not usually troublesome.

Propranolol is given i.v. slowly, 1 to 10 mg.

Practolol (Eraldin) (100 mg). The usual oral dose is 100 mg twice daily, increased to about 600 mg/dose as required. Practolol is preferred where bronchoconstriction may be a hazard. An injectable form is available.

Oxprenolol (Trasicor) is an alternative.

Treatment failure. If in, say, angina, a β-blocker fails due to unwanted effects it may be worth trying another.

Intrinsic heart rate.

If the sympathetic (β) and the parasympathetic (vagus) drives to the heart are simultaneously adequately blocked by a β-adrenoceptor blocker plus atropine, the heart will be its own master and will beat at its "intrinsic" rate. The intrinsic rate at rest is usually about 100/min (i.e. normally there is parasympathetic vagal dominance). It decreases with age.

DRUGS ACTING ON POSTGANGLIONIC SYMPATHETIC NERVE FIBRES OR NERVE TERMINALS (*19, 22, 26, 35*)

Adrenergic neurone blocking drugs are taken up into adrenergic nerve endings and reduce the amount of noradrenaline released (but not from the adrenal medulla). There is a variety of differences in their actions, e.g. whether they deplete the stores of noradrenaline in the nerve endings, but these are not of critical importance in clinical choice for oral therapy.

The facts that they sensitise effector cells (vascular muscle) to catecholamines and that when injected some may transiently release noradrenaline and so raise the blood pressure have clinical relevance in phæochromocytoma (they are contraindicated) and in emergency control of severe hypertension (they must not be given in large doses i.v.).

The group includes *guanethidine* (Ismelin), *bethanidine* (Esbatal), *debrisoquine* (Declinax), *guanoxan* (Envacar), *guanoclor* (Vatensol).

Unwanted effects of sympathetic block. Postural and exercise hypotension may be troublesome. Harmless bradycardia is common. But heart failure may be made worse, because a failing heart needs its sympathetic drive. Failure of ejaculation may occur and also diarrhœa (which may have other mechanisms).

Uses: in addition to *hypertension*, some of these drugs (guanethidine, bethanidine) have been used to reduce sympathetic overactivity in hyperthyroidism in cases where it is important to relieve symptoms before antithyroid drugs have time to take effect.

The first member of this group of drugs was **bretylium** (Darenthin) but tolerance was common and so was parotid pain, a curious effect, rarely encountered with guanethidine. For these reasons bretylium is obsolete as an antihypertensive, but it has a use in cardiac arrhythmias. Unlike other antiarrhythmic drugs, bretylium has a positive inotropic (i.e. cardiac stimulant) effect.

Guanethidine (10, 25 mg) is only partially, though reliably, absorbed from the alimentary tract. Owing to the fact that the action of a single dose lasts 2 to 4 days, probably due to storage and slow release of the drug from the tissues, guanethidine is cumulative and dosage should only be increased at 5-day intervals. This is a disadvantage, in that it means that adequate control of the blood pressure may not be achieved for several weeks, but dosage need only be once daily, which is convenient. There is little effect on the supine blood pressure, hypotension being mainly postural. Harmless bradycardia is usual with guanethidine, but where digitalis is also being used the pulse may become alarmingly slow.

Other unwanted effects include postural hypotension (as with other adrenergic neurone blockers), and hypotension with exercise, which can be extreme and which may occur at a dose that has little effect on the blood pressure when erect. When this happens therapy should be changed.

Diarrhœa is common and can be controlled by a small dose of a ganglion-blocking drug, say pempidine 2·5 mg. twice a day orally, which has the

added advantage of synergism with the hypotensive effect of guanethidine so that a lower dose of the latter may be used; propantheline, atropine or codeine may also be tried.

Parotid gland pain, fluid retention with cardiac failure, failure of ejaculation without impotence, tremors, weakness and mental depression occur occasionally. Many hypotensive drugs cause nasal obstruction due to vasodilatation of the mucous membrane, and guanethidine is no exception.

Dosage. 10 mg once a day orally is a suitable dose to begin with in an outpatient, and it may be increased weekly by 10 mg. Since many patients need 100 to 300 mg a day, and some need more, this leisurely process is unsuited to the severe cases who, in hospital, may be given 30 mg. increased by 10 to 20 mg every third day. As the total dose increases, and this increment becomes a smaller proportion of the total, the increment may be raised.

The effects of overdose may last for several days, which can be serious.

Despite its cumulative course, blood pressure control may not be consistent over 24 hrs and this is not remedied by dividing dosage. It may be therefore found convenient to add a small dose of another drug, e.g. thiazide or reserpine.

Bethanidine (10, 50 mg) acts more briefly than guanethidine so that the oral dose can be increased more rapidly (daily in hospital, alternate days on out-patients) and control of blood pressure may thus be obtained more rapidly; a matter of importance in severe cases. It can also be given i.v. for even quicker control. Diarrhœa is rare, in contrast to guanethidine.

The oral dose is 5 mg 12-hrly, increased every 24 or 48 hrs by one dose, to 5 mg 6-hrly, and then by 5 or 10 mg per dose. Total daily dosage is likely to be in the range of 20 to 650 mg.

Methyldopa (Aldomet) (125, 250, 500 mg) *may be classed separately from the above.* It is a decarboxylase inhibitor, preventing the conversion of natural L-dopa (also of the same substance used as a drug, levodopa) to dopamine, a precursor of noradrenaline. Tissue and nerve ending noradrenaline concentrations are reduced. But the drug α-methyldopa is converted to α-methylnoradrenaline which is released by nerve stimulation, i.e. a false transmitter is formed. The notion that methyldopa produces its antihypertensive effect by forming a false (and less potent) neurotransmitter is attractive, but α-methylnoradrenaline is almost as potent as noradrenaline, and the exact mechanism of the sympathetic blocking effect of methyldopa is uncertain. There may be some direct action on peripheral vessels as well as an effect in the CNS.

The chief clinically important advantage of methyldopa over the adrenergic neurone blockers is that methyldopa commonly has a greater effect on the supine blood pressure and there is less troublesome postural drop.

Methyldopa also interferes with the formation of 5-HT (by decarboxylation) and has been tried in carcinoid syndrome with variable results.

Methyldopa is reliably absorbed when taken orally, and is excreted unchanged and conjugated by the kidney. (Urine of treated patients may blacken on standing.)

Unwanted effects include sedation, which is usually transient, but which may limit therapy, and headache and weakness, also gastrointestinal upsets, dry mouth, nasal congestion, weight gain and œdema, lactation, arthralgia,

Parkinsonism, depression, nightmares, and rashes, fever and other allergic effects. Interference with sexual function is rare.

Up to 20% of patients taking methyldopa develop (usually during the second 6 months of therapy) a positive direct Coomb's blood test. The occurrence is dose-related. Hæmolytic anæmia can occur (*24*). The chief importance of this is that the positive Coomb's test can interfere with cross-matching of blood for transfusion. It would therefore seem wise not to use methyldopa for hypertension of pregnancy.

Methyldopa is potentiated by hepatic and renal disease. It interferes with measurement of urinary catecholamines by fluorimetry.

Dosage begins with 250 mg orally 8-hrly, and one dose can be increased by about that amount every two days. Control is generally achieved at 2 to 3 g a day, total.

Methyldopa can be given i.v., when the onset of effect may begin in 4 hrs suggesting an indirect mode of action.

Reserpine (Serpasil) (0·1, 0·25, 1 mg) and alkaloids related to it act by depleting tissues including CNS and nerve endings of stored noradrenaline (and also of 5-HT). The antihypertensive effect is chiefly peripheral, but the CNS effect is the cause of the severe depression (even suicidal) that can occur and for its use as a tranquilliser (obsolescent).

Reserpine is generally used in combination, e.g. with a thiazide diurectic or hydrallazine, in hypertension. It is extremely important to restrict the dose to avoid mental depression and it should not be used in patients liable to endogenous depression.

Unwanted effects are fairly common, but at doses recommended are seldom serious. The following occur: lethargy and apathy, nasal stuffiness, gain in weight and diarrhœa. Dyspnœa, not associated with cardiac failure, occurs, and onset of cardiac failure has also been reported. Fluid retention with œdema occurs occasionally in the absence of cardiac failure. Anæsthesia in patients taking reserpine, or within two weeks of ceasing, may cause severe hypotension. Prolonged use may promote breast cancer.

With large doses an extrapyramidal syndrome, clinically indistinguishable from Parkinsonism, occurs. However, it is reversible and is controlled by anti-parkinsonian drugs, although it is preferable to stop the drug. Decreased libido and nightmares may occur. Epileptics may have more fits. Peptic ulcers may be activated.

Reserpine is well **absorbed** from the alimentary tract; parenteral preparations are available. Small **doses** (0·3 to 0·5 mg a day) should be used in hypertension because of the risk of mental depression, though large doses (5 mg i.m.) have been used temporarily to control hypertensive emergencies, but the effect may take two hours to reach a maximum.

Older male turkeys are liable to fatal hypertensive aortic rupture, no doubt a consequence of their characteristic stupidly furious behaviour. This can cause serious economic loss. The addition of reserpine to their drinking water reduces their blood pressure and preserves their lives without noticeably moderating their rage.*

Rescinnamine and deserpidine (Harmonyl) are other Rauwolfia alkaloids which have not been shown to offer significantly different

* *Conf. on use of tranquilising agent Serpasil in animal and poultry production.* (1959). Coll. Agriculture, Rutgers, State Univ., U.S.A.

therapeutic effects from reserpine. **Methoserpidine** (Decaserpyl) is a synthetic isomer of reserpine which may cause mental depression less frequently, though this is disputed.

Pargyline (Eutonyl) is a MAO inhibitor that has a more selective effect on the blood pressure than others (which see). But the hazards of MAO inhibitors render them unsuitable for routine use.

DRUGS ACTING AT AUTONOMIC GANGLIA

Ganglion-blocking Drugs

Because they are not selective, and block sympathetic and parasympathetic systems alike, the ganglion-blockers have been replaced in routine therapy of hypertension by the adrenergic neurone blockers. Because some of these are slow in acting, ganglion-blockers are still used by some for a quick effect in malignant hypertension. They are being replaced here as quicker acting adrenergic neurone blockers are developed, e.g. bethanidine, as well as by drugs acting directly on the blood vessels, e.g. diazoxide, sodium nitroprusside.

The principal unwanted effects of ganglion block can be predicted from a knowledge of autonomic physiology (students are advised to make the attempt). The most serious in clinical practice is constipation proceeding to intestinal obstruction (parasympathetic block).

Ganglion blockers include mecamylamine (Inversine) and pempidine (Perolysen) which are orally active and hexamethonium (the first clinically useful drug in severe hypertension), tetraethylammonium (TEA) and trimethaphan (Arfonad) (a short-acting agent, given by i.v. infusion and used for producing hypotension to give a blood free field during surgery).

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Clonidine (Catapres) (0·10 mg). Clonidine is related to tolazoline, but its site of action is in the CNS, not at the peripheral α-adrenoceptor. Its site of action is largely in the CNS, reducing sympathetic outflow. It is likely that there is a peripheral effect with chronic administration. Clonidine does not notably disturb homeostatic reflexes and so postural and exercise hypotension are not troublesome. Its efficacy is comparable to methyldopa. See also *migraine*.

Unwanted effects include sedation and dry mouth. Sudden withdrawal, e.g. if patient forgets, has an accident or goes to surgery, may be followed by a sudden rise in blood pressure (treatable with an injection of α-adrenoceptor blocker, or by more clonidine); this is a serious disadvantage of the drug. Sodium retention may occur.

The oral dose is 0·05 to 0·10 mg three times/day increasing every 3 days by the same dose. It is rarely necessary to exceed 1·2 mg total/day. Clonidine can be injected; rapid i.v. injection may cause a transient rise in pressure.

DRUG ACTING AT AFFERENT NERVE ENDINGS

Veratrum alkaloids reduce the threshold of response of nerve receptors in general. Those in the coronary vessels and ventricular wall are first affected and the drug found a use in hypertension, since these receptors institute (via vagal afferents) a bradycardia (vagal efferents) and a decreased blood pressure (exact path uncertain). The therapeutic dose is close to the toxic dose and veratrum alkaloids are obsolete.

TREATMENT OF HYPERTENSION

Evaluation of Hypotensives

Evaluation falls into two classes:

(1) Whether long-term reduction of blood pressure benefits the patient (see below); these studies take years.

(2) Whether a drug is capable of effective, safe and comfortable control of blood pressure; these studies last weeks or months. They commonly are conducted double-blind, which can involve complicated arrangements when accurate titration of the dose/effect of potent drugs is involved. Careful design and conduct are essential because of the very great natural variations in the disease. Emotion may result in changes of up to 100 mm Hg systolic and 40 mm diastolic over a few minutes. In addition, these changes may persist for weeks. In therapeutic trials the short period of control observation on new patients which often precedes a few weeks' treatment can be valueless for comparative purposes. "A period of treatment is a period of reassurance to a hypertensive patient, and reassurance will obviously lead to greater emotional calmness and a lowering of blood pressure. . . . I have seen many patients whose blood pressure at the first visit may be, for example, 260 systolic and 120 diastolic, and at a second visit, a few weeks later, may be 118 systolic and 80 diastolic after only mild sedation and great assurance. I have given placebos to hypertensive patients and obtained 80% symptomatic improvement." Ayman, who wrote the above words (*21*), has also shown that merely increasing the frequency of a patient's visits to the physician can result in a drop in blood pressure, presumably due to the reassuring effect of such frequent contact. "Yet this scheme of increased frequency of visits is commonly applied by clinical investigators of new drugs. . . ." He also points out that in evaluating sympathectomy "the glaring defect is the usual brief control period of observation before operation".

In another study it was found that regular placebo injections i.m. were accompanied by a reduced blood pressure for over a year, where an oral placebo had insignificant effect.

It is clear that double-blind carefully controlled studies are essential when evaluating the response to treatment in hypertension, especially over short periods, for effective hypotensive drugs are capable of causing serious harm and it is important that only those who will actually benefit from their pharmacological effects should take them.

The aim of treatment is to reduce the blood pressure as near to normal as possible in the erect posure, and to keep it there. Unfortunately it cannot always be reduced to normal when the patient is supine without risk of excessive drop when gravity operates on standing. When this aim is achieved there is usually very great symptomatic improvement, retinopathy clears and vision improves: headaches are often abolished. However, a variable amount of irreversible damage has often been done by the high blood pressure before treatment is started; renal failure may progress despite treatment; arterial damage leads to cardiac or cerebral catastrophes. It is obviously desirable to start treatment before irreversible changes occur even if symptoms do not demand relief.

Which patient to treat. The prognosis in untreated **malignant hypertension** is so bad that it was ethically impossible to withhold treatment from any patients when ganglion-blocking drugs became available. Thus in the therapeutic trials of hexamethonium the controls had to be similar patients observed in previous years. In a series of 82 patients suffering from malignant hypertension treated with ganglion-blocking drugs the expectation of life was six to eight times that of patients not so treated (*20*).

Thus any patient with malignant hypertension, or **severe hypertension** likely to become malignant, or with disabling symptoms, requires effective drug treatment, as do those in whom there is evidence of progression; worsening of fundi or appearance of cardiac enlargement or failure. *Treatment requires as much care and attention as the use of insulin in diabetes.*

In **moderately severe and mild** cases there is evidence that *efficiently conducted* therapy is 75% effective in preventing deaths and major complications in middle-aged men with diastolic pressures between 105 and 114 mm Hg; it is 35% effective with diastolic pressures between 90 and 105 mm Hg. Women are more resistant to morbidity from hypertension.

A reasonable conclusion on present evidence is that all men under 65 years with diastolic pressures consistently of 110 mm Hg or higher at rest should be treated. The critical level for women may be taken as 115 mg Hg. For lesser levels, opinion on whom to treat varies and factors such as the likelihood of the patient reliably taking his medicine weigh heavier.

Treatment will be life-long.

Some factors influencing treatment. Physiological or external events that decrease vascular resistance in various areas (exercise, hot environment, digestion) also potentiate the effect of hypotensives, and straining to open the bowels can have catastrophic circulatory effects. Diurnal fluctuations in blood volume add to the difficulty of getting even control. Blood volume is lower in the morning and, with the longer acting drugs (e.g. guanethidine) this causes hypotension on first getting out of bed.

Potent drugs should be given after food to avoid high peak plasma concentrations and consequent postural hypotension.

In a few patients with severe hypertension lowering the blood pressure may make the patient worse, for instance if there is severe renal impairment (blood urea over 100 mg/100 ml), or advanced cerebral or coronary arteriosclerosis. In these cases blood flow to vital organs may depend upon a high perfusion pressure; but when such patients have severe hypertensive symptoms a very cautious trial of hypotensive drugs is worth while. Weight reduction in an obese hypertensive patient often relieves breathlessness on exertion and sometimes lowers the blood pressure, although this may be more apparent than real, since arm thickness affects sphygmomanometer readings, fat arms providing higher readings than thin arms. Sympathomimetic appetite suppressants (but not fenfluramine) will antagonise the effects of hypotensive drugs.

Choice of Drugs in Hypertension

For **long-term oral clinical use** hypotensives can be grouped as:

(1) **More potent***: adrenergic neurone blockers (guanethidine, bethanidine, etc.), methyldopa, clonidine, β-adrenoceptor blockers. The most potent are the adrenergic neurone blockers, which are likely to be needed in severe cases. The advantage of β-adrenoceptor blockers is lack of postural and exercise hypotension due to retention of α-receptor activity.

Drugs in this group are adjusted accurately to each patient's need. One of the less potent drugs in fixed dose is often added to give smoother control and to allow a lower dose of the more potent drug to be used so that unwanted effects are minimized.

(2) **Less potent***: diuretics (e.g. thiazides), reserpine, hydrallazine. These drugs are generally given in fixed dose or over a limited range because they have a short, steep dose-response curve (diuretics) or dose is limited by an adverse effect (reserpine depression). They are used either in combination with another drug of the same group (mild cases) or to potentiate the therapeutic effect of a more potent drug so that its non-circulatory adverse effects can be avoided.

Therapy with more than one drug is usual, for reasons given above.

On theoretical ground the combination should not include drugs acting at the same site, e.g. guanethidine uptake into nerves may be interfered with by reserpine or methyldopa, but in practice interference has not been observed.

Every conceivable drug and many combinations of drugs have been advocated for hypertension. The best course is to decide on a routine for mild, moderate and severe cases, to achieve skill by practice in using the chosen drugs and only to change from them where there are obvious reasons for doing so. Choice may be summarised:

(1) Mild and moderate hypertension

thiazide diuretic alone or plus reserpine or hydrallazine.

The disadvantage of a thiazide diuretic is that monitoring of plasma K is necessary if patients are to be protected from hypokalæmia (see below).

* *Therapeutic* potency, i.e. *efficacy*, is intended here: see *potency*, ch. 6.

Because of this some prefer to use lower doses of drugs used for severe hypertension; but *spironolactone* (antialdosterone diuretic) may be preferred, or a K-retaining diuretic plus a thiazide (Moduretic).

(2) **Severe hypertension**

bethanidine or guanethidine
methyldopa
propranolol*
} alone or plus a diuretic.

Potassium supplements are commonly used with K-losing diuretics for hypertension, and though not essential they probably prevent a few cases of serious hypokalæmia. Fixed dose combination formulations may be convenient for routine use, though they do not contain enough potassium for replacement for all cases. Ideally patients should be monitored for K loss for a few months until they are stabilised and their requirement known. Since K is mostly intracellular, plasma concentrations are not always a reliable guide. Control of K balance is particularly important if the patient is also taking digitalis. K-retaining diuretics (ch. 20) may be used.

(3) **Hypertensive emergency** (drugs should be given with regard to what the patient has taken recently and to his renal function).

diazoxide, i.v. 300 mg acts in 5 mins and lasts 2–6 hrs.
guanethidine,† i.m. 10–20 mg acts over 1–2 hrs and lasts 4–6 hrs.
methyldopa,† i.v. 0·5–1 g acts in 2–4 hrs and lasts 10–15 hrs.

Sodium nitroprusside, 50 mg in one litre of isotonic dextrose solution is infused continuously i.v., preferably with a reliable pump because sudden changes in rate of infusion such as may be inevitable with ordinary gravity drip and patient movement can cause big fluctuations in pressure; the dose needed is likely to be 1–5 mg/hr (20–100 ml); the effect begins and stops within 2 mins of starting and stopping the infusion. It is not widely available.

Reserpine, i.m. 1–5 mg begins to act in 2–4 hrs; hypotension may persist for days.

Pentolinium, s.c. (1–2 mg) or i.v. (0·5–1 mg) begins to act in a few mins, and increments are commonly needed about 6 hrly.

Blood pressure monitoring is plainly essential and doses and intervals are judged by response. It is obvious that a drug acting quickly and briefly (sodium nitroprusside) needs closer supervision than a drug with slower onset of a smoother action, and this may be a factor in choice of drug.

Excessive hypotension with erect posture and with exercise is often troublesome, particularly with drugs blocking the adrenergic neurone (drive to both α and β receptors reduced); it is not troublesome where

* The inclusion of propranolol here is based on:
ZACHARIAS, F. J., *et al.* (1972). *Amer. Ht. J.*, **83**, 755.
PRICHARD, B. N. C., *et al.* (1969). *Brit. med. J.*, **1**, 7.
TARAZI, R. C., *et al.* (1972). *Amer. J. Cardiol.*, **29**, 633.

† If an initial rise of pressure should occur due to release of noradrenaline it can be blocked by phentolamine i.v. (α-adrenoceptor blocker).

α-receptor drive is spared (β-block) so that a rise in peripheral resistance can occur; methyldopa is intermediate in this respect.

Oral maintenance treatment for severe hypertension should be started at once if possible; parenteral therapy is seldom necessary for more than 48 hrs.

Unwanted Interactions

Sympathomimetics, including appetite suppressants (but excluding fenfluramine) and tricyclic antidepressants can, even in small doses, reverse the effects of hypotensives, especially of adrenergic neurone blockers. Phenothiazine tranquillisers may also exert a similar antagonism. The mechanism is interference with amine and drug uptake in nerve endings.

Methyldopa plus an MAO inhibitor may cause excitement and hallucinations.

Surgical anæsthesia may lead to a brisk fall in blood pressure in patients taking antihypertensives.

Phæochromocytoma

This tumour of the adrenal medulla secretes principally noradrenaline, but also variable amounts of adrenaline. Symptoms are related to this. Hypertension may be sustained or intermittent.

Diagnostic tests include measurement of catecholamine concentrations in blood and urine or concentrations of metabolites in urine.

Pharmacological tests are also used.

The phentolamine test if hypertension is sustained. 5 mg is given into the tubing of an i.v. infusion. If the high blood pressure is due to circulating adrenaline and noradrenaline, then phentolamine lowers it within 2 mins by at least 35 mm systolic and 25 mm diastolic, or to normal levels, most of the effect persisting for at least 5 mins. Equivocal results are common, especially in the presence of sedatives or hypotensives, or uræmia. Patients should remain supine.

The histamine test if hypertension is intermittent. The equivalent of 0·05 mg base is given into the tubing of an i.v. infusion. This may directly stimulate the tumour, and hence cause a brisk rise of blood pressure, often preceded by a brief fall. It sometimes precipitates a typical paroxysmal attack. Phentolamine should be available to terminate this if necessary. In a normal there is a brief drop followed by an overshoot of not more than about 10 mm. Hg systolic. The histamine test is potentially dangerous in the presence of hypertension.

Tyramine, which releases stored noradrenaline, is being tried as a test for phæochromocytoma. It may act by discharging tissue stores kept full by circulating catecholamines rather than by discharging the adrenal medulla.

Control of blood pressure and heart rate where the tumour cannot be located or removed is achieved best by a combination α- and β-adrenoceptor block.

The α-block chiefly controls the blood pressure by abolishing peripheral vasoconstriction, and the β-block controls the tachycardia. A β-blocker should not be given alone, for although it blocks the cardiac stimulation, it also abolishes the peripheral vasodilator effects of adrenaline, leaving the powerful α-effects unopposed, so that there is a rise in peripheral resistance and a further rise of blood pressure. At present, no β-blocker is sufficiently selective for the heart to avoid this effect.

The notion of using a β-blocker as a provocative test for phæochromocytoma is unattractive, for it is only likely to work where there is sufficient circulating catecholamines to enable the diagnosis to be obtained by measuring these in the urine, supported, perhaps, by the less potentially dangerous phentolamine test. Provocative tests are never tests of choice.

For *surgical removal*, where the site of the phæochromocytoma is known, the patient may be spared the effects of liberation of dangerous amounts of catecholamines due to anæsthesia and handling of the tumour, by preparation for two to three days with α- and β-blockers (phenoxybenzamine plus propranolol), so that operation is conducted under complete or partial adrenoceptor blockade. This prolonged preparation allows the ordinarily low blood volume (due to vasoconstriction) to be restored to normal before surgery. The patient must, of course, be kept supine if large doses of α-blocker are used. Maintenance of blood volume during and after surgery is essential, for the blood pressure depends on it, though the vessels retain their responsiveness to angiotensin, which could be used in an emergency.

Where the site of the tumour is unknown, blood pressure changes can provide a useful guide to indicate when the surgeon has found it; complete adrenoceptor block would prevent this. A quick-acting α-blocker (phentolamine), plus a β-blocker (practolol) should be kept at hand to control the blood pressure and heart rate and rhythm. After the adrenal veins have been clamped, a pressor infusion may be needed to maintain the blood pressure; angiotensin may be best for this.

α-methyl tyrosine has been used successfully to block catecholamine synthesis. It inhibits tyrosine hydroxylase which converts tyrosine to dopa, a precursor of dopamine and noradrenaline.

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Chapter 19

DIGITALIS AND ANTI-ARRHYTHMIC DRUGS

DIGITALIS AND OTHER CARDIAC GLYCOSIDES (*1* to *23*)

"We think the Public under great obligations to Dr. Withering. . . ."

(From a 1785 review of *An Account of the Foxglove*, by William Withering.)

In 1775 Dr. William Withering was making a routine journey from Birmingham, his home, to see patients at the Stafford Infirmary. Whilst the carriage horses were being changed half way he was asked to see an old dropsical woman. He thought she would die and so some weeks later when he heard of her recovery he was interested enough to enquire into the cause.*

Recovery was attributed to a herb tea containing some twenty ingredients amongst which Withering, already the author of a botanical textbook, found it "not very difficult . . . to perceive that the active herb could be no other than the foxglove." He began to investigate its properties, trying it on the poor of Birmingham, whom he used to see without fee each day. The results were inconclusive and his interest flagged until one day he heard that the principal of an Oxford College had been cured by foxglove after "some of the first physicians of the age had declared that they could do no more for him." This put a new complexion on the subject and, pursuing his investigation, Withering found that foxglove extracts caused diuresis in some œdematous patients. He defined the type of patient who might benefit from it, and, equally important, he standardised his foxglove leaf preparations and was able to lay down accurate dosage schedules. His advice, with little amplification, would serve today. Crude foxglove preparations are called "digitalis."

Considerable skill and practice are needed to get the best results from digitalis and Withering knew this when, after ten years study, he wrote, "it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable."† In other words, digitalis, like most potent therapeutic agents can be a potent poison if misused. What Withering feared might happen, did happen; physicians ignored his instructions based on careful observation and long experience, poisoned their patients and blamed him. After seeing how other physicians used digitalis Withering observed, "shall we wonder then that patients

* Peck, T. W. and Wilkinson, K. D. (1950). *William Withering.* Wright: Bristol.

† Withering, W. (1785). *An Account of the Foxglove.* London: Robinson.

refuse to repeat such a medicine, and that practitioners tremble to prescribe it."

The result was that digitalis fell into disrepute, although it continued to be used in various diseases, including tuberculosis. 150 years were to pass before it finally became accepted as the asset that it is, and the details of its use in heart failure were worked out again and extended to cardiac arrhythmias.

Digitalis contains a number of active glycosides (digitoxin, digoxin, lanatosides) whose actions are qualitatively similar, differing principally in rapidity of onset and duration. In the present description, the word digitalis applies to all preparations. In prescribing it is necessary, of course, to specify the exact preparation intended.

The **mode of action** of digitalis is obscure. It increases the ability of the myocardial contractile proteins to convert chemical energy into useful work without requiring more oxygen, i.e. it increases the efficiency of the heart. Digitalis is thought to act chiefly by altering the distribution of Ca (but also of Na and K) in the myocardial cells.

Digitalis causes a loss of myocardial potassium, and *some* cardiac effects of severe poisoning can be reversed by giving potassium. Conversely, loss of potassium caused by vigorous diuretic or adrenal steroid therapy potentiates digitalis. Calcium increases digitalis effects in animals, so if calcium must be given i.v. to digitalised patients caution is obviously necessary. Reduction of ionised calcium in the blood by means of a chelating agent has been used in therapy of digitalis poisoning.

The principal clinical uses of digitalis are:

1. **heart failure:** positive inotropic action.
2. **atrial fibrillation:** to control rate (see below).

The effects of digitalis may be summarised:

1. *Direct stimulation of the myocardium* (increased *contractility* or positive *inotropic* effect) and reduction in size of a failing dilated heart, leading to increased cardiac output with increased efficiency, i.e. more work per ml oxygen consumed.
2. *Increased myocardial* (a) *excitability* (capacity to respond to a stimulus) and (b) *automaticity* (capacity to initiate beats): leading to cardiac arrhythmias.
3. *Depression of conducting tissue* with increased refractory period, which protects the ventricles from excessive bombardment in atrial arrhythmias, but may cause bradycardia and sometimes even complete heart-block.
4. *Increased vagal activity* leading to:
   a. Decrease in atrial refractory period with conversion of flutter to fibrillation.
   b. Delay in atrio-ventricular conduction (effects as above).
   c. Bradycardia.

5. *Direct effects on the peripheral vessels* (constriction) are of negligible practical importance.

Details of the Effects

1. **Direct stimulation of the myocardium** with increased *velocity* and *force* of contraction occurs. In the failing heart there is a greater stroke and minute output with increased emptying in a shorter systole, which allows a longer diastolic rest for a given cardiac output.

Digitalis increases the work done by the dilated and failing heart without increasing its oxygen consumption. This is the principal therapeutic action in heart failure and is not related to that which is made use of in controlling atrial fibrillation (*9*).

A note on pathophysiology. Within physiological limits, a load imposed on the heart that causes increased end-diastolic pressure or volume (stretching of the myocardial fibres) results in an increase in cardiac contractility and cardiac output is maintained or increased (Starling's law). But if the load causes stretching beyond the physiological limit the heart fails to generate sufficient systolic work to eject all the blood and it dilates and venous filling pressure increases and dilates it more. One reason it fails to generate the necessary work is that in a dilated heart (with over-stretched muscle fibres) the muscle must generate several times as much tension (using more oxygen) to achieve a given intraventricular pressure as in a non-dilated heart.

The effect of digitalis is to increase the contractility of the ventricle so that it empties fully, the dilatation is reversed and venous filling pressure falls.

Digitalis is used in all sorts of heart failure. Where the cause is mechanical (e.g. valvular disease) and the myocardium is healthy, the response is generally better than where the cause is disease of the myocardium itself (e.g. ischæmia).

Where heart failure is associated with rapid rate, digitalis benefits by slowing it; especially when pulmonary œdema develops in mitral stenosis as a result of rapid atrial fibrillation.

With cardiac tamponade digitalis is of little use unless the tamponade is relieved, which may itself suffice to relieve failure.

In patients with heart disease and enlargement, but without clinical evidence of failure, digitalis reduces the oxygen debt following exercise (*12*) This raises the question of using digitalis in latent heart failure; there is no generally accepted opinion.

In the normal heart, myocardial stimulation occurs, but it is not translated into increased output (*23*).

2. **Increased myocardial excitability and automaticity** carries no therapeutic benefit. With high doses, ventricular ectopic beats occur and give rise to the classic digitalis-induced arrhythmia, coupled beats or bigeminal pulse, when each normal beat is followed closely by an ectopic

ventricular beat which is followed by a compensatory pause. Beats thus occur in pairs. Regular coupling may not occur and the appearance of any ectopic beats in a patient on digitalis gives food for thought.

If the ventricular ectopic beats show complexes of different shape on the electrocardiogram, that is, if there is more than one focus in the ventricle initiating impulses (multifocal ectopic beats), there is risk of ventricular tachycardia and fibrillation and action must be taken (see under toxicity).

Atrial tachycardia with atrioventricular block can be a sole manifestation of digitalis intoxication and may occur with quite low doses, especially with diuretics that cause K loss. It should be suspected in a digitalised patient, without thyrotoxicosis, if an initially high ventricular rate either does not fall or increases, or if congestive cardiac failure suddenly worsens, or reappears without obvious cause. The differential diagnosis may be difficult, but is important as this arrhythmia is an indication for withdrawing digitalis and treating (see under *toxicity*).

Sympathomimetic amines and aminophylline also increase cardiac excitability, and so are liable to cause arrhythmias in digitalised patients. They should therefore be used cautiously. Reserpine may promote digitalis arrhythmia.

In the ventricle, digitalis shortens the refractory period and this may contribute to the occurrence of ventricular fibrillation which is the usual cause of death in digitalis poisoning. For effect on atrium see below.

3. **Depression of conducting tissue.** The refractory periods of the atrioventricular node and bundle of His (junctional tissues) are increased and conduction velocity is slowed (prolonged P–R interval on the electrocardiogram). In therapeutic doses this has no effect on the normal heart rate. In atrial fibrillation the result is to protect the ventricle from bombardment with the too numerous impulses which often make it contract before diastolic filling is complete. With toxic doses complete heart-block may occur. The vagal stimulant action also slows conduction.

Where heart failure is accompanied by marked tachycardia, as in atrial fibrillation, cardiac slowing is important in relieving the failure.

Heart rate in atrial flutter is controlled (less readily) by the same action as in fibrillation, but in addition the flutter may be converted to fibrillation by the vagal effect on the atrial refractory period, see below.

4. **Increased vagus nerve activity.** The site of this action is not agreed. It may be by sensitising the pacemaker to acetylcholine or by lowering the threshold of carotid baroreceptors.

The vagal activity induces slowing chiefly due to an effect on the pacemaker, but also by slowing velocity of conduction in the atrioventricular conducting system.

The tachycardia of low-output heart failure is a sympathetic reflex response to reduced cardiac output. The slowing that occurs with digitalis is chiefly due to restoration of normal output rather than to vagal or other actions.

The slowing of the tachycardia of atrial fibrillation is due to both vagal and direct action on the conducting tissue.

Digitalis does not directly depress the pacemaker except in toxic doses.

Vagal slowing can be differentiated from that due to direct action on conducting tissue or to relief of heart failure by blocking the vagal nerve endings with atropine. At lower doses vagal predominates over direct effect. At higher doses the heart remains slow in the presence of atropine. This slowing may be due to interference with response to sympathetic transmitter.

In addition, vagal stimulation shortens the refractory period of atrial muscle and increases the speed of atrial impulse conduction. This overcomes the direct action of digitalis on atrial muscle which is to lengthen refractory period. Whether this effect is responsible for converting atrial flutter into fibrillation as commonly occurs with digitalis is uncertain.

When treating atrial arrhythmias the number of impulses reaching the atrioventricular node may thus be actually increased, but the effects, both vagal and direct, on the conducting system predominate so that the desired degree of conduction block can be got.

5. **Direct effect on the peripheral vessels.** Digitalis has a slight direct constrictor effect on both arteries and veins. However this is of little clinical importance, for in low output cardiac failure there is already marked constriction of both kinds of vessels, and the increase in cardiac output due to digitalis is followed by a reflex reduction of this constriction.

Other effects of digitalis

Electrocardiographic effects of digitalis are as follows: The T wave becomes smaller, disappears or may become inverted. The S–T segment sags below the iso-electric line. The P–R interval is prolonged (delayed conduction). The Q–T interval is shortened (shorter ventricular systole). These changes are small in a normal heart, but may be very conspicuous in a diseased myocardium.

Blood pressure. In ordinary doses the blood pressure is not affected and any change is secondary to improvement of heart failure. Thus a rise of blood pressure may occur if it is low due to heart failure, or, if the pressure is abnormally high, as it is in some cases with intense peripheral vasoconstriction, it will be lowered towards normal. However, a large i.v. dose of strophanthin or digoxin may occasionally cause a transient rise of blood pressure by stimulating the myocardium. There is no direct effect on the **kidney,** diuresis being secondary to improvement in the renal circulation.

Pharmacokinetics. After oral administration peak plasma concentrations of digoxin are reached in 30–60 mins so that parenteral use is only necessary if there is reason to fear impaired absorption or if there is real urgency. The plasma half-life is about 40 hrs (digitoxin 160 hrs). With chronic use it is unimportant whether the drug is taken on a full or empty stomach.

Plasma concentration is measured by radioimmunoassay and studies

in patients show that the range of concentration consistent with effective digitalisation is wide and numerous factors affect the relative concentration of digoxin in plasma and myocardium. The place of measurement of digoxin (or other glycoside) concentrations in plasma in the routine optimising of therapy is still undecided. This is largely because myocardial concentration is not constantly linked to plasma concentration and because numerous factors affect response, plasma K, state of myocardium, age, etc.

But where it is doubtful whether worsening failure, increasing rate in atrial fibrillation or an arrhythmia may be due to disease or to digitalis toxicity, measurement of plasma concentration can be useful. Blood should be taken not less than 6 hrs after a dose, obviously.

The range of plasma concentration for therapeutic effect is about 0·5 to 1·5 ng/ml; toxicity is likely at about 2 ng/ml and almost invariable above 3 ng/ml. But correlation is not good and figures must be considered with full knowledge of the patient's state.

Digoxin is about 30% bound to plasma albumin and if this is low then the patient may be intoxicated with a total concentration within the normal range.

Digoxin is a little metabolised in the liver and largely excreted unchanged.

Digitoxin is largely metabolised in the liver and only a little is excreted unchanged.

Hepatic insufficiency potentiates both drugs, but in **renal insufficiency** there is an importance difference. The half life of digoxin increases with renal insufficiency until it may equal that of digitoxin (creatinine clearance is a better guide than plasma urea concentration). But that of digitoxin remains much the same or even decreases, probably due to increased inactivation by the liver. Digitoxin may thus be preferred in progressive renal failure.

Accumulation. Because of the long half-lives (see above), daily administration is liable to lead to accumulation and dose must be carefully adjusted. After a change of dose, stability will be attained in about 4 half-lives. In the case of digoxin, some effect of a single dose persists for 2 or 3 weeks (see table). It is important to ask patients if they have had any form of digitalis recently prior to giving a full digitalising dose. If they have had it, a lower dose must be used (see table).

Direct current shock is liable to induce dysrrhythmia in a fully digitalised patient; it is best to withdraw digitalis for 24–48 hrs before applying shock.

Intolerance occurs in thyrotoxicosis and in the aged and in neonates. Children may be relatively tolerant.

The Principal uses of digitalis may be summarised:

1. **In cardiac failure,** left ventricular or congestive, benefiting the patient chiefly by the direct stimulant action on the myocardium.

2. **In atrial fibrillation,** benefiting chiefly by vagal and direct effects on conducting tissue.

3. **In paroxysmal supraventricular tachycardia,** benefiting chiefly by vagal effects on the sino-atrial node and on the conducting tissue.

4. **In atrial flutter,** acting chiefly by vagus nerve effect on the refractory period of the atrial muscle (shortened), to convert flutter to fibrillation.

The principal preparations are included in the table. The pure glycosides, digoxin and digitoxin, are now generally used, but good results can, of course, be obtained with a crude preparation of the dried leaf (Prepared Digitalis). But, other things being equal a pure substance is preferable to a crude and potentially variable mixture; it contains digitoxin.

Digoxin (Lanoxin) is available as a tablet (see table) and as an oral solution, a pædiatric elixir, pædiatric/geriatric tablets, and as an injection.

Digitoxin (Crystodigin, Nativelle's Crystallised Digitaline) is available as a tablet and an injection solution.

Lanatoside C (Cedilanid) is available as a tablet, it is unstable in solution and the deacetyl derivative, deslanoside, is given by injection. Absorption from the gut is irregular. It is the quickest acting glycoside i.v.

Ouabain (strophanthin-G) is obtained from a strophanthus plant and is used i.v. for quick effect. It is unreliable orally. Strophanthin-K is a mixture of glycosides of variable potency. The word strophanthin used alone is therefore liable to misinterpretation.

Acetylstrophanthin is reliably absorbed after oral administration. After injection its action appears in a few minutes and lasts up to two hours. It is used experimentally only.

The choice of a preparation of digitalis is easy. **Digoxin** or **digitoxin** are generally satisfactory for all purposes. The other preparations only need to be considered in special cases, for instance, in those rare patients who vomit on low doses of the above preparations it may be possible to obtain effective digitalisation with lanatoside C by mouth without inducing vomiting. The word *digitalis* should not be used in prescribing.

There are yet other digitalis preparations, often mixtures of glycosides, which have confusing names and which, since they offer no advantages over the preparations named above are best avoided. Digitalin or digitaline especially should be shunned as it may be any one of a number of preparations of varying composition and dose. Nativelle's Crystallised Digitaline is pure digitoxin. Various other substances with digitalis-like action occur in nature. Little success has attended attempts to use them in therapeutics but they make useful weapon and ordeal poisons (*4*).

Biological standardisation is not necessary for pure glucosides. Crude plant preparations have to be standardised biologically. There is no satisfactory method despite enormous slaughter of frogs, pigeons and cats. At one stage it was found that preparations could be "legally weak but therapeutically strong".*

Administration and dosage. Digoxin is given orally or i.m. whenever possible. For i.v. use lanatoside C is preferred, since the sole objective

* Gold, H. (1959). *In Quant. Methods in Human Pharmacol. and Therap.* Ed. Laurence, D. R. London: Pergamon.

of i.v. use is speed; it acts in 10–30 min (digoxin, 15–60 min). The optimum dose of digitalis is fairly easy to find in cases of atrial fibrillation where the heart rate is a useful indication of the therapeutic effect. But in congestive cardiac failure the heart rate is not a useful guide and if the average dose does not produce all the improvement desired, it is necessary to increase it up to the point of producing toxic effects and then to reduce it slightly to ensure that the optimal therapeutic amount is being given, i.e. maximum tolerated dose. Fluctuations of plasma K render dose adjustment more difficult.

THE DOSAGE AND DURATION OF ACTION OF THE PRINCIPAL CARDIAC GLYCOSIDES

Glycoside (Source) (*Tablet size in mg*)	*After single i.v. digitalising dose:*		*i.v. digitalising dose*	*Total oral digitalising dose given in 3–4 doses 6 hrs apart*	*Total daily oral maintenance dose*	*Remarks*
	Time of max. effect	*Duration of effect*				
digoxin (from digitalis lanata) (0·25, 0·0625)	3 hrs	5 days	0·75–1·0 mg* (or i.m.)	2·0–4·0 mg	0·25–0·5 mg	Satisfactory for all routine therapy
digitoxin (from digitalis purpurea) (0·1, 0.2, 0·25)	8 hrs	18 days	1·0–1·2 mg†	1·0–2·0 mg	0·05–0·2 mg	Satisfactory for all routine therapy; very cumulative
lanatoside C (from digitalis lanata) (0·25, 0·5)	3 hrs	5 days	1·2 mg, then 0.4 mg 2-hrly till heart slowed	Start oral digoxin with i.v. lanatoside C		For quick effect. Not used orally as absorption irregular.

A full digitalising dose should not be given if digitoxin or crude digitalis have been taken in the previous 14 days, nor if digoxin or lanatoside C in the previous 5 days; otherwise toxic effects are likely due to persistence of action of the previous doses. If there is doubt about how much to give i.v., a small dose may be given and repeated in a few hours if there is neither clinical improvement nor toxicity.

* Rarely 1·5 mg.
† Rarely 2·0 mg.

An Adult may be digitalised thus:

In haste: digoxin 1·0 mg. or i.m. (occasionally 1·5 mg) followed by 0·5 to 0·75 mg i.v. or i.m. 6-hrly until a therapeutic or a toxic effect appears. An adult is likely to need a total of 4 mg. Then give an oral maintenance dose of 0·25 mg two or three times a day and adjust it by results. Lanatoside C is quickest i.v. (see above); oral digoxin is started at the same time.

At leisure: the same doses of digoxin can be given orally, or less, e.g. 0·5 mg three times a day. Equivalent doses of digitoxin (see table) will be equally satisfactory.

Bioavailability of the drug in different formulations may differ substantially. The difficulties of using the drug are sufficient without this factor added. It is important that a formulation from a reliable source be chosen and adhered to. It seems that there may be differences in different localities (*18*, *20*).

Maintenance therapy with digitalis for *heart failure* is generally necessary permanently, provided the indication for starting it was known cardiac disease. It may be withdrawn if the cause of the failure is removed, e.g. by surgery.

For *atrial fibrillation* digitalis is the best drug to control rate if the fibrillation cannot be terminated.

In one study of 53 elderly patients in general practice digoxin was successfully withdrawn in 48. The criterion for prescribing must be *known* cardiac disease, not merely an inference of it, e.g. œdema which may be due to varicose veins; breathlessness which may be due to lung disease.

Toxicity of Digitalis (*21*, *22*)

Toxicity of digitalis was well described by Withering. "The Foxglove, when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, dizziness, confused vision, objects appearing green or yellow . . . slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death."

In 1969 a manufacturer made "digoxin tablets" with a mixture of digitoxin and digoxin by mistake (*22*). This caused a large number of patients to receive a dose of cardiac glycoside 2 to 4 times higher than intended. Intoxication developed in 179 patients mainly between the second and ninth weeks. On withdrawal symptoms disappeared over 1–4 weeks in most cases. The overdose contributed to death in 6 patients (arrhythmias).

Symptoms in order of frequency were: fatigue (95%), visual, e.g. haziness, colours altered and indistinct, moving spots, rings, flames, red, green or dark colours, etc. (95%), muscle weakness (82%), nausea, anorexia (80%), psychic symptoms, e.g. dreams, restlessness, agitation, etc. (65%), abdominal pains (65%), dizziness (59%), headache (45%), diarrhœa (41%), vomiting (40%), retrosternal pains (9%).

Cardiac disturbances were chiefly heart block (first degree) and unifocal ventricular extrasystoles but a wide variety of other arrhythmias occurred including ventricular tachycardia. Bradycardia does not necessarily precede these arrhythmias.

Symptoms of intoxication have been reported in from 7 to 20% of patients under routine treatment.

Vomiting is principally central, due to stimulation of the chemoreceptor trigger-zone connected to the vomiting centre in the brain, but is to some extent due to local effect in the alimentary tract. As vomiting in relation to therapeutic effect is less when digitalis is injected, the i.m. route may be useful in patients disabled by vomiting at low doses.

Milder toxic manifestations require only omission of the drug for a day or two. Dangerous arrhythmia may demand administration of potassium chloride orally (5 to 7 g), which acts in 30 mins and lasts for several hours. Since toxic effects are liable to return 1 g potassium chloride may be given orally three times a day subsequently, for a day or two. In desperate circumstances, 1 g. potassium chloride may be given slowly (1 hr) i.v., provided the pulse and preferably the electrocardiogram are monitored continuously. Too rapid injection is liable to stop the heart. One recommendation is that oral or i.v. dosage should total less than 0·5 mEq./min. (*10*). Serum potassium should not be allowed to exceed the normal limit. Potassium is dangerous by any route if there is renal failure. Potassium itself prolongs myocardial refractory period and slows conduction, and these effects may be as important as replacement of myocardial cellular potassium extracted by digitalis.

Phenytoin, lignocaine or a β-adrenoceptor blocker are often effective in digitalis dysrrhythmia. There is a risk of inducing heart block, but in an emergency when the plasma K is unknown it may be necessary to use one of them.

If there is bradycardia or heart block atropine can be used to block the vagus.

Electrical pacing may be needed.

After overdose it may be necessary to withdraw digitalis for up to a week, and then to recommence cautiously with very small doses. Allergy to digitalis is extremely rare.

Diuretics, especially the thiazide group, and adrenal steroids may precipitate digitalis toxicity by depleting the body of potassium. In a similar way i.v. administration of glucose may induce cardiac arrhythmias in digitalised patients.

The toxic effects of digitalis on the normal heart differ from those seen in therapeutic practice. The chief source of information is obtained from young children who have eaten digitalis intended for others.

In one series (*14*) of 48 cases of **accidental poisoning in children** (generally 1½ to 3 years old) the drug was intended for the grandmother in 40 cases. She was often only on a visit to the child's home so that her drugs may have escaped any domestic safe-keeping routine. The principal effects of acute digitalis poisoning in the normal child are: exaggeration of normal sinus arrhythmia, with bradycardia (probably due to increased vagal tone); heart block is uncommon (it is the commonest sign of toxicity in diseased adults), the classic electrocardiograph changes may be absent; vomiting and drowsiness are prominent.

Treatment of Cardiac Failure

The possibility of treating the cause should always be considered, e.g. anæmia, thyrotoxicosis, respiratory disease, beri-beri and valvular disease (by surgery).

In cardiac failure due to myocardial infarction there has been a difference of opinion on whether it is safe to use digitalis, for fear of rupturing the damaged ventricle and of promoting the ventricular arrhythmias which are prone to occur in that condition. The matter is not settled finally but it is probably the lesser risk to use the drug when failure is present or if atrial arrhythmia occurs. The oral route should be used if possible, to reduce the risk of arrhythmia, which is probably greater with i.v. injection.

In cardiac failure complicated by arrhythmias the appropriate drug therapy of the arrhythmia is not affected by the presence of the heart failure, except that attempts to convert it to normal rhythm are less likely to succeed.

Severe cardiac failure (see also œdema)

1. General: Morphine may be useful to relieve distress of acute pulmonary œdema. It may cause dangerous respiratory depression in patients with heart failure due to pulmonary insufficiency but is very useful in paroxysmal nocturnal dyspnœa. Constipation, with consequent straining at stool (Valsalva's manœuvre) and increased oxygen demand should be prevented.

2. The patient may be digitalised i.v. and, if very ill, 500 mg of aminophylline may also be given very slowly i.v. Digitalis is continued by mouth (see table). In very severe cases the dose needed to produce maximal therapeutic effect may be only just below or, rarely, just above that which causes serious toxicity.

3. Diuretics play an important part in relieving heart failure. For speed and certainty frusemide or ethacrynic acid by injection gives excellent results, but in many patients an oral diuretic is adequate from the start. If frusemide is used at first, an oral thiazide may be substituted after one or two injections. Spironolactone may be added.

4. Acute pulmonary œdema due to hypertension can be treated by frusemide i.v., repeated as necessary or by a vasodilator (see hypertensive emergency). The vasodilator reduces the filling pressure of the heart by causing pooling of blood in the periphery, and frusemide acts by reducing the blood volume. Alternatively venous cuffs on the limbs or actual venesection will give relief but they are rarely needed.

5. A low sodium diet is not necessary with the effective diurectics now available. But it is worth remembering that patients sometimes take much sodium as antacids, which can be an obscure cause of failure of therapy.

6. Deliberate induction of hypothyroidism with drugs or ^{131}I has been used in otherwise intractable cases, to reduce oxygen requirements.

Milder cardiac failure

The general treatment is the same as for severe cases but is carried out more leisurely. The patient may be digitalised orally and oral diuretics used at appropriate intervals.

In cases of congestive cardiac failure where the cause is untreatable, digitalis will probably be needed for the rest of the patient's life as well as occasional use of diuretics. In chronic heart failure dyspnœa on exertion may be better relieved by diuretics than by digitalis.

DRUGS USED FOR CARDIAC ARRHYTHMIAS

The physiology of cardiac arrhythmias is complex and the actions of drugs that are useful in stopping or controlling them are equally so. Useful drugs either delay repolarisation of myocardial cells and increase refractory period (quinidine, procainamide) or hasten repolarisation and shorten refractory period (lignocaine, phenytoin, digitalis, propranolol). Automaticity is depressed by all.

Conducting tissue is depressed by most drugs (quinidine, procainamide, digitalis, propranolol, lignocaine), but phenytoin usually enhances conduction. But effects vary according to different cardiac sites and with the state of the heart.

It is not possible to provide a rational basis for clinical choice of the drugs, despite the large amount of detailed experimental knowledge.

Many antiarrhythmic drugs can also cause arrhythmias in overdose, posing a difficult problem of diagnosis.

β-adrenoceptor blockers (which see) are increasingly used; practolol may be a drug of first choice as it depresses the heart less than propranolol.

QUINIDINE

Quinidine is used to prevent and to stop certain arrhythmias and tachycardias (see below). It has no direct beneficial effect in heart failure as it is primarily a cardiac depressant. Its use in *acute* arrhythmias is declining (replaced by direct current shock), but it is still valuable in *prevention.*

Quinidine is the optical isomer of quinine. Both substances have cardiac and antimalarial effects, but their relative potency differs. The cardiac effect of quinine was observed in 1749 when it was used against "rebellious palpitation", but this was not followed up. In 1912 Wenckebach was visited by a Dutch merchant who wished to get rid of his attacks of atrial fibrillation, which, although they did not unduly inconvenience him, offended his notions of good order in life's affairs. On receiving a guarded prognosis the merchant enquired why there were heart specialists if they could not accomplish what he himself had already achieved. In the face of Wenckebach's incredulity he promised to return the next day with a regular pulse and he did so, at the same time revealing that he had done it with quinine. At that time quinine had a reputation as a general

remedy rather like that of aspirin today and, taking it empirically, the merchant had found that a gram of quinine would abolish his attacks in about 25 mins (*24*).

Examination of quinine derivatives led to the introduction of quinidine in 1918.

It is a cardiac depressant with the following principal actions. It:—

Depresses the excitability of cardiac muscle, thus suppressing ectopic pacemakers. This effect is utilised when quinidine is used to stop and to prevent arrhythmias.

Prolongs the effective refractory period of cardiac muscle. This action is utilised in converting atrial fibrillation to normal rhythm and in preventing recurrence.

Depression of contractility (negative inotropic effect): slight only at ordinary doses with normal myocardium: may be important in diseased myocardium.

Depresses cardiac conducting tissue and prolongs its effective refractory period; it also slows the speed of impulse conduction throughout the heart.

Pacemakers are slowed.

Reduces vagus nerve activity on the heart, like atropine, and therefore protects it from the effects of cholinergic drugs, e.g. methacholine. This antagonism may have clinical importance in causing the failure of cholinergic drugs to arrest severe tachycardias in patients on quinidine. Reduction of vagal tone prolongs the atrial muscle refractory period and so may contribute to the antifibrillatory effect of quinidine.

Other effects include hypotension when it is given i.v. (a combination of peripheral vasodilation and depression of the vasomotor centres and of heart muscle).

Electrocardiographic changes occur with therapeutic doses. The most characteristic effect is prolongation of the Q–T interval due to prolongation of ventricular systole. In addition there may be prolongation of the P–R interval (atrio-ventricular conduction block), and inversion and prolongation of the T wave.

Pharmacokinetics. Absorption of quinidine from the gut is rapid, the action of an oral dose being maximal in about 3 hrs and lasting for about 8 hrs. Therefore when an increasing effect is required, as in attempts to stop arrhythmias, the drug is given every 2 or 3 hrs. If a steady effect is desired doses are usually given 6-hrly when there is slight cumulation for 5 days, after which the effect is constant. It is about 60% bound to plasma albumin. Its plasma half-life is 3–4 hrs.

The drug is partly metabolised and partly excreted unchanged in the urine. These processes are slower in patients with cardiac failure.

There is wide individual variation in plasma concentration following standard doses, and maximum benefit with minimum risk can be got by controlling therapy with frequent measurements of *plasma concentration*, though this may be seldom practicable.

Contra-indications. Quinidine is dangerous in the aged, in patients with severe infections, cardiac damage (e.g. bacterial endocarditis, myocardial infarction, severe valvular disease, atrio-ventricular conduction defects, cardiac enlargement, a history of embolism) or allergy to the drug.

The presence of therapeutic amounts of digitalis does not add to the danger of quinidine, though it is dangerous in digitalis intoxication, chiefly because of the additive effects of the two drugs on conducting tissue.

The decision when to use quinidine requires considerable skill and experience.

Unwanted effects. Cardiac effects vary from ectopic beats to cardiac arrest, ventricular tachycardia or fibrillation even at low doses. This effect is perhaps surprising at first sight in a drug which is used to suppress and prevent these irregularities when they are due to other causes. It is suggested, however, that severe depression of the sinoatrial and atrio-ventricular nodes, the areas with greatest rhythmicity, allows other areas of the heart to form foci of contraction.

Cinchonism occurs, as with quinine, and generalised muscle weakness. Allergy is not rare: rashes, urticaria, angioneurotic œdema, hypotension and collapse, respiratory failure and thrombocytopenic purpura occur. There is sometimes cross-allergy with quinine.

Administration and dosage of quinidine

Oral administration of quinidine (0·2 g) is used except in emergency or when there is vomiting. A test dose (0·2 g) to reveal the presence of intolerance or allergy is often recommended, 4 hrs before starting, but it is probably valueless. Digitalisation prior to using quinidine is also advised by some, but there is only general agreement on the desirability of this in atrial fibrillation and flutter. Some physicians consider both these precautions to be unnecessary, but it is impossible to be dogmatic on either point as the necessary evidence does not exist.

The usual method of giving quinidine to convert an arrhythmia or stop a tachycardia is 0·2 g 2-hrly, orally, for 6–7 doses. If this fails each dose is increased to 0·4 g on the next day, then 0·6 g, then 0·8 g. The patient must be closely watched and an electrocardiogram between the 4th and 5th dose is useful in detecting overdose.

An alternative which may be effective in cases where the 2-hrly regimen causes toxic effects is to give quinidine 0·2 g 6-hrly for 5 days, then 0·4 g 6-hrly for a further 5 days then 0·6 g, 0·8 g and so on.

The moment the desired change is achieved the dose is dropped to a maintenance level which is usually about 0·2–0·4 g, 3–6 times/day, although more may be needed. This may be continued for 3 weeks, when it may be stopped to see what happens. Indefinite administration may be needed and a slow-release formulation (Kinidin Durules) is available for maintenance.

Patients with frequent attacks of an arrhythmia with an apparently normal heart commonly need permanent prophylactic administration, but those with

mild and infrequent attacks can sometimes do without it even from the moment of conversion.

Patients with organic heart disease are also likely to need permanent prophylaxis and some physicians consider this to be dangerous when fully adequate doses (1·2 g/day) are used.

Quinidine should never be continued indefinitely if an arrhythmia is not converted. It then does no good and may interfere with adequate digitalisation for heart failure.

Quinidine should be stopped if toxic effects more serious than nausea, tinnitus or mild diarrhœa occur, or if the QRS complex on the electrocardiogram exceeds the control value by more than 50% (or 25% if there was initially some prolongation of the QRS), or if frequent (one every 6 secs) ectopic beats occur.

Toxic effects are common when total dosage exceeds 3 g in 24 hrs.

Intramuscular and intravenous routes are not generally used; they carry hazard and require close monitoring.

PROCAINAMIDE, LIGNOCAINE, ETC.

It has been known for a long time that procaine has quinidine-like effects, but its rapid destruction in the blood as well as its convulsant action, prevented its use as a substitute for quinidine. Study of related substances showed that procainamide is less quickly destroyed than procaine whilst retaining the cardiac and local anæsthetic actions, but having less central stimulant effect.

DOSAGE OF PROCAINAMIDE IN CARDIAC ARRHYTHMIAS

Route of administration	*Ventricular arrhythmia*	*Atrial arrhythmia*	*Prophylactic maintenance*
Oral	0·5 to 1·0 g 6-hrly	1·25 g first dose and then 0·5 or 1·0 g 2-hrly	0·5 to 1·0 g 4 to 6-hrly
Intramuscular	0·5 to 1·0 g 6-hrly		—
Intravenous	100 mg per minute up to a total of 600 mg or rarely higher		—

Procainamide is well absorbed from the alimentary tract giving a maximum effect in 1 hr (30 mins, given i.m.). It can also be given i.v. Its half-life is 3–4 hrs. Unwanted effects include hypotension, nausea and vomiting, diarrhœa, giddiness and mental depression or hallucinations. Allergic reactions occur, including agranulocytosis. There is cross-allergy with procaine.

Contra-indications and precautions during use are the same as those for quinidine.

Doses are given in the table. Atrial arrhythmias may be less sensitive to procainamide than to quinidine, and so require higher doses than ventricular. The principle of administration is the same as for quinidine, that is, the dose of the drug is increased until either a therapeutic or a toxic effect is obtained.

Choice between Quinidine and Procainamide

Those who regard the two drugs as interchangeable may be right; conclusive evidence does not exist. But procainamide may be less effective than quinidine in atrial arrhythmias, and more effective in ventricular arrhythmias. Hypotension during i.v. injection is usually less severe than with quinidine. With either drug, if hypotension is prolonged, a pressor sympathomimetic may be used to counteract it.

Other drugs used in arrhythmias include:

Lignocaine is used chiefly in ventricular arrhythmias, especially after acute myocardial infarcts.

The plasma $t_{\frac{1}{2}}$ of a single dose is 20 min but of repeated doses is about 2 hrs and if it is given every 30 min it will accumulate over about 10 hrs. It is metabolised in the liver and metabolism is considerably delayed in congestive heart failure.

Adverse effects include hypotension, dizziness, blurred sight, sleepiness, subjective difficulty in talking, or swallowing, numbness, sweating and confusion, twitching and fits. It can be given intermittently, 1–2 mg/Kg every 30 min until a therapeutic effect has occurred or 750 mg has been given: continuously, 1–2 mg/Kg initially and then 1–4 mg/min: it can be given i.m. and orally.

Phenytoin (see also under *antiepileptics*) is not a cardiac depressant, indeed it has positive inotropic effect and enhances conduction, though it generally decreases automaticity. It can be useful in ventricular arrhythmias especially these due to digitalis.

A usual i.v. dose is 3–5 mg/Kg in 3 min and repeated every 5–10 min until something happens (watch B.P.) or 1·0 g has been given. Orally, a priming dose of 1·0 g is given and 100 mg 6-hrly for maintenance. The half-life is about 24 hrs.

Bretylium is an adrenergic neurone blocker though it is not used in hypertension because tolerance soon develops. It also has a positive inotropic effect and increases automaticity. Its antiarrhythmic effect is chiefly employed in ventricular arrhythmias after myocardial infarction. The i.m. dose is about 5 mg/Kg followed by 2–3 mg/Kg, 8–12 hrly; it can be given i.v.

β-adrenoceptor blocking drugs (which see) have an important place in arrhythmias; some have quinidine-like effects too.

In addition, *verapamil* (Cordilox), disopyramide (Rythmodan) and *antihistamines*, are used and also α- and β-adrenoceptor stimulants and cholinergic drugs when their particular actions seem likely to be useful.

DRUG TREATMENT OF ABNORMALITIES OF CARDIAC RATE AND RHYTHM

Pharmacology of the Cardiac Autonomic Nervous System

Some of the drugs used in heart diseases exert their effects through the autonomic nervous system by mimicking or antagonising the effects of parasympathetic or sympathetic nerves.

The vagus nerve (cholinergic, **parasympathetic**), when stimulated, causes the following effects on the heart:

a. bradycardia due to depression of the sino-auricular node
b. slowing of conduction in the bundle of His
c. reduced force of contraction of the heart
d. shortening of the refractory period of myocardium
e. decreased myocardial excitability

Some of the effects, *a*, *b*, *d*, and *e*, are used in the therapy of tachycardias and arrhythmias.

The vagus nerve may be stimulated reflexly by various physical manœuvres. These include painful pressure on one or both eyeballs for about half a minute, pressing *one* carotid sinus (the right is said to give better results) for the same time, Valsalva's manœuvre, swallowing ice cream and production of nausea by inviting the patient to put his fingers down his throat. Apomorphine "should be prescribed only by those physicians who have injected the drug into themselves".* A brisk rise of blood pressure (e.g. metaraminol) also causes reflex vagal stimulation via baroreceptors.

Cholinergic receptors serving the vagus may be stimulated by drugs which are destroyed less rapidly than acetylcholine (methacholine, carbachol) or by anticholinesterases (edrophonium) which prevent the destruction of the acetylcholine naturally produced at the nerve endings.

Digitalis increases vagal nerve effects.

The vagus nerve is blocked by atropine and similar drugs and to some extent by quinidine; these drugs also protect the heart from the effects of cholinergic drugs.

The sympathetic division (adrenergic) of the autonomic nervous system, when stimulated, has the following **effects on the heart** (β-effects):

a. tachycardia due to increased rate of discharge of the sino-auricular node.
b. increase in conductivity in the bundle of His.
c. increased force of contraction (contractility).
d. shortening of refractory period.
e. increased automaticity.

(It may be noted that the effects in the two lists above are not all opposites.)

The actions used in therapy of heart disease are *b*, when heart-block is treated by ephedrine or isoprenaline, and perhaps *c* in severe hypotension

* SCHERF, D. (1953). *Circulation*, **8**, 756.

due to myocardial infarction. All the sympathomimetic drugs produce these effects to a greater or lesser degree. Those with predominantly α-effects can also be used to obtain reflex vagal stimulation by raising the blood pressure.

Sympathetic cardiac stimulation (β-effect), can be reduced by β-adrenoceptor block (practolol is comparatively selective for the heart).

The Choice Between Drugs and Electric Shock Therapy to Terminate Arrhythmias

Direct current electric shock applied externally is now being widely used to convert cardiac arrhythmias to sinus rhythm. Many atrial or ventricular arrhythmias start as a result of transiently operating factors, but once they have begun, the abnormal mechanisms are self-sustaining. When an electric shock is given, the heart is depolarised, the ectopic focus is extinguished and the sinus node, the part of the heart with the highest automaticity, resumes as the dominant pacemaker. Drugs act by interfering with circulating waves of excitation and by depressing nodal and conducting tissue.

Electric conversion has the advantage that it is immediate, unlike drugs, which may take days or longer to act; also, the effective doses and unwanted effects of drugs are largely unpredictable.

Electric conversion can be particularly successful in supraventricular and ventricular tachycardia, and in atrial fibrillation and flutter.

Drugs can be useful to prevent relapse.

There is great variety in the use of drugs for arrhythmias.

Note: arrhythmias after acute myocardial infarction are relatively serious.

Ectopic Beats

Ectopic beats that are not due to organic heart disease seldom demand drug treatment. When they do, reassurance and sedation are best tried first, but small doses of a β-adrenoceptor blocker, quinidine or procainamide may be used if the former fail. Digitalis is effective but its use may lead the patient to think he has serious heart disease.

Paroxysmal Supraventricular Tachycardia

The mainstays of treatment are sedation, *vagal stimulation* by physical manœuvres (see above) and rapid *digitalisation.* If these fail, lignocaine, β-adrenoceptor block, or phenytoin may be tried.

Paroxysmal supraventricular tachycardia is usually a mild disease and it is well to remember that a patient may suffer more unpleasantness from a lens dislocated or a retina detached by heavy-handed eyeball pressure or from drug toxicity than from the disease.

Sometimes digitalis can induce attacks of supraventricular tachycardia if the vagal effect on atrial muscle (shortening refractory period) is not adequately counterbalanced by the direct effect on the pacemaker (prolongs refractory period). If there is any heart block digitalis may be

suspected as a cause of arrhythmia. In such cases a β-adrenoceptor blocker is useful in treatment and prophylaxis.

Prevention. Recurrent attacks may be prevented by a β-adrenoceptor blocker or by digitalis, procainamide, phenytoin, quinidine; they should be used in the lowest effective dose. Sedation can help. Causes such as thyrotoxicosis, excessive tea or coffee drinking or smoking should be eliminated.

Paroxysmal Ventricular Tachycardia

Electrical conversion is successful and probably safer than drugs.

Paroxysmal ventricular tachycardia, which is almost always due to severe organic heart disease, does not respond to vagal stimulation by any method. Lignocaine i.v. is a drug of first choice and β-adrenoceptor blockers can be successful. A thump on the mid-sternum or precordium may stop a tachycardia as well as restart an arrest (*45*). Quinidine or procainamide are often effective but may induce ventricular fibrillation. Digitalis, by increasing the excitability of the myocardium, may also cause fatal ventricular fibrillation, though it may have to be used for heart failure.

Ventricular Fibrillation (see Cardiac Arrest, below)

Ventricular fibrillation is usually due to severe organic heart disease. It may also be caused by excessive dosage of digitalis, procainamide, quinidine, adrenaline, cyclopropane, trichloroethylene and chloroform. In the case of the three anæsthetics the arrhythmia is probably largely due to the interaction of the drugs and naturally secreted adrenaline on the heart; it therefore follows that adrenaline should not be given to patients anæsthetised with these drugs. Noradrenaline is less dangerous in this respect.

Atrial Fibrillation

The heart is less efficient in atrial fibrillation, e.g. some ventricular beats fail to open the aortic valves, and patients feel and perform better when in normal rhythm.

Control. With long-standing rheumatic mitral valvular disease it is generally better to control the heart rate with digitalis than to convert it to sinus rhythm. If digitalis does not readily control the rate, propranolol may be added, rather than increasing the dose of digitalis. The patient needs rate control to allow adequate time for the ventricle to be filled through the narrow mitral valve.

Conversion. Where the arrhythmia has been present for less than 6 months it is usually possible to stop it, but there is a risk of causing embolism.

Embolism is the result of the resumed coordinated atrial contraction detaching recent, rather than old, organised, clot from the atrial wall. It occurs whether fibrillation is of recent onset or of long duration. Some

physicians give an anticoagulant for 2 weeks before conversion to lessen this risk.

If cardiac failure is present this should be treated before attempting conversion.

Electrical conversion is supplanting drugs. The chief indications are, uncontrollable ventricular rate and fibrillation persisting after removal of its cause, e.g. hyperthyroidism.

Conversion may also be achieved with *quinidine* and it is generally desirable to *digitalise* the patient before attempting it. Digitalis opposes the cardiac depressant action of quinidine (particularly important if the quinidine fails). In addition, the quinidine alone may, paradoxically, lead to sudden tachycardia as follows: the reduction of the high rate of atrial contraction with a considerable heart-block, to a lower rate without heart-block may result in a sudden tachycardia which can be disastrous, e.g. if 500 impulses per minute come from the atrium and the bundle of His transmits only one out of four (4 : 1 heart-block) the ventricular rate will be 125/minute. When quinidine slows the atrial rate to 200/minute, the bundle of His may, despite the effect of the drug in delaying conduction, conduct all the impulses, so that the ventricular rate rises suddenly from 125 to 200/minute. Prior full digitalisation prevents this by an additional A-V nodal depression.

After conversion, digitalis with or without quinidine may be needed to prevent reversion.

"Idiopathic" atrial fibrillation may be continuous or paroxysmal and digitalisation may be followed by resumption of normal rhythm. If not, it can be converted by quinidine. Prophylaxis with digitalis, quinidine or propranolol may be effective. If relapse is frequent or conversion difficult, it is better to put aside therapeutic ambition and to control the heart rate with digitalis.

Hyperthyroidism often causes atrial fibrillation, which usually reverts to normal rhythm when the patient has become euthyroid. If it does not, quinidine or procainamide can be used, with or without digitalis. In active hyperthyroidism, should it be necessary to use digitalis, it may not be possible to reduce the pulse rate below 80/minute without poisoning the patient; a β-adrenoceptor blocker is useful to reduce rate.

Atrial Flutter

Electrical conversion is effective, or it can be converted to fibrillation by *digitalis* (the pulse becomes irregular), which is then treated with *quinidine* if spontaneous reversion does not occur. Electrocardiographic control is important as irregularity may also be due to changing atrio-ventricular block. Digitalisation alone may restore normal rhythm, but if it does not alter the flutter quinidine may be added. Quinidine used alone may result in a sudden tachycardia as in atrial fibrillation. An alternative is digitalis plus *β-adrenoceptor blocker* i.v. Attacks of flutter may be prevented by prophylactic digitalis or quinidine.

Heart Block

Heart-block does not generally need treatment unless it produces Stokes-Adams attacks or congestive failure. The use of artificial pacemakers is beyond the scope of this book.

In an emergency i.v. atropine (0·6 mg) may be effective.

In acute cases of complete heart-block, e.g. after an infarct, an adrenal steroid (hydrocortisone i.v. or prednisolone orally) may be tried but is often ineffective. It may act by suppressing inflammatory reactions involving conducting tissues.

Sympathomimetic drugs may be used to improve conduction, isoprenaline i.v., 5 to 10 mcg./min, or sublingual tabs.: or, for prolonged therapy, a sustained-action preparation of isoprenaline to be swallowed (Saventrine).

Molar sodium lactate i.v. is sometimes successful in cases of multiple Stokes-Adams attacks and may succeed when the above drugs fail. Its mode of action is uncertain.

If congestive heart failure is present with heart-block, digitalis may be used and therapeutic effects achieved in doses which do not increase the heart-block. There is, however, a possibility of making the block complete. If block is already complete digitalis may be used freely.

Stokes-Adams attacks may be due to ventricular arrest, tachycardia or fibrillation, and some aspects are considered above.

Arrhythmias in Myocardial Infarction

Any kind of arrhythmia can occur and should be treated as serious.

Sinus bradycardia, often due to opiate analgesics (stimulate vagal centre), may cause severe hypotension; it can be relieved by atropine 0·6–1·0 mg by injection, though there is risk of arrhythmia with 1 mg or more.

Treatment of arrhythmia is as above, taking into account the amount of damage to the myocardium and any conduction defects in relation to the pharmacology of the drugs; e.g. a β-adrenoceptor blocker can cause heart failure; lignocaine or procainamide can render partial heart block complete.

Prophylaxis of arrhythmias. Since about 50% of patients develop severe ventricular arrhythmia in the first few hours after infarction and these are responsible for many deaths, attempts at prophylaxis have been made. Procainamide and β-adrenoceptor blockers are in use, but are not indicated for routine use in all cases.

Cardiac Arrest (*30, 31*)

Anyone who uses drugs may find himself faced with, and indeed sometimes responsible for, this emergency. The author is grateful to Prof. M. K. Sykes for telling him what to do, as follows:

"Cardiac arrest is a term used to describe a sudden failure of the heart to maintain an adequate circulation. It may be due to a marked weakening or slowing of the normal heart beat, to asystole or to ventricular fibril-

lation. The circulatory stasis which results leads to tissue hypoxia, cellular damage and, ultimately, death. The organ most sensitive to hypoxia is the brain: at normal body temperatures irreversible changes may occur if the circulation fails for more than 2 or 3 mins. If, however, the circulation is restored within this time complete recovery is possible. Indeed, effective treatment by artificial ventilation and external cardiac compression sometimes produces a complete return of consciousness, even though the heart is in asystole or ventricular fibrillation.

"Successful treatment depends on speed. Diagnosis must be rapid and an effective artificial ventilation and circulation must be produced without delay. Once this has been achieved the immediate danger is over and specific treatment designed to restart the heart may be delayed until an electrocardiogram has been obtained.

"The diagnosis of cardiac arrest is based on four signs:

unconsciousness
absent pulses
absent respirations
widely dilated pupils, usually

"These signs indicate that the cerebral circulation is inadequate and that external aid is required.

"*All other attempts to establish a diagnosis are valueless and only waste time.* For example, normal E.C.G. complexes can persist for up to a minute after cessation of effective cardiac contractions.

"Treatment

1. Move the patient to the firm edge of the bed or place a board under the mattress. Raise the legs to improve venous return.

2. Clear the airway by removing the pillow and extending the neck fully. If foreign material in the pharynx is suspected, turn the head to one side and scoop it out with the forefinger before extending the neck.

3. Perform mouth-to-mouth or mouth-to-nose artificial ventilation. Check that the chest expands well with each breath. If expansion is poor, extend the neck further, pull the chin forward and try again.

4. After 2 to 3 breaths, commence external cardiac compression. Place the left hand over the lower end of the sternum and press the right hand sharply on the back of the left so that the chest is compressed (60 to 80 times a minute). The sternum should be depressed 3 to 5 cms. Check that a pulse is produced in the femoral or carotid arteries. Since chest compression does not produce effective pulmonary ventilation, intersperse one breath of mouth-to-mouth ventilation between each group of 6 to 8 cardiac compressions. Continue this sequence until normal ventilation and circulation are re-established.

"Effective treatment should produce a good pulse and the pupils should constrict. If treatment has been initiated rapidly spontaneous ventilation and consciousness may return at this stage. Return of consciousness during cardiac compression is unpleasant, in different ways, for both

patient and operator. For this reason the resuscitation trolley should contain anæsthetic drugs, or pre-mixed 50% nitrous oxide/oxygen cylinders.

5. Pass an endotracheal tube and ventilate with oxygen.

6. Take an electrocardiograph:

a. If normal complexes are present give (i.v.) a vasopressor (for hypotension), atropine (for sinus bradycardia) or isoprenaline (for heart-block).

b. If ventricular fibrillation is present, defibrillate using an A.C. or D.C. defibrillator. Cover the electrodes with conductive jelly and place one over the sternum and another over the cardiac apex region. Give a shock of 300 to 700 volts for 0·1 or 0·2 secs (A.C. defibrillator) or 100 to 400 joules (D.C. defibrillator). Start at the lower figure and, if this fails, increase the setting. Ensure an adequate coronary blood flow by effective external compression between shocks. If a defibrillator is not available it is worth giving lignocaine 1 mg/kg i.v. at once (not by slow infusion).

c. If asystole is present inject 5 ml. of 10% calcium chloride i.v. Continue cardiac compression and defibrillate when rapid fibrillation appears. If asystole persists inject 5 ml. of 1 in 10,000 adrenaline (i.e. one in ten dilution of Adrenaline Inj. B.P.) into the heart. If asystole still persists, consider exposing the heart by a left thoracotomy through the fifth interspace; compression then being performed directly. The above drugs may be repeated at 10 min intervals A pacemaker may be used.

7. Give 120 to 240 mEq. of sodium bicarbonate i.v., to correct the metabolic acidosis resulting from tissue hypoxia.

8. If consciousness is slow to return consider the use of dehydrating agents, dexamethasone or induced hypothermia."

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Chapter 20

DIURETICS, ŒDEMA, URINARY pH

A diuretic is any substance which increases urine and solute production, but this wide definition includes many drugs not commonly thought of as such. For instance, when digitalis is given to a patient in congestive cardiac failure there is usually a diuresis, but the mechanism is cardiovascular and digitalis is not classed as a diuretic. Everyone has personal experience of the diuretic properties of water. To be therapeutically useful a diuretic should increase the output of sodium as well as of water, since diuretics are normally used to remove œdema fluid which is composed of water and of solutes, of which sodium is the most important.

DIURETIC DRUGS

That mercury had some diuretic effect has been known since the 16th century, but the first potent diuretic for clinical use was introduced in Vienna in 1920, when an organic mercury compound, merbaphen (Novasurol), was tried as an antisyphilitic in a hospital ward where measurement of urine output was part of the nursing routine. Merbaphen, though unsatisfactory as an antisyphilitic, was then given to many œdematous patients, in whom it proved to be an effective diuretic, though toxic. It was soon replaced by mersalyl, which is still occasionally used.

The next important development arose from the observation that acidosis occurred in patients taking sulphanilamide (this does not occur with currently used sulphonamides). The acidosis was found to be due to inhibition of the enzyme carbonic anhydrase in the kidney. Further research resulted in the introduction, in 1951, as a diuretic, of a potent carbonic anhydrase inhibitor, acetazolamide. In 1957 chlorothiazide appeared, following studies of compounds related to acetazolamide, but chlorothiazide is only a weak carbonic anhydrase inhibitor and does not owe its diuretic effect to this property. Both acetazolamide and chlorothiazide are chemically related to sulphanilamide.

Later introductions include frusemide, triamterene and ethacrynic acid.

Diuresis may be initiated by **renal** or by **extra-renal** mechanisms.

1. **Outside the kidney:**

a. By inhibiting the release of antidiuretic hormone, e.g. water, hypotonic solutions, alcohol.

b. By raising the cardiac output and increasing renal blood flow, e.g. digitalis in cardiac failure.

c. By mobilising peripheral œdema fluid, e.g. albumin i.v. in hypoproteinæmic states; obviously, *b*. and *c*. are interrelated.

2. On the kidney

Normally the daily volume of glomerular filtrate is about 200 litres and the daily volume of urine just over 1 litre, the balance (over 99%) being reabsorbed by the renal tubule.

Thus it is easy to conceive of a drug more than doubling the urine volume by a small (1%) reduction in renal tubular reabsorption. But alteration of the enormous volume of glomerular filtrate would require major cardiovascular effects.

The diuretics used clinically act on the renal tubule and not on the glomerulus.

The principal sites of action of clinically useful diuretics:

(1) **Proximal renal tubule:** here most of the glomerular filtrate is reabsorbed: sodium plus water, so that there is no change in sodium concentration in the fluid remaining in the tubule: **osmotic diuretics** act here by preventing water, and therefore sodium reabsorption.

(2) **Loop of Henle:** here sodium is actively reabsorbed without water so that a concentration gradient develops between the tissue fluid and the tubular fluid: **frusemide and ethacrynic acid** act here.

(3) **Distal tubule:** sodium is further actively reabsorbed without water: gradient (above) increases:

(a) *proximal part:*	thiazides
(b) *distal part:*	spironolactone (antialdosterone)
	triamterene, amiloride

Potassium exchange takes place in the distal part of the distal tubule and *diuretics acting here cause K retention.*

Ranking for natriuresis is as follows:

(1) **powerful:** frusemide, ethacrynic acid, mercury.
(2) **moderate:** thiazides (benzothiadiazines).
(3) **weak:** triamterene, amiloride, spironolactone.

(N.B. Drugs in (1) and (2) cause potassium loss: drugs in (3) cause potassium retention.)

Reabsorption of chloride (fixed anion) is reduced along with the sodium and groups (1) and (2) induce hypochloræmic alkalosis.

When sodium is not absorbed, water will also not be absorbed and the result is a diuresis.

A consequence of reduction in proximal tubule or loop of Henle absorption of Na is that this Na is delivered to the distal renal tubule. Here the Na is exchanged for hydrogen ion and for potassium, but not sufficiently to counterbalance the drug effect in the proximal tubule. This distal tubular exchange results (for drugs in groups (1) and (2) above) in **potassium loss** which can be sufficient to deplete seriously the total body potassium. Mechanisms other than the above are involved.

Potassium depletion is particularly liable to occur if the diuresis is brisk and continuous and if the diuretic is continued after cessation of diuresis. In the latter situation Na depletion induces secondary hyperaldosteronism.

For these reasons intermittent administration of the diuretics provides some protection.

Potassium depletion may exist in the presence of a normal plasma concentration (most of the K is intracellular) and this fact renders accurate assessment of K balance difficult.

Symptoms and signs of hypokalæmia include muscle weakness, constipation, anorexia and ECG changes (commonly S–T depression, low amplitude or inversion of T wave merging with U wave to give impression of prolongation of Q–T interval).

Potassium depletion can be minimised or corrected by:

(1) Maintaining good dietary intake (about 80 mEq K/day)
(2) intermittent use of K-losing drugs
(3) potassium supplements
(4) combination with a K-retaining drug (group (3) above)

Potassium supplement should be given whenever œdema is great and/or the diuretic is to be continued for more than a week daily or on alternate days.

Potassium choride is preferred because with the potent diuretics chloride is the predominant anion excreted along with the sodium, i.e. hypochloræmic alkalosis occurs. Where there is chloride lack the exchange of K for Na in the distal tubule is enhanced and K depletion proceeds further.

Unfortunately solid KCl is unpleasant to take (gastric irritation) and enteric-coated tablets are liable to disintegrate at one site in the small bowel, causing ulceration, or may not disintegrate at all.

Satisfactory formulations include:

Potassium chloride effervescent tabs (Sando-K tabs) containing 12 mEq K and 8mEq Cl: 2–6 tabs daily or alternate days.

Potassium chloride slow-release tabs (Slow-K tabs) containing 8 mEq each of K and Cl: 2–6 tabs daily or alternate days.

Combined tablets of diuretics and KCl do not contain enough KCl.

The normal requirement is 16–50 mEq/day.

K supplement may be better retained if it is not given on the same day, or if on the same day, not at the same time as the diuretic.

Potassium conserving diuretics (group (3) above) may be combined with the potent potassium depleting drugs. Amiloride is satisfactory.

Hyperkalæmia may occur and regular measurement of plasma K concentration is necessary when K conserving diuretics are used.

Dangerous hyperkalæmia can occur if K conserving drugs and K supplements are given to patients with renal failure.

Symptoms and signs of hyperkalæmia include abdominal discomfort, muscle weakness, metallic taste and stiffness and paræsthesiæ in the hands and feet. ECG changes: tall T wave, low P wave, QRS spread. But symptoms may be absent till cardiac arrest occurs.

Treatment of hyperkalæmia. In a severe case the initial objective is to shift K from plasma into cells. This can be done most quickly by giving (1) sodium bicarbonate i.v. (40–160 mEq) and repeating it in a few mins if ECG changes persist, (2) dextrose plus insulin (300–500 ml 20% soln dextrose plus insulin 1 unit/3 g dextrose).

If ECG changes are marked, calcium i.v. opposes the myocardial effect of K (Ca chloride or gluconate 10 ml, 10% soln i.v. and repeat if necessary in a few mins). Ca may potentiate digitalis and should be used cautiously, if at all, in a patient taking digitalis.

Na bicarbonate and Ca salt must not be mixed (Ca precipitates).

Cation exchange resin (sodium polystyrene sulphonate) (which see) can be used orally or rectally.

Dialysis, of course, is highly effective.

Dehydration due to **acute saline depletion** follows vigorously instituted and maintained therapy that produces a brisk response. The patient first improves and then becomes lethargic and sleepy (and is usually free from œdema). Blood pressure may fall as a result of reduced plasma volume (high hæmatocrit) and the blood urea concentration will rise. Plasma sodium and chloride concentrations are usually normal, for the loss of sodium is in isotonic or hypotonic solution; but total body sodium is low.

Chronic saline depletion is not common. The body has retained water to keep the blood and extracellular volume normal at the expense of osmolality; therefore plasma sodium and chloride concentrations are low.

It is vital to distinguish **chronic saline depletion** (low plasma sodium, no œdema) from **dilutional hyponatræmia** (low plasma sodium plus œdema) that occurs in some cases of congestive heart failure and in which the low serum sodium is due to *retention* of relatively more water than sodium by the kidney. The cause of dilutional hyponatræmia is a disturbance of body homeostasis in severe heart failure, it is not primarily due to diuretics but is aggravated by those diuretics that tend to cause loss of sodium in excess of isosmotic amounts of water (most, but not mersalyl). The importance of the distinction is that the treatment of the two conditions is different. Administration of salt improves chronic sodium depletion, but only temporarily increases plasma sodium in dilutional hyponatræmia; redilution then occurs and the patient is even more œdematous and may develop pulmonary œdema. Treatment of dilutional hyponatræmia is difficult; water restriction is needed, but may not be tolerated by the patient; diuretics are withdrawn; a glucocorticoid, e.g. prednisolone may start a diuresis.

Urate retention, with hyperuricæmia and sometimes gout occurs by an uncertain mechanism. Thiazides, frusemide and ethacrynic acid cause it. Hg, amiloride and triamterene do not.

The hyperuricæmia can be antagonised by allopurinol or probenecid.

Carbohydrate metabolism. Thiazides decrease carbohydrate tolerance, probably by reducing insulin secretion. The effect is generally reversible, but some pre-diabetics may develop permanent diabetes mellitus. Other potent diuretics may occasionally produce the same effect.

Urinary retention. Sudden vigorous diuresis is reputed to cause acute retention of urine in the presence of prostate enlargement.

Abuse of diuretics. Psychological abnormality sometimes takes the form of abuse of diuretics and/or purgatives. The subject usually desires to "slim" to become "attractive" or "healthy" or may have anorexia nervosa. There can be severe depletion of sodium and potassium, with renal tubular damage (due to chronic hypokalæmia).

Notes on Individual Drugs and Groups of Drugs

Thiazides (Benzothiadiazines)

These are widely used diuretics, for they are reliably effective when taken orally and produce few unwanted effects except potassium depletion.

Thiazides depress sodium chloride transport in the distal tubule just proximally to the site of potassium exchange. Effects are similar to Hg but there is less disturbance of acid-base balance. But, unlike mercurials, thiazides remain effective even in the presence of severe sodium depletion and of hypochloræmic alkalosis, so that they are capable of causing serious electrolyte disorders.

This group of diuretics also increases **potassium excretion** to an important extent.

Thiazides are also **hypotensive**. The chief mode of action is probably reduction of plasma volume,* but there may also be reduced responsiveness of vascular muscle to noradrenaline. But a similar drug (diazoxide, which see) induces sodium retention and yet is antihypertensive.

Paradoxically, thiazide diuretics can reduce urine volume in **diabetes insipidus** (which see).

Pharmacokinetics. Thiazides are well absorbed from the gut and most are rapidly excreted unchanged by the kidney (polythiazide, chlorthalidone and bendroflumethiazide are longer acting because they are more slowly excreted than the others).

Hydrochlorothiazide (25, 50 mg) is a satisfactory member of this group for routine use. It is well absorbed from the gut and the tablets

* This original view, once discounted, now seems reinstated:
TARAZI, R. C., *et al.* (1970). *Circulation,* **41,** 709.

are small (chlorothiazide is not well absorbed and the tablets must be large, 500 mg). The daily oral dose is 25 to 100 mg and diuresis usually lasts less than 12 hrs so that it should be given in the morning.

Hydrochlorothiazide, *used primarily for diuresis*, may be given daily for the first few days and then intermittently, say 1 to 3 days a week. Potassium supplements are needed if the diuretic is given more than twice a week, and potassium is retained best if not given on the same day, or if on the same day, not at the same time, as the drug, so that combined tablets are unsuitable.

As a hypotensive, hydrochlorothiazide is given daily. In the absence of diuresis potassium depletion is rather less likely, but potassium supplements are generally needed.

Unwanted effects: Some have already been mentioned (see above). Rashes (sometimes photosensitive), thrombocytopenia and agranulocytosis occur.

Bendrofluazide (2·5, 5 mg) is a satisfactory alternative. The oral dose is 2·5 to 10 mg per day.

Other members or relatives of the group include hydroflumethiazide, bendroflumethiazide, flumethiazide, polythiazide, cyclopenthiazide, benzthiazide, methyclothiazide, chlorthalidone, disulphamide,* quinethazone, metolazone, clorexolone.† Parenteral preparations of some are available but seldom are needed.

Clopamide (Brinaldix) is related to the thiazides.

Frusemide (furosemide, Lasix)

Frusemide (40 mg) is structurally related to the thiazides but its pharmacology is similar to ethacrynic acid. Frusemide is probably rather easier to handle than ethacrynic acid as its dose response curve is less steep and adjustment of dose to obtain graded effects is therefore easier.

It acts on the loop of Henle and on distal renal tubules and produces sodium, chloride and potassium loss. Although the latter may be relatively less than with thiazides with a single dose, long-term use demands potassium supplements.

Taken orally it acts in 1–2 hrs and diuresis lasts about 6 hrs. It is extremely effective and enormous urine volumes, e.g. 10 l in 24 hrs can result. Given i.v. it acts within 30 min and can relieve acute pulmonary œdema and probably cerebral œdema, producing effects beyond the reach of thiazides.

An important feature is that it can be effective in renal failure and in severe heart failure when other diuretics fail.

It is chiefly excreted in urine and fæces: only a little is metabolised.

* Though this drug was promoted as "the British oral diuretic", British prescribers seem to have been unimpressed, for it is no longer marketed. Nationality is not a relevant factor in the choice of a drug.

† It is reasonable to discover which of the group is cheapest at the place and time of use, and to use that as a routine.

Though it can be used for the same purposes as the thiazides, it is probably best reserved for emergency use and for cases resistant to other diuretics, because it is so effective. Mere efficacy is not, of course, a reason for not using a drug, but it does mean that the patient has to be supervised more closely, with measurement of blood electrolyte changes, because overdose is so serious. Unwanted effects, in addition to electrolyte disturbance and hypotension (low plasma volume) and those mentioned in the general account are uncommon, but include nausea and, rarely, deafness, usually transient.

Frusemide or ethacrynic acid can be used with blood transfusion in severe anæmia where cardiac failure is imminent. They allow transfusion without increasing blood volume which would precipitate heart failure.

The oral dose is 20–120 mg: i.m. or i.v. 20–40 mg initially. Larger tablets (500 mg) are available for use in renal failure in which it may be preferred to ethacrynic acid as deafness is less likely.

Mefruside (Baycaron) is similar to frusemide.

Ethacrynic acid (Edecrin)

Ethacrynic acid (Edecrin) (50 mg) is unrelated to the other diuretics described here, but its pharmacology is similar to frusemide.

Ethacrynic acid is partly metabolized and partly excreted unchanged in the urine.

The oral dose is 50 to 150 mg in 1 or 2 doses, but more (up to 400 mg/day) may be given in refractory cases. For urgent situations it is given i.v. 50 mg, rarely more. It is too irritant to be given i.m. or s.c.

As with frusemide, the response may be torrential so that acute saline depletion with hypotension due to serious reduction in plasma volume may occur. Deafness, usually transient, occurs, and gut upsets and blood disorders.

Bumetanide (Burinex) resembles frusemide pharmacologically but is unrelated chemically.

Organic Mercurial Diuretics

Organic mercurials (e.g. mersalyl) have declined greatly in importance since the introduction of chlorothiazide, and still further with the more effective frusemide and ethacrynic acid. They are rarely used; they act throughout the nephron; they cause a hypochloræmic alkalosis; they do not cause urate retention or significant K loss; they will not be further considered here.

Triamterene (Dytac)

Triamterene (50 mg) is not chemically related to other diuretics. It increases sodium excretion, but *reduces* potassium loss by an action in the distal tubule. Its action is therefore complementary to the thiazides and, used with them, sodium loss is increased and potassium loss reduced. It also increases urate excretion (thiazides reduce it). It is not a very efficacious diuretic and is normally used in combination with thiazides in cases of refractory œdema or where there is heavy potassium loss.

Hyperkalæmia can occur especially if potassium supplements, already in use with a thiazide, are continued when triamterene is added. Gastrointestinal upsets occur. The oral dose is 50 to 300 mg; its effect lasts up to 24 hrs.

Amiloride (Midamor)

Amiloride (5 mg) is also a potassium-sparing diuretic. It is structurally related to triamterene and acts and is used similarly. The oral dose is 5–20 mg a day.

Carbonic Anhydrase Inhibitors

Acetazolamide (Diamox) is a sulphonamide carbonic anhydrase inhibitor which is of greater theoretical than therapeutic importance. Its diuretic effect is due to this property.

Mode of action. Carbonic anhydrase facilitates the reaction between carbon dioxide and water to form carbonic acid:

$$CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

the reaction being slow in the absence of the enzyme. The carbonic acid is, of course, in equilibrium with its dissociation products, hydrogen and bicarbonate ions. The reaction is fundamental to the production of either acid or alkaline secretions, and a high concentration of carbonic anhydrase is present in the gastric mucosa, pancreas and kidney. In the kidney the function of carbonic anhydrase is to provide hydrogen ions to be exchanged for sodium in the glomerular filtrate, so that body sodium is conserved.

Hydrogen ions are secreted by the distal tubule cells into the glomerular filtrate (containing $NaHCO_3$) as it passes along the renal tubules. Sodium ions enter these cells from the filtrate in exchange for the hydrogen ions. Thus H_2CO_3 is formed in the filtrate and $NaHCO_3$ in the tubule cells. The H_2CO_3 dissociates to form CO_2, which probably diffuses passively into the cells, and H_2O. The $NaHCO_3$ is passed from the cells into the extra-cellular fluid.

This reabsorption of sodium in exchange for hydrogen ions can only continue so long as there is a good supply of hydrogen ions, and this depends upon the action of carbonic anhydrase. Inhibition of the enzyme reduces the supply of hydrogen ions and so the sodium and bicarbonate remain in the renal tubule lumen. Thus an alkaline urine with a high sodium bicarbonate content results. The increase in sodium excretion leads to a diuresis.

Potassium excretion is also increased by acetazolamide, because it normally competes with hydrogen ions in the exchange with sodium, and when hydrogen ion excretion is reduced more potassium will be lost. This continues in the absence of diuresis.

Tolerance. The excretion of an alkaline urine makes the extracellular fluid more acid, i.e. a metabolic acidosis. Carbon dioxide is blown off through the lungs to compensate, leading to a reduction in the plasma bicarbonate. The reduction in the plasma bicarbonate necessarily reduces the amount of sodium bicarbonate in the glomerular filtrate. If repeated doses of acetazolamide are given this fall in the amount of sodium bicarbonate presented to the renal tubules continues until the level is reached at which the sodium

can be reabsorbed by exchange with the relatively small supply of hydrogen ions which are available even though carbonic anhydrase is inhibited. A new equilibrium is thus set up in which there is a metabolic acidosis but in which the sodium and water diuresis stops.

Therefore acetazolamide is only effective as a diuretic if given intermittently so as to allow the plasma bicarbonate to be restored before the next dose; if given 8-hrly diuresis usually stops after the second dose. Maximal diuresis occurs in the first 6 hrs after a single dose but the drug is ineffective compared with mersalyl or chlorothiazide, and it often fails.

Unwanted effects are not common; high doses may cause drowsiness and fever, rashes and paræsthesiæ may occur, blood disorders have been reported. It is not used in liver failure as it has occasionally precipitated hepatic coma. Renal calculi may occur, perhaps because the urine calcium is in less soluble form owing to the low citrate content of the urine.

The inhibition of carbonic anhydrase in sites other than the kidney produces few significant effects. Acid secretion in the stomach is reduced, but not enough to be useful.

Dichlorphenamide (Daranide) is similar to acetazolamide, but also has some direct effect on sodium and chloride reabsorption.

In glaucoma, the chief use of carbonic anhydrase inhibitors, intraocular pressure falls due to reduced formation of aqueous humour.

Xanthine Diuretics

The general properties of the xanthines (theophylline, theobromine, caffeine) are discussed elsewhere. These compounds are weak diuretics and are useless for this purpose in therapeutics. They act by inhibiting absorption of sodium, chloride and water in the renal tubules to produce a small diuresis. Theophylline (as aminophylline) can be used to increase glomerular filtration by its cardiac action which increases renal blood flow.

Osmotic Diuretics

Any substance which passes across the glomerular membrane and which is not completely reabsorbed in the renal tubules necessarily has some diuretic effect as it is excreted with its isosmotic equivalent of water.

Proximal renal tubular fluid is isosmotic with plasma (sodium is the principal osmotic solute). If another substance (mannitol, urea) replaces the sodium as the principal osmotically active solute then, as the concentration of this substance rises, that of sodium will fall by dilution and less sodium will be reabsorbed. Urine volume will increase according to the load of the osmotic diuretic.

Uses: 1. To prevent acute renal tubular necrosis, e.g. after severe injury or abortion.

2. To eliminate drugs that are reabsorbed in the renal tubule in acute poisoning (salicylate, barbiturate, bromide).

3. To reduce intracranial or intraocular pressure by osmotic effect in the blood (not primarily by diuresis).

4. Rarely in resistant œdema.

Glucose in diabetes mellitus provides an example of an osmotic diuresis. It is responsible for much of the sodium and water loss in diabetic ketosis.

Urea. If urea is given to the patient the amount filtered will increase. The blood urea is necessarily raised, but this is not in itself of any clinical importance. The amounts of urea required to obtain a satisfactory diuresis are large (15 to 20 g orally 2 to 5 times a day). In the majority of patients such doses cause nausea and sometimes vomiting, even if the unpleasant taste is disguised with fruit juices. However, a few chronically œdematous patients will tolerate it, and in them urea can be a useful maintenance diuretic. Urea (30% solution) i.v. is an effective agent for **reducing intracranial pressure**, but careful attention to detail is necessary. It is also effective by gastric tube.

Mannitol is a polyhydric alcohol which is filtered across the glomeruli, but not reabsorbed to any significant extent in the tubules. It may be given i.v. (or orally, when it induces osmotic diarrhœa).

Sucrose given by mouth is split into glucose and fructose before absorption, but an i.v. injection of 50% sucrose, which is very hypertonic, temporarily expands the volume of circulating fluid by drawing fluid out of the tissues. It is used to lower the intracranial pressure, 50 to 100 ml being given and repeated according to the response. The effect is only transient and triple strength plasma, or better, urea (see above) are more satisfactory. Sucrose i.v. also acts as an osmotic diuretic but is not used for this as the effect is transient and because large amounts damage the renal tubules, though reversibly

ALDOSTERONE ANTAGONISTS

Certain synthetic steroid lactones (spirolactones) have been found to antagonise the effect of aldosterone on the renal tubule by competitive inhibition. One of these, **spironolactone** (Aldactone-A) (25 mg) has proved useful in therapy of refractory œdema (with diuretics that inhibit Na absorption in the proximal tubule) and to prevent K loss.

Aldosterone causes sodium reabsorption and potassium loss in the distal tubule. Excessive secretion of aldosterone contributes, at least in part. to the œdema of hepatic cirrhosis and nephrotic syndrome, and it is in these cases that spironolactone is most useful. It is much less effective in congestive heart failure. However, it is relatively ineffective, given alone, and should be used with a drug that directly reduces sodium reabsorption in the proximal tubule, e.g. a thiazide. It may induce a response where the thiazide alone fails. It can induce hyponatræmia, especially in patients with hepatic cirrhosis.

Spironolactone will reduce the potassium loss that occurs with thiazides and some other diuretics, though it may not abolish the need for potassium supplements, but if given with triamterene (which reduces potassium loss) or in renal failure, there is risk of hyperkalæmia. Spironolactone is also effective in hypertension used alone.

It abolishes the therapeutic effect of carbenoxolone in peptic ulcer.

Spironolactone is given orally, 50 to 100 mg a day in divided doses; maximum diuresis is delayed for up to 4 days. If after 5 days the response

is inadequate, 200 mg may be given. Ill-effects are rare, but include mental confusion, drowsiness, rashes and abnominal pain. It causes a spurious increase in plasma cortisol estimations.

CATION-EXCHANGE RESINS

Cation-exchange resins are substances used to remove cations (e.g. sodium, potassium) from the intestinal contents. Though not themselves diuretics, they found their initial clinical use as part of long-term *diuretic and œdema prevention* regimens until modern potent diuretics abolished the need for them. The chief use now is in **hyperkalæmia**.

The resins consist of aggregations of big insoluble molecules carrying a fixed negative charge, which therefore loosely bind positively charged ions (cations). These cations are exchangeable with the cations in the fluid environment.

The nature of the cations on the resin when it leaves the body in the fæces will depend on:

(1) The time spent by the resin in the intestine.

(2) The relative concentration of cations in the intestinal contents.

(3) The order of natural affinity for cations which runs from large divalent to small monovalent ions, thus, $Ca > Mg > K > NH_4 > Na > H$.

One of the principal difficulties in the use of cation-exchange resins is to ensure as nearly as possible that only the desired ion is removed from the body.

In **hyperkalæmia** oral administration or retention enemas of sodium-polystyrene sulphonate form resin (Resonium A) can be used. The resin does not merely prevent absorption of ingested potassium when given orally, but takes up that potassium normally secreted into the large intestine and ordinarily reabsorbed. A sodium phase resin may give up too much Na in patients with renal failure so that sodium retention occurs. Calcium phase resins may cause hypercalcæmia. Aluminium phase resins have been used, though the consequence of hyperaluminæmia are uncertain. Enemas should ideally be retained for at least 9 hrs, but this is usually impossible.

Other uses for resins include the "tubeless" test for gastric acid (see *gastric secretion*): see also *cholestyramine*.

The discovery of the phenomenon of ion-exchange occurred in the mid-nineteenth century when a Yorkshire landowner became interested in the possible loss of ammonia from his manure heaps. He consulted a chemist who began an experimental study, in the course of which he found that if an ammonium sulphate solution percolated down a soil column, calcium sulphate came out at the bottom. This was a surprise for him, not least because the phenomenon of electrolytic dissociation of salts was then unknown.*

SOME CLINICAL ASPECTS

Assessment of diuretics. It is possible to decide if a substance is an effective diuretic by giving it to œdematous patients and measuring changes in weight, in sodium output, in the pattern of ion excretion and in urinary concentration. The incidence of unwanted effects is taken into

* KITCHENER, J. A. (1957). *Ion-exchange Resins.* London: Methuen.

account, of course, in deciding whether the drug is likely to be useful. Although all this sounds simple enough there are a number of practical difficulties, because patients are seldom in a stable condition for long.

Measurement of weight changes is the simplest guide to the success or failure of diuretic regimens. Intake and output charts are a more complicated, and often less accurate, alternative.

Salt restriction. When abnormal retention of sodium occurs, retention of water follows; thus one obvious way of removing œdema is to get rid of sodium. Clinically useful diuretics increase the excretion of sodium, but this will only lead to mobilisation of œdema fluid if its replacement by sodium from the diet is prevented. Dietary sodium restriction was an important part of treatment until the introduction of the most potent diuretics. A normal diet contains about 10 g of sodium chloride a day (1 g of sodium chloride contains about 17mEq of sodium). If no salt is added in cooking or at mealtimes this may fall to about 3 to 5 g. a day, which is often low enough, but special low-salt diets (about 1 g daily) may be needed. Really extreme salt restriction, is usually intolerable and unnecessary. It is unnecessary to restrict water intake unless hyponatræmia is present.

Efficacy. The most effective diuretics (frusemide, ethacrynic acid) cause such a vigorous effect that they are useful in acute pulmonary œdema and they can cause collapse due to serious acute loss of extracellular volume.

Because oral agents are easily given continuously, lack of supervision can result in chronic electrolyte and volume depletion.

The efficacy of the thiazides and of ethacrynic acid and frusemide is not affected by changes in acid-base balance (the efficacy of Hg and carbonic anhydrase inhibitors is affected). This constitutes an advantage if the drugs are used skilfully, but a hazard if they are used ignorantly.

TREATMENT OF ŒDEMA

The removal of œdema involves more than simply giving diuretic drugs. It is also important to ensure that there is adequate glomerular filtration, in the absence of which diuretics acting on the renal tubule are less effective.

Cardiac œdema occurs when the cardiac output is not sufficient to perfuse the kidney adequately. Therapy is directed both to reducing the demands of the body for blood flow and to increasing the efficiency of the heart.

The demands of the body can be reduced by rest and sometimes by treating disease, as when hyperthyroidism is reduced (drugs, surgery), anæmia is corrected (drugs, transfusion), an arteriovenous shunt is abolished (surgery) or the peripheral resistance is reduced (hypertension treated by drugs).

The efficiency of the heart can be increased by digitalis or by aminophylline, by abolishing arrhythmias, by correcting valvular deformities and by correcting anæmia.

In cardiac failure the extracellular fluid volume is increased due to sodium retention as a result of the alteration of renal hæmodynamics. It can be lowered by reducing sodium intake (low salt diet) and increasing sodium output (diuretics). Choice of drugs depends on degree of urgency, e.g. diuretic orally or i.v. with or without digoxin orally or i.v.

Renal œdema. By the time chronic renal disease causes œdema, reversal of the disease process in the kidney is seldom practicable. The œdema of *nephrotic syndrome* is only indirectly due to renal disease, hypoalbuminæmia being the major factor.

Reduction of sodium intake and prevention of excessive retention are the chief therapeutic aims. A reduced salt diet helps. Reduction of sodium reabsorption in the renal tubule by diuretics is most effective where glomerular filtration has not been too much reduced by disease. But frusemide or ethacrynic acid can be effective even when it is very low. Spironolactone may be added usefully to potentiate the diuretic, antagonise the secondary hyperaldosteronism and conserve K, loss of which can be severe. Reduced plasma colloid osmotic pressure due to protein loss in the urine may also need correction by albumin infusion which temporarily raises plasma albumin concentration and may induce a diuresis. An adrenal steroid or immunosuppressive drug may be needed.

In *chronic renal failure* œdema is often absent. When it occurs high doses of potent diuretics may be needed.

In *acute renal failure:* once the condition is established use of diuretics is controversial, but they may be effective in preventing it: mannitol with or without ethacrynic acid or frusemide is used.

Diuretics are not usually needed in **acute nephritis** as most cases recover spontaneously, but they may be necessary if pulmonary œdema develops (frusemide or ethacrynic acid would probably be preferable).

Hepatic ascites is due to portal venous hypertension, decreased plasma colloid osmotic pressure (hypoalbuminæmia) and hyperaldosteronism (which may be a response to the increased extra-cellular volume, with low osmotic pressure, due to the first two factors).

Treatment is therefore to reduce sodium intake, to reduce sodium reabsorption by diuretics, using drugs that directly reduce sodium reabsorption in the renal tubule as well as an aldosterone antagonist. The aim should be a slow or gradual diuresis. If it is vigorous, depletion of Na and K and hypochloræmic alkalosis which may result in hepatic coma. A thiazide may be the best initial choice. Albumin infusions are useless in most cases, but do occasionally work.

Large accumulations of ascitic fluid or pleural effusions are often removed by tapping, partly for the sake of speed and partly because diuretics are more effective in preventing fluid re-accumulating in the body cavities than in removing it once a large effusion has formed. Ascitic fluid contains relatively large amounts of protein and repeated paracenteses may aggravate hypoproteinæmia.

Choice of Diuretics

Oral administration is obviously preferable, and thiazides are generally satisfactory for use at home, though if a quick and vigorous response is particularly needed in hospitalised patients, frusemide or ethacrynic acid, orally, or by injection in very urgent cases, are preferable.

Spironolactone should only be used in combination with other diuretics when these fail to be effective when given alone (see below). Acetazolamide supplements mersalyl, as does ammonium chloride.

Combinations of Diuretics

There is no advantage in combining two diuretics that are very close to each other chemically. In general, dissimilar diuretics summate with or potentiate each other. However, the most potent diuretics (frusemide, ethacrynic acid) do not generally need the assistance of a second drug, though they may be combined with triamterence, amiloride or spironolactone in order to reduce potassium loss (as well as to enhance natriuresis) when prolonged use is contemplated.

The following combinations are also appropriate: mersalyl plus acetazolamide or ammonium chloride: a thiazide plus triamterene (to reduce potassium loss) or spironolactone (to reduce potassium loss and where secondary hyperaldosteronism is a factor in the causation of the œdema).

Failure of Diuretic Therapy

Œdema sometimes persists despite the most vigorous diuretic regimens. This is most common in the terminal phase of an illness when homeostasis is grossly deranged, but the cause of failure can sometimes be removed.

In severe cardiac failure the cardiac output, and hence the glomerular filtration rate, may be so low that the renal tubules can easily reabsorb nearly all of the sodium and water presented to them. The glomerular filtration rate must be improved before any diuretic is likely to be successful and so, in addition to fully digitalising the patient it is useful to give 500 mg of aminophylline by slow i.v. injection at a time when the effect of the diuretic may be expected to be approaching its maximum. See *dilutional hyponatræmia* (above).

Sodium depletion due to excessive diuretic therapy causes refractory state.

ALTERATION OF URINARY pH

It is sometimes desirable to alter the pH of the urine:

(a) To increase the efficacy of antimicrobials in the urine, e.g. sulphonamides (alkaline), streptomycin (alkaline), tetracycline (acid), hexamine (acid), penicillin (acid);

(b) to discourage the growth of certain organisms, e.g. *E. coli* (alkaline);

(c) to increase the renal elimination of drugs, e.g. amphetamine, pethidine (acid) and salicylate, phenobarbitone (alkaline).

(d) to render drugs or metabolites more soluble in urine and so to reduce the risk of crystalluria: sulphonamides (alkaline), to prevent uric acid and cystine stone formation (alkaline);

(e) to reduce irritation in an inflamed urinary tract (alkaline).

Ideally urinary pH should be tested with indicator paper daily to ensure the desired pH is attained (except in (e) above).

Diuretics change urinary pH, but not consistently or sufficiently to be used for the special purpose.

The urine may be made acid by ammonium chloride or arginine hydrochloride (equivalent to drinking HCl); by a sulphur-containing amino-acid (methionine) (equivalent to drinking H_2SO_4) or by ascorbic acid (see urinary tract infections). Long term use is unsatisfactory (hard to maintain and adverse effects); it is seldom needed.

To make the urine acid quickly in therapy of poisoning, 10 g arginine HCl can be given i.v. over 30 mins, with ammonium chloride 4-hrly orally. But this is rarely needed.

Sodium acid phosphate also acidifies the urine.

The urine can be made alkaline by sodium bicarbonate, or by acetate, citrate or lactate, for these latter are all oxidised, and the cation becomes combined with bicarbonate. The bicarbonate neutralises gastric acid, but the others do not.

Sodium or potassium citrate is commonly used and at least 3 to 6 g. orally, 6-hrly, is needed (Potassium Citrate Mixture, B.P.C.). The cation can be dangerous in heart failure (sodium) or renal failure (sodium, potassium).

Trometamol (tromethamine, Tham-E) is an alkaline amine buffer used for treating metabolic and mixed acidosis.

Ammonium Chloride

The chief use is to acidify the urine as therapy or as a test of renal acidifying capacity. It is also a weak diuretic.

When absorbed from the intestine the ammonium is converted by the liver into urea (not enough to provide useful osmotic diuresis) and hydrogen ion, so that *the effect is as though an equivalent amount of hydrochloric acid had been drunk*, causing a hyperchloræmic metabolic acidosis. The result is an increased load of chloride in the glomerular filtrate which, on the first day, is neutralised by sodium (from sodium bicarbonate), on the second and third by sodium and potassium,* but by the fifth day the chloride is neutralised by ammonium made in the kidney as part of a homœostatic device to excrete hydrogen ions ($NH_3 + H^+ \rightarrow NH^+_4$) and to preserve the valuable cations sodium and potassium. The diuretic effect therefore ceases because extra sodium and potassium, and therefore water, are no longer excreted. Availability of the most potent diuretics have rendered its use unnecessary.

* Any acidifying agent causes potassium to pass from the cells into extracellular fluid so that more is available for urinary excretion.

High dose causes gastric irritation, abdominal pain, nausea and vomiting, but any dose may be dangerous in patients with poor renal function, whose kidneys are unable to produce ammonia, and, although a diuresis may result it may be at the expense of a severe acidosis. Patients with hepatic failure should not be given ammonium chloride because they cannot convert the ammonium to urea and may therefore go into coma.

Arginine HCl similarly is equivalent to taking hydrochloric acid.

Methionine. Sulphur-containing aminoacids are converted to sulphate and are equivalent to taking sulphuric acid. They are hazardous in hepatic failure (coma).

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Chapter 21

GASTRIC SECRETION, DRUGS USED IN PEPTIC ULCER, PURGATIVES, CONSTIPATION, DIARRHŒA

GASTRIC SECRETION (*1–3, 10*)

Reduction: *anticholinergics* and *antigastrins* (see H_2 receptor blocker).
Neutralisation: see *antacids.*
Stimulation: to test the capacity of the stomach to secrete acid (e.g. to detect anacidity or hypersecretion or to test completeness of vagotomy). These tests "are of value only if done carefully by an experienced team"* and so only an outline will be offered here.

Gastrin is a polypeptide of 17 amino-acids, only four of which are necessary for gastric secretory stimulation. A synthetic 5 amino-acid, **pentagastrin** (Peptavlon) has been found a satisfactory agent to test gastric secretory capacity. Pure gastrin has been made but is more expensive since most of the molecule is unnecessary.

Drugs that have been used include histamine (plus an antihistamine to block non-gastric effects) and a synthetic histamine analogue, betazole (Histalog).

Pentagastrin increases gastric secretion (acid and pepsin) perhaps by liberating histamine locally. It also increases antral motility.

The gastric secretion test consists in measuring the level of basal secretion every 15 mins for about 1 hr, then injecting (i.m.) or infusing (i.v.) a standard dose of pentagastrin and collecting further specimens and determining the maximum acid output or hourly acid output. For accuracy a well placed stomach tube is necessary. Tubeless techniques using a cation-exchange resin, in which the acid displaces a dye, azuresin (Diagnex Blue), which is excreted and measured in the urine, are less reliable.

GASTRIC ANTACIDS (*4–7, 14, 16–20*)

Antacids relieve the pain of peptic ulcer, which occurs when the pH is less than 3·5, but they do not alter the rate of healing or prevent recurrence. Their benefit probably depends on protecting the ulcer from acid (neutralisation) and from pepsin (raising pH and in the case of Al, Ca, Bi, precipitating pepsin). Neutralisation of acid reflexly increases gastric acid secretion, perhaps by releasing gastrin.

The amount of antacid needed depends on the rate of acid secretion, on the presence or absence of food in the stomach and on the rate of gastric emptying. The dose therefore cannot be accurately calculated for any one case.

* Editorial (1971). *Brit. med. J.*, **1**, 186.

The rate of gastric emptying is the most important limiting factor in achieving continuous neutralisation by intermittent administration. Continuous sucking of antacid tablets (or an intragastric drip) are the most effective methods of neutralisation. Only the intragastric drip can, of course, be effective during the night.

The purpose of giving antacids is to remove H ion. This is achieved by chemical neutralisation (sodium bicarbonate, magnesium oxide and hydroxide, calcium carbonate) or by reversible chemical combination (aluminium hydroxide gel, magnesium trisilicate). The relative efficacy of these substances is shown in the table.

For 90% of peptic ulcer patients 50 mEq neutralising capacity per hour (male, duodenal) and 26 mEq per hour (female, duodenal: male gastric) is adequate. Dosage of antacids to achieve this are given below:

Amounts of antacids to neutralise 50 *mEq HCl*
(titrated to pH 4·5)

Sodium bicarbonate	4·4 g*
Magnesium oxide or hydroxide	5·9 g
Calcium carbonate	4·5 g
Magnesium trisilicate	50 g
Magnesium carbonate	63 g
Aluminium hydroxide gel	715 ml
(as Aludrox	294 ml)

It is obvious from the above that the first three are much the most efficient. Also, they react quickly, which is important, because half a single dose of antacid will generally have left the stomach in 20 mins, and this is why about one sixth of these amounts are adequate when given by continuous gastric drip. Magnesium trisilicate and aluminium hydroxide are relatively slow acting.

It is also obvious that adequate doses of the less efficient compounds need, on these calculations, to be enormously greater than is generally used, or indeed, than is practicable.

Total neutralisation is generally impossible by antacids alone, taken intermittently.

Antacids may be classified as:

1. **non-systemic;** not significantly absorbed, and so will not disturb acid-base balance of the body: Al, Mg salts, Ca carbonate (but a significant amount of Ca can be absorbed).

2. **systemic:** absorbed, and can cause metabolic alkalosis: Na bicarbonate.

Alkalosis can cause confusion in diagnosis. Prevention is best accomplished by awareness of the possibility. Alkalosis solely due to absorption of alkali seldom causes symptoms in the absence of renal or circulatory failure. Patients have been kept in severe alkalosis with sodium

* A level teaspoonful of the solid is 3·5 to 4 g.

bicarbonate for 3 weeks without significant symptoms, although the possibility of renal damage is not excluded in more prolonged alkalosis (*17*).

But alkalosis due to loss of chloride in vomit is accompanied by dehydration and renal ischæmia and gives rise to severe symptoms. Both kinds may be present simultaneously. Reduction in ionised calcium can cause tetany.

The most effective antacids (sodium bicarbonate, magnesium oxide and hydroxide and calcium carbonate) all have disadvantages.

Sodium bicarbonate reacts and relieves pain rapidly. It is absorbed and causes alkalosis, but this is only a serious matter in patients with renal insufficiency. It can release enough CO_2 in the stomach to cause discomfort and belching, which may have a psychotherapeutic effect or not, according to circumstances. Sodium citrate is sometimes used in effervescent preparations.

Magnesium oxide and hydroxide react quickly, but cause diarrhœa, as do all magnesium salts which are also used as purgatives.

Magnesium carbonate is rather less effective.

Magnesium trisilicate reacts slowly, to form magnesium chloride which reacts with intestinal secretions to form the carbonate, the chloride being released and reabsorbed. Acid-base balance is thus not significantly altered. It adsorbs pepsin. Magnesium salts are trivially absorbed, but retention toxicity can occur with renal insufficiency.

Calcium carbonate reacts quickly and forms calcium chloride. This is absorbed, but does not disturb acid-base balance. However, excessive doses, especially combined with heavy milk drinking, which is often advised in peptic ulcer, can cause the hypercalcæmic (milk-alkali) syndrome (headache, weakness, anorexia, nausea, vomiting, abdominal pain, constipation, thirst, poluria) with temporary, or rarely permanent, renal damage.

Ca chloride reaching the intestine is precipitated (as Ca soaps) and constipates.

Aluminium Hydroxide reacts with HCl to form aluminium chloride which reacts with intestinal secretions to form insoluble salts, especially phosphate, the chloride being released and reabsorbed. It does not alter acid-base balance. Aluminium hydroxide can be used in patients who habitually form phosphatic urinary calculi, to increase fæcal, and decrease renal, phosphate excretion, but enormous amounts are needed. In addition to neutralising acid, aluminium hydroxide inactivates pepsin. It tends to constipate. Kaolin (aluminium silicate) may also be used as an antacid to act by adsorption. See also under *tetany*.

Bismuth salts are feeble antacids but adsorb pepsin.

Food, especially proteins, and drink are also antacids, though they also stimulate gastric secretion.

Choice of antacid. It is plain that no single antacid is satisfactory; mixtures are generally used.

They often consist of sodium bicarbonate for quickest effect, supplemented by magnesium hydroxide or carbonate.

Sometimes magnesium trisilicate or aluminium hydroxide is added, but these are often used alone, though they are relatively slow-acting. All formularies contain numerous antacid preparations; the choice is not critical.

If bowel habit is disturbed this can be corrected by altering the proportions of magnesium salts that tend to cause diarrhœa, and calcium and aluminium salts that tend to constipate, sometimes severely.

Choice of preparation and administration. For intermittent use, liquids or powders are more efficient than tablets. In severe cases they may be given 1 to 2 hrly, with or between small feeds, or included in a continuous intragastric drip (particularly if there is nocturnal pain). For less severe cases an antacid may be given between meals (not immediately after, when food is present) to help reduce the high acidity before the next meal.

Tablets are best sucked to give a continuous flow of antacid. This is specially useful in reflux œsophagitis.

The routine use of antacids after meals "is worthless" (*9*).

ANTICHOLINERGIC DRUGS

A general account of these is given in chap. 16. The choice is not critical; propantheline or poldine will serve.

Despite expectations, based on theoretical considerations of the importance of the parasympathetic in gastric secretion, these have not proved to have great importance in the therapy of peptic ulcer.

They have been shown, when *injected*, to be capable of substantially *reducing gastric juice production*, but they are less effective when taken orally. Also, it is the volume of secretion rather than its concentration that is reduced so that, in an empty stomach, the pH is not affected. The pH will only be reduced if food or drink is present to dilute the acid. However, the drugs have less effect on food-induced secretion than on fasting secretion.

Anticholinergic drugs may also benefit by *delaying gastric emptying* and so allowing the antacid to remain longer in the stomach. But in the presence of pyloric stenosis the patient needs his peristalsis and complete obstruction may be precipitated.

They are specially worth trying in relatively high dose at night in duodenal ulcer where acid secretion continues during sleep (unlike gastric ulcer). The combined benefits on secretion and delaying gastric emptying can be worthwhile.

Maximum tolerated doses are likely to be needed; side-effects of parasympathetic block are the limiting factors.

Their use remains controversial owing to disagreement on how effective they are under conditions of ordinary clinical use.

The classic combination of belladonna or atropine with phenobarbitone does not deserve its reputation.

ANTI-ULCER DRUGS (*11*, *12*)

These drugs can certainly hasten the healing of gastric ulcers and somewhat less certainly the healing of duodenal ulcers. Their effects are not dramatic and they are difficult to evaluate because: 1. ulcers heal spontaneously, 2. there is no correlation between size of crater and clinical attacks.* In addition duodenal ulcer craters are difficult to measure unlike gastric ulcer craters.

Though the drugs *accelerate* healing, the *end-results* may not differ from those obtained with other measures. Long-term use to prevent relapses is not at present justified by conclusive evidence.

Liquorice derivatives. Crude liquorice contains two sources of anti-ulcer activity, one related to glycyrrhizin (a glycoside) and one that remains after glycyrrhizin is removed.

Carbenoxolone (Biogastrone) (50 mg) is a tri-terpene derived from glycyrrhetinic acid which is made from the glycoside in liquorice root. It was discovered as a result of investigations of the casual observation that patients who took a liquorice-containing indigestion mixture got better unexpectedly soon. It accelerates healing of gastric ulcer. Benefit is approximately equivalent to that of bed rest, though the two measures are not additive. The effect on duodenal ulcer is less certain, but it probably occurs. Because the drug is absorbed in the stomach and its therapeutic effect may be topical (as opposed to systemic) special "position-release" capsules (Duogastrone) have been devised which, it is hoped, lodge in the pylorus and discharge the carbenoxolone into the duodenum.

The *mode of action* may involve an increase in the amount of mucus so that the ulcer is protected from pepsin and acid and heals sooner.

Use of carbenoxolone should be considered where antacids fail to give quick relief.

Unwanted effects include sodium retention with œdema, hypertension and heart failure. Hypokalæmia occurs (this cannot be antagonised by spironolactone without antagonising the therapeutic effect also). Potassium supplements may be needed, especially if a diuretic is used to relieve carbenoxolone-induced œdema. These effects are more common in older patients: weight and blood pressure should be closely watched.

Carbenoxolone should be avoided in patients taking digitalis (due to electrolyte changes) unless frequent monitoring (say, weekly) of electrolytes (particularly K) is done.

A diuretic may be used prophylactically.

Impaired glucose tolerance may occur.

Carbenoxolone is generally given for 4 to 6 weeks (100 mg 8-hrly, for first week, then 50 mg 8-hrly) and relief may occur in a few days. In resistant cases it may be continued, but not for longer than 3 months.

Deglycyrrhinized liquorice preparations do not cause fluid retention but appear to retain some ulcer-healing effect (they antagonise muscle

* SIRCUS, W. (1972). *Prescr. J.*, **12**, 1.

spasm experimentally). Further clinical assessment is needed. Preparations include Ulcedal, and Caved-S, a mixture including antacids and frangula bark (a mild purgative).

Gefarnate (Gefarnil) derives from the juice of a kind of cabbage. It is less effective than carbenoxolone, but safer.

Antipepsins are being developed.

Protective coatings might be formed by precipitation of the products of necrosis from the ulcer, e.g. De-Nol (a buffered bismuth solution). Both theory and practice need confirmation.

Œstrogens may be helpful in reducing recurrences of duodenal ulcer in men. Their place in routine therapy, if any, is undecided. In general, men dislike taking œstrogens as they attach importance to their libido even if some of them would be happier without it.

PEPTIC ULCER

The aims of therapy are to achieve relief of pain, healing and prevention of recurrences.

A complete account of the medical treatment of this disease involves a lot more than the mere use of drugs and is outside the scope of this book, but it may be summarised thus:

1. *Relief of pain by raising gastric pH*:

Antacids (food, drugs).

Avoidance of substances that increase gastric secretion or irritate the gastric mucous membrane. These include alcohol and tobacco, excess of tea or coffee, adrenal steroids and corticotrophin, salicylates, phenylbutazone and reserpine. (When these drugs must be used, antacids can be given with them.)

Anticholinergic drugs (for high acid secretors and for nocturnal pain).

2. *To promote healing*:

Bed rest, especially for gastric ulcer.

No smoking.

Carbenoxolone, etc.

It might be supposed that diet and antacids, which give such great symptomatic relief in peptic ulcer, would also promote healing and prevent relapses, but this is not so.

3. *Prevention of recurrences*:

General management of life: this involves inviting the patient to behave sensibly about food (rigid diets are not necessary), e.g. small frequent meals, avoiding only foods that the patient knows by experience cause pain.

Sedation should be used for a positive indication, but not routinely.

Œstrogens may reduce recurrences in male duodenal ulcer patients, but they are not popular.

Iatrogenic sodium retention. Sometimes patients needing low sodium diets or taking drugs that promote sodium retention such as œstrogens, phenylbutazone, adrenal steroids, reserpine, carbenoxolone, are made ill by sodium-containing antacids. The risk may be known to the physician, but we "do not always remember as we scribble our prescriptions" (*18*).

MISCELLANEOUS

Œsophagitis may be helped by sucking tablets of antacids with or without a local anæsthetic, e.g. Mucaine (oxethazine plus Al and Mg hydroxides). Alginic acid and alginates are offered in a variety of forms for œsophagitis and gastric reflux. They are supposed to produce a floating viscous gel that blocks reflux.

Metoclopramide (which see) may reduce reflux by hastening gastric emptying. It may help flatulent dyspepsia.

Dimethicone is a silicone polymer that lowers surface tension and allows the small bubbles of froth to coalesce into large bubbles that can more easily be passed up from the stomach or down from the colon. Claims of clinical usefulness for the relief of flatulence, as well as the claim that it protectively coats mucous membranes require supporting evidence; it may help aviators to belch at high altitudes. It is available with an antacid, e.g. Asilone.

Carminatives are substances which are used to assist in expelling gas from the stomach and intestines. They have been shown to induce relaxation of the cardiac sphincter. They include peppermint, dill, anise and other herbs which are commonly included in liqueurs and in non-alcoholic solutions for babies.

Charcoal is also used for flatulence to adsorb gas in the stomach. It may help sometimes, but the theory of action is unproved.

Bitters are substances taken before meals to improve appetite. They have not been scientifically investigated. They include gentian, nux vomica and quinine. Preparations can be found in the B.N.F. and at wine merchants (Byrrh, Dubonnet).

Demulcents are supposed to coat and soothe mucous membranes. They are used in sore throat, gastritis, peptic ulcer, and in cases of ingestion of corrosive or irritant poisons. They include starch, tragacanth, acacia, mucin, raw egg-white (albumin) and milk.

Since mucous membranes secrete and are coated by mucus, whose chief property is its inability to stick to anything but itself, and to slide one layer of itself over another, it is unlikely that demulcents, which have not these properties, will help. There is no reason to think that they stick to mucous membranes. Radiologists are still looking for a substance that will coat mucous membranes with barium sulphate. Tannic acid has been used for this purpose in the colon, but it is dangerous.

Chlorophyll. Whether chlorophyll in any form taken orally, is an effective deodorant remains a subject of dispute.* The comment by one critic of claims on its behalf that,

> "The goat that stinks on yonder hill
> Has browsed all day on chlorophyll,"

* *J. Amer. med. Ass.* (1953), 153, 728, 749. *Brit. med. J.* (1953), **1**, 832–3.

has been stigmatised as irrelevant as well as unfair. Local application of high concentrations to wounds or in the gut may have some deodorant effect.

Digestive Enzymes. Pancreatic extracts, in large doses, are useful in cases of pancreatic insufficiency. They may reduce the frequency and urgency of bowel actions in pancreatic steatorrhœa, but may not normalise the amount of fat in the stool. Preparations are of variable potency. Attention to detail is necessary to get the best results.

It is doubtful whether there is any place in therapeutics for pepsin preparations. Papain, a proteolytic enzyme from the pawpaw melon, is used to "tenderise" meat. Diastase is included in a variety of proprietary preparations with no demonstrated therapeutic effect.

Bile Salts are essential for the digestion and absorption of fats and fat soluble vitamins. When there is a lack of bile salts in the intestine due to obstruction of the flow or to fistula, they may be supplied by mouth. Absorption leads to higher blood levels of bile salts in cases of obstructive jaundice, but this may be less important than preventing vitamin deficiency.

Bile salts are given as either Extract of Ox Bile, B.P. or sodium tauroglycocholate, after meals.

Bile Acid, as dehydrocholic acid, is a cholagogue, i.e. it increases the secretion of a watery bile, and is used with uncertain benefit in cholangitis in the hope of preventing ascending biliary infection. It does not materially help digestion and should not be used in the presence of complete biliary obstruction. Dehydrocholic acid is given in tablets or capsules, after meals. Its therapeutic efficacy has not been proved.

Gallstones (*24, 25*) Cholesterol is a major component of human gallstones. Cholesterol is carried in the bile in a micelle (polymolecular aggregate) of bile salt (detergent), phospholipid and cholesterol. It seems that patients who form gallstones may have a metabolic defect that results in insufficient secretion of detergent bile salts (patients have been shown to have a reduced bile salt pool), the result of which is that the capacity of the bile to hold cholesterol in solution is reduced and it becomes supersaturated, and the cholesterol is therefore liable to precipitate.

Administration of a bile salt (*chenodeoxycholic acid*) has been shown to enlarge the bile salt pool and to increase cholesterol solubility in bile. Prolonged administration of chenodeoxycholic acid can sometimes eliminate gallstones that are *chiefly* cholesterol (probably not others). But the metabolic abnormality will remain uncorrected.

Cholestyramine (Cuemid, Questran) is an anion exchange resin that, taken orally, binds bile acids in the bowel and so prevents their absorption.

Most of the bile acids in the body are going round the cycle of hepatic secretion, reabsorption from the gut, hepatic secretion. Only a small amount is synthesised.

Thus, if reabsorption from the gut is prevented, the plasma concentration will fall. Cholestyramine is used in hepatic disease (e.g. primary biliary cirrhosis) in which the liver cannot adequately excrete bile acids, and it may relieve **itching** in about 2 weeks. Jaundice does not increase, as it may with testosterone. Serum bilirubin level is unaffected. Obviously, cholestyramine will be ineffective in jaundice due to total biliary obstruction.

Cholestyramine lowers plasma cholesterol by two mechanisms: first by binding bile acids in the gut (bile acids are necessary for cholesterol

absorption); second, where hepatic function is good, prevention of absorption of bile acids will be followed by compensatory increased hepatic synthesis of bile acids from cholesterol.

Excess bile salts in the colon causes diarrhœa, e.g. after ileal resection. Cholestyramine can be used to bind the salts and stop diarrhœa, though this may result in some steatorrhœa. Prolonged use may require injection of fat soluble vitamins.

Drugs should not be given orally within two hours of cholestyramine lest they be taken up by the resin.

Prolonged use may lead to metabolic disturbances, and high dosage to steatorrhœa due to binding of bile salts in the intestine.

PURGATIVES (*32–34*)

The terms purgative, cathartic, laxative, aperient and evacuant are synonymous.

Purgatives may be classified as (1) **bulk,** (2) **stimulant,** (3) **fæcal softeners.** The time a purgative takes to act determines whether it should be given in the morning or evening and will be found in the table below together with the dose.

Bulk Purgatives

Bulk purgatives act by increasing the volume and lowering viscosity of intestinal contents and so both encouraging and rendering more effective, normal reflex bowel activity. If taken repeatedly with too little fluid they can cause intestinal obstruction, especially if there is any organic obstruction or if peristalsis is weak. They include two different groups of substances:

(1) Hydrophilic colloids and indigestible vegetable fibre, which promote a large, soft, solid stool by holding water in the gut.

Methylcellulose takes up water to swell to a colloid about 25 times its original volume. It can be taken as tablets, granules or in solution (Celevac, Cologel etc). It is used in constipation (alone or mixed with other kinds of purgative), in control of colostomies, in diverticular disease of the colon (where the high colonic pressures are lowered) and in irritable bowel syndrome. Its use to fill the stomach and suppress appetite in obesity (which see) is probably irrational. It is also used as a suspending agent in pharmacy, in lubricating jellies and in contact-lens wetting solutions. Sodium carboxymethylcellulose is similar.

Agar is obtained from seaweed. With water it swells and forms a jelly.

Psyllium seeds (Isogel) contain mucilage which swells with water. Various other plant substances swell with water including *slippery elm, sterculia* and *plantago*.

Bran, the residue left when flour is made from cereals, is widely used to add to the diet, especially for diverticular disease. If a lot is eaten with a very low fluid intake it is specially liable to cause intestinal obstruction.

Prunes and figs act as bulk purges and also contain mild irritant organic substances. It should be remembered that Compound Syrup of Figs, B.P.C., and proprietary preparations in which the word "fig" is prominent,

suggesting very mild and "physiological" action particularly suited to children, owe most of their efficacy to the substantial doses of cascara or senna which are incorporated. They can be violently effective.

Bulk purgatives are often combined with liquid paraffin and stimulant purges in proprietary preparations.

COMMONLY USED PURGATIVES

Mode of action (Site)	*Purgative (Tablet size in mg)*	*Dose*	*Conventional time of oral administration (Time to act)*
Bulk solid stool (small and large intestine)	methylcellulose	1–1·5 g	morning (1–3 hrs)
	agar	4–16 g	
	psyllium	4–16 g	
	bran	much	
Bulk semi-liquid stool (small and large intestine)	magnesium sulphate	5–15 g	morning (1–3 hrs)
	magnesium hydroxide	3 g	
	sodium sulphate	5–15 g	
	sodium potassium tartrate	5–15 g	
Fæcal softener	liquid paraffin	14–45 ml	evening or in 2–4 equally spaced doses
	dioctyl-sodium sulphosuccinate (20 mg)	20–100 mg daily	single or divided doses
Stimulant (small intestine)	castor oil	5–15 ml	morning on an empty stomach (2–6 hrs)
Stimulant (large intestine)	phenolphthalein*	0·1–0·2 g	night (6–8 hrs)
	cascara (125)	100–250 mg	night (8–12 hrs)
	senna†	5–10 mg	night (6–10 hrs)
	bisacodyl (5) (10, suppos.)		night (6–10 hrs)

* Incorporated in emulsions (Liq. Paraff. and Phenolphth. Emuls. B.P.C.) and tablets (Phenolphth. Cpd. Pil., B.P.C.) and numerous proprietaries, including chocolate.

† A variety of biologically standardised proprietaries with differing doses, e.g. Senokot Tabs., dose 2 to 4, also Pursennid Tabs., dose 1 or 2.

(2) **Inorganic salts** which promote a fluid stool are but little absorbed. They increase the bulk and reduce viscosity of intestinal contents by osmotic effect, retaining water in the intestinal lumen or, if given as hypertonic solution withdrawing it from the body. The principal ions which are little absorbed are magnesium, sulphate and tartrate. The principal substances used as saline purges are **magnesium sulphate** (Epsom salt), **sodium sulphate** (Glauber's salt) and **sodium potassium tartrate** (Rochelle salt); the latter mixed with tartaric acid and sodium

bicarbonate as in Compound Effervescent Powder B.P. (Seidlitz powder) makes a not unattractive effervescent drink which is promoted also for its psychological effect when taken on getting up in the morning. If prescribed, it is as well to mention to the patient how to make the drink for it is reported* that one young man swallowed the ingredients separately. "He afterwards declared that his stomach exploded and that he was thrown against a wall." Fortunately the gastric rupture was successfully repaired.

All saline purges are nauseous if taken in too little water; about a cupful is minimal, except with **magnesium hydroxide** which is insoluble in water and is also used as a gastric antacid; the soluble magnesium salts formed in the alimentary tract act as a saline purge. It is relatively feeble and much used for children and for counteracting the constipating effects of aluminium and calcium salts in gastric antacid therapy. It is often combined with liquid paraffin in an emulsion.

In patients with renal failure the small amount of magnesium absorbed when the sulphate is frequently used can be enough to cause magnesium poisoning, the central nervous system effects of which somewhat resemble those of uræmia. Magnesium poisoning can also occur with hypertonic enemas for lowering intracranial pressure. Again, the symptoms of poisoning and those of the disease process may be confused.

Fæcal Softeners (emollients)

Liquid paraffin is a chemically inert mineral oil and is not digested. It is tasteless although some find its oiliness nauseating. It is generally said to act by lubricating the bowel, although only about the last few feet can be in need of this, for elsewhere the contents are fluid. Paraffin has been said to increase the rate of passage of small intestinal contents by reducing water absorption and it may be this effect as well as the lubricant and softening powers of the oil that promotes the passage of softer fæces. It is often given in an emulsion with magnesium hydroxide or phenolphthalein. It is perhaps best not taken with meals as it delays gastric emptying.

Liquid paraffin is particularly useful when straining at stool may be painful or dangerous, as after anal surgery or in cardiac disease, although it may retard healing of anal wounds. If used with surgery it should be given for several days before operation and not only after, when there is a "fæcal chain" ahead of it.

Some paraffin is absorbed from the intestine and collects in the mesenteric lymph nodes where paraffinomas may form. Absorption of fat-soluble vitamins is reduced, but there is no conclusive proof that harm has resulted from either of these effects, although harm is clearly possible.

Liquid paraffin (or other oils) taken over long periods orally, especially at night, or as nasal drops, may cause chronic lipoid pneumonia, especially in the old or very young. An unusual case resulted from successful attempts by a patient to lubricate his larynx with liquid paraffin.

* TANNER, N. C. (1959). *Proc. roy. Soc. Med.*, **52**, 379.

Large doses may leak out of the anus causing both physical and social discomfort. Liquid paraffin may not be as harmless as its chemical inertness suggests (*27*).

Surface-active agents, e.g. dioctyl-sodium (or calcium) sulphosuccinate (Dioctyl-Medo) and poloxalkol soften fæces by lowering the surface tension of fluids in the bowel which seems to allow more water to remain in the fæces. They are often combined with a stimulant purgative (Normax, Dulcodos, Dorbanex). They should not be used with liquid paraffin because they may increase its absorption.

Stimulant Purgatives

Bisacodyl (Dulcolax) is a synthetic substance. Few new purgatives are introduced for, with the range of drugs available, research by a commercial organisation would not offer very high prospects of financial return and academic organisations, not surprisingly though perhaps mistakenly, see little of interest in the study of purgatives.

Bisacodly is effective orally and as a suppository. It stimulates sensory endings in the colon by direct action from the lumen. In a geriatric unit it was found that bisacodyl suppositories reduce the need for regular enemas in some patients (*29*). There are no important unwanted effects.

Phenolphthalein. The purgative action of phenolphthalein was discovered in 1900 by von Vamossy who was investigating its properties because the Hungarian government wished to use it to "denature" artificial wines. He administered it to a pet dog which was at first unmoved although it later passed a constipated stool. Unsuspecting, von Vamossy and a colleague took 1·5 and 1 g each (normal adult dose, 0·1 to 0·2 g) and in a few hours passed 3 to 5 watery stools, repeated in the evening and again the following morning. They reported no griping and their work, unspecified, was not hindered. Clinical trials followed and phenolphthalein was introduced into clinical practice in 1902. Stories that phenolphthalein was put in wine and its purgative action discovered by the general population are denied by von Vamossy (*28*).

Solid phenolphthalein is dissolved in the small intestine, a little is absorbed and excreted in the urine and bile. It stimulates the colon directly. The excretion of some in the bile tends to prolong its action, as von Vamossy discovered. If the urine or fæces are alkaline they will become red which may alarm the patient.

Phenolphthalein is a safe and reliable drug and is therefore widely incorporated in proprietary purgatives, including those sold in the form of chewing gum and sweets, for it is tasteless. Formularies contain many preparations.

Occasionally a rash occurs which evades diagnosis, for it may never occur to the patient to volunteer the fact that she is using purgatives.

The anthraquinone group includes cascara, senna, danthron, rhubarb and aloes. In the small intestine soluble anthraquinone derivatives are

liberated and absorbed. These are excreted into the colon and act there, along with those that have escaped absorption, probably after being chemically changed by bacterial action. They are said to stimulate Auerbach's plexus in the large intestine and so to provide "physiological purgation". Enough may be excreted in the milk to affect an infant.

This group of purgatives is sometimes described as the "emodin group" as emodin was thought to be the active principle. In fact it is merely one of the active substances and perhaps not the most important.

Patients taking senna or rhubarb may notice their urine is coloured brown (if acid) and red (if alkaline) due to the presence of chrysophanic acid. Prolonged use of this group can cause melanosis of the rectum.

Erratic results with these purgatives, which are usually crude plant extracts, have in the past been due not only to the marked individual variation which occurs and to the development of tolerance, but also to the absence of methods of biological assay, employment of which has now revealed great variations in potency of official preparations. Biologically standardised senna preparations are available.

Cascara is obtained from the Californian buckthorn. It is popular.

Senna is obtained from an Arabian shrub. Extracts of the fruit (pod) are said to be less griping than those of the leaf, and these are used in the modern biologically standardised preparations. For those who like ritual and are not scientific about dosage, the practice of soaking pods in water and drinking the extract may be preferred.

Rhubarb (a Chinese plant) and **aloes** are still supplied in the more old-fashioned mixtures. There is nothing much to be said either for or against them, but they are still popular with the public because they work.

Oxyphenisatin (Bydolax) is obsolete because of toxicity.

The **drastic purgatives** (jalap,* colocynth and podophyllum) are obsolete as they are too drastic, and so is croton oil. Sulphur (brimstone), though not drastic, is obsolete because of offensiveness.

Mercury as calomel (mercurous chloride) or as the metal finely divided with chalk (grey powder) has been used as a ritual purgative in children. However, the dangers of mercury poisoning are substantial and mercury is no longer used as a purgative, or even in "teething powders" in which it was incriminated as a probable cause of pink disease (*41*) and the nephrotic syndrome. The substitution of phenolphthalein for calomel in these damnable domestic remedies has followed a public outcry. This may result in disconcerting mauve or red coloration of babies' napkins, but is better than being poisoned by a heavy metal.

Castor oil acts as a purgative after hydrolysis in the small intestine where the irritant ricinoleic acid is formed. The liquid contents of the small intestine pass rapidly onwards, resulting in a soft or fluid stool after 2 to 6 hrs. Having regard to the fact that it has to be digested, castor oil should obviously be given on an empty stomach. The ricinoleic acid is absorbed and there is insignificant irritation of the large intestine. Colic (griping) is

* In the 19th century "young men proceeding to Africa" were advised to take pills, named Livingstone's Rousers, consisting of rhubarb, jalap, calomel and quinine (*Brit. med. J.*, 1964, **2**, 1583).

usually trivial, and so complete is the evacuation of the intestine that there is usually constipation afterwards. Castor oil is therefore chiefly used as a "once for all" purgative, as after a dietetic error. Its irritant action is powerful enough for it to be capable of starting pregnant women in labour (*37*).

Most patients find castor oil objectionable to take. It is less offensive if given well cooled and floating in fruit juice, milk or whisky according to taste.

Castor oil is also used in ointments, hair lotions and eye drops as a simple non-irritant lubricant and vehicle.

Miscellaneous

Lactulose is a synthetic disaccharide. Taken orally (Duphalac Syrup), it is unaffected by small intestine disaccharidase and is not absorbed. In the colon it ferments to lactic and acetic acids. Its mode of action as a purgative is undecided.

It is also used in treatment of hepatic encephalopathy; it may inhibit the organisms in the colon (by lowering pH) that form toxic substances from protein. These substances, when absorbed are a cause of the encephalopathy

CONSTIPATION

In general constipation is better treated by decreasing the viscosity of the fæces than by increasing the motor activity of the gut.

Constipation may occur with any **acute illness**, especially if it involves confinement to bed and is accompanied by loss of appetite. Dependence on others for assistance to the water closet or, worse, to bring a bedpan, is also a factor. The bedpan is not only objectionable as a cause of constipation, but it has also been shown that its use requires a 50% greater oxygen consumption than does use of a bedside commode, so that the humiliation of a bedpan should only be inflicted on those for whom it is absolutely necessary. These are fewer than is sometimes imagined (*30*). If severe enough to warrant attention, this kind of constipation can usually be dealt with by bulk purgatives, by fæcal softeners or by senna or cascara or by suppositories of glycerine or bisacodyl.

Sedatives taken continuously also constipate.

Constipation is a usual accompaniment of **painful anal lesions** because, when defæcation hurts, it is postponed for as long as possible, with the result that the motion becomes harder and so hurts even more when it is eventually passed. This vicious circle is best broken by cure of the anal lesion, but a fæcal softener, or a saline purgative to make the stool semi-fluid, may give relief temporarily.

Constipation may be part of the syndromes associated with **obstruction of the bowel,** but other symptoms are then always more prominent; treatment is of the cause, and purgatives are dangerous.

It is important to ensure that the patient stops taking purgatives after resumption of normal life, for a common cause of constipation is purgative dependence, which may be solely emotional at first, though physical **dependence** may follow.

Dependence may arise following an illness or in pregnancy, or the individual may have the mistaken notion that a daily bowel motion is essential for health, or that the bowels are only incompletely opened by nature, and so indulge in regular purgation. This effectively prevents the easy return of normal habits because the more powerful purges empty the whole colon, whereas normal defæcation empties only the descending colon. Cessation of use after a few weeks is thus inevitably followed by a few days' constipation whilst sufficient material collects to restore the normal state. This may be claimed by the patient as evidence of the continued necessity for purgatives. Patients feel they understand their own bowels far better than anyone else possibly could, an opinion they seldom extend to other organs, except perhaps the liver. In Britain there is a tradition that nurses have an intuitive understanding of the bowels that is denied to doctors.

To prevent purgative dependence is easier than to cure it.

Uses. Purgatives are sometimes indicated before certain X-ray examinations (cascara, senna, bisacodyl), for the removal of ingested poisons (a saline purge or castor oil), in hepatic coma (magnesium sulphate), in megacolon and with some drugs that cause constipation, such as opiates.

Correction of **habitual constipation** is best achieved by a small dose of a hydrophilic substance or Mg with each meal rather than a large dose once a day. Fæcal softeners may also be tried, and if a stimulant is necessary, senna is perhaps the least objectionable. In general, choice of a purgative is not critical.

Excessive use of stimulant purgatives may, especially in the old, lead to severe **water and electrolyte depletion,** even to hypokalæmic paralysis; also to malabsorption and protein-losing enteropathy. Atonic colon due to damage to gut nerve plexus may occur (cathartic colon).

Purgatives are dangerous if given to patients with undiagnosed abdominal pain, inflammatory intestinal disease or obstruction. Nor should they be used to get rid of **hardened masses of fæces** in the rectum, for they will fail and cause pain. Digital removal, generally prescribed by a senior and performed by a junior doctor, is required. A fæcal softener helps to prevent recurrence.

Purgatives should be avoided in patients taking broad spectrum antimicrobials orally as they may precipitate an attack of diarrhœa.

Routine use of purgatives in children, on the principle that a "good clear out" is healthful, is deplorable and casts doubt on either the intelligence or the mental health of the prescriber.

In **pregnancy** constipation is best treated by the milder purgatives (e.g. senna) as vigorous purgation can cause abortion, though this is less reliable than some women hope. The use of vigorous purgation, traditionally with castor oil, to promote the onset of labour is unpleasant for the patient but moderately effective (*37*).

All stimulant purgatives can cause colic and this can be combated, if

necessary, with atropine or similar drugs, but generally it is a symptom of overdose.

There has been very little **scientific study of purgatives** in man. The importance of psychic factors in one study is indicated by the observation that after the substitution of an "inert placebo . . . an average of almost one bowel movement a day was reported by patients who claimed to be constipated. . . . At least, in our clinics, constipated persons are those who think they are not having enough bowel movements."*

In this study a beverage containing bran extract was not distinguished from a placebo by 40 normal subjects nor by 20 constipated patients. This does not, of course, condemn bran, but only bran in the form and dose used in this experiment, although it is permissible to expect similar results from bran in any form or dose.

There are innumerable preparations of purgatives (see any formulary), many of the proprietary ones being elegant and pleasanter than the official preparations. Both are effective, except some of the official anthraquinone group, but elegance must be paid for.

Suppositories (bisacodyl, glycerin or soap), may be used to obtain a bowel action in about 1 hr. A novel contribution is a suppository containing anhydrous sodium acid phosphate and sodium bicarbonate (Beogex). On contact with the wet rectal mucosa CO_2 (about 300 ml) is liberated and stimulates peristalsis by distension. Occasionally, drugs such as aminophylline or phenylbutazone are given by this route for the systemic effect.

For anal and rectal disease suppositories which are astringent (hamamelis), or anti-inflammatory (adrenal steroid) or which are imagined to provide an inert coating of the mucous membrane (bismuth subgallate) or local anæsthesia (lignocaine) are used as seems necessary.

Enemas produce **defæcation** by distending the bowel. They have the disadvantage of requiring time and equipment as well as having, in some patients, psychological disadvantages. Dependence may occur. Plain water or a soapy solution are generally used.

Turpentine enema is a folk remedy used to promote the passage of gas in distended patients. Whether it does this more successfully than a simple enema is unproved. Turpentine is a very strong irritant.

Enemas to be retained may be used for a variety of conditions. To reduce intracranial pressure for a few hours 150 ml of saturated magnesium sulphate solution is slowly run into the rectum. It acts by withdrawing water from the body into the bowel. Magnesium poisoning may occur in patients with poor renal function.

Small retention enemas may be used to rehydrate patients, but this is an inefficient way of replacing water and even more so, of electrolytes.

Paralytic Ileus

When this condition is due to potassium deficiency the treatment is clear enough. In other cases the mechanism is uncertain. Use of cholinergic stimulant drugs has been unsatisfactory as there has been a wise tendency

* GREINER, T., *et al.* (1957). *J. chron. Dis.*, **6**, 244.

to avoid drugs and to use intestinal suction and attend to electrolyte balance.

The suggestion that ileus may be due to excessive sympathetic inhibitory activity (both α-and β-adrenoceptors in the gut mediate inhibition, but the α is the more important) has led to the use of adrenergic neurone blockers and α-adrenoceptor blockers. There seems to have been some success, but this interesting approach needs further evaluation.

DIARRHŒA

Diarrhœa may be controlled by a variety of drugs which have no effect on the cause, but, as always, removal of the cause is obviously the best treatment. Symptomatic and specific treatment are often combined, as for instance in dysentery where an antimicrobial, such as a sulphonamide or amœbicide, may be given together with a kaolin or chalk mixture. If a severe diarrhœa cannot be quickly controlled, replacement of the abnormal losses of water and electrolytes, including potassium, is essential.

Drugs used in the treatment of diarrhœa fall into two classes. They are often used in combination. Both increase viscosity of fæces.

1. *Increase viscosity of gut contents directly*: kaolin, chalk, bismuth subgallate.

2. *Delay passage of gut contents* so that there is time for more water to be absorbed: opiates, smooth muscle depressants, anticholinergics.

Adsorbent powders. These are generally thought to act by providing a coating for the bowel and by adsorbing toxic substances, both unsatisfactory explanations. They probably do not coat the bowel; adsorption is not selective and there is no reason to believe that most of their adsorptive capacity is not taken up by non-toxic substances. But whatever the explanation they seem to work, though the fact that they are often combined with an opiate demonstrates that they are ineffective in severer cases.

Preparations include Kaolin Compound Powder, B.P.C. (one level teaspoonful, 4-hrly or more often) and Kaolin and Morphine Mixture, B.P.C. (15 to 30 ml 4-hrly).

The opium group of drugs act directly on the smooth muscle of the bowel reducing peristalsis. **Codeine** is a drug of choice (Codeine Phosphate Tabs. B.P. (30 mg), dose 15 to 60 mg) or various mixtures of kaolin or chalk plus opium or morphine. Chlorodyne is Chloroform and Morphine Tinct., B.P.C. (dose 0·3 to 1 ml), dependence can occur.

Diphenoxylate is related to pethidine and affects the bowel like morphine. It is effective in diarrhœa. It is offered mixed with a trivial dose of atropine as Lomotil (1 or 2 tablets, 6–8 hrly). It is antagonised by nalorphine.

Mebeverine (Colofac) (a reserpine derivative) depresses colonic activity and may be useful in irritable bowel syndrome.

Anticholinergic drugs such as propantheline, atropine or belladonna are sometimes helpful in chronic diarrhœas where it is undesirable to use opiates indefinitely, but intestinal paralysis may be precipitated by large doses of propantheline, which also blocks autonomic ganglia.

It is now known that constipated patients commonly have greater spontaneous activity of the sigmoid colon than do non-constipated people, and patients with diarrhœa have less than normal.

In the case of diarrhœa the important factor may be the loss of the normal segmenting contractions that delay passage of food, so that an occasional peristaltic wave may have greater effect. Also, liquid fæces trickle along passively to reach the sensory areas for the defæcation reflex in the rectum (stretch receptors) and anus (touch receptors).

Irritable bowel syndrome: this common condition is not regularly benefited by any drugs. Sedation or mebeverine may help, as may anticholinergics or methylcellulose.

Travellers' Diarrhœa

"The bête noire of the international traveller is an explosive, often demoralising diarrhœa which has been subject more to speculation than to investigation" writes one of the few scientific investigators of this disease* that is known by experience to most and by hearsay to all travellers.

So familiar is travellers' diarrhœa that it has acquired a variety of popular names, the Aztec 2-Step, Montezuma's Revenge, Delhi Belly, Gyppy Tummy, Hong-Kong Dog and Casablanca Crud all indicate some of the areas most dangerous to visitors. The Mexican name *turista* indicates the principal sufferers.

Although there is a considerable body of medical folklore, there is little useful information available to the prospective traveller fearful of the consequences of being stricken during his coach tour of 5 European capitals in 7 days.

Scientific studies on travelling populations are difficult, but some have been done.

It has been shown that amongst U.S.A. students visiting Europe those who went to France and the Mediterranean areas suffered an incidence twice as high as those who went to North Europe; that amœbæ, shigellæ and salmonellæ are not a significant cause of this disease that generally runs a self-limited course of less than a week, often only 1–3 days. Stool cultures have shown a slightly higher incidence of Friedlander's bacillus and of enteropathic coliforms.

It seems likely that the most common causes are food contaminated with bacterial toxin, e.g. staphylococcal, the bacteria having been killed by cooking, or with living enteroviruses or pathogenic subtypes of Escherichia coli.

If this view of the causes is true, it explains why antimicrobial drugs have been found to provide only partial protection. Suggestions that changed environment, diet and psychological causes are important receive no support from the fact that the incidence of travellers' diarrhœa is

* KEAN, B. H., *et al.* (1962). *J. Amer. med. Ass.*, **180**, 367.

radically different in Mexico and Hawaii, that there is not a higher incidence amongst those known to respond to stress with diarrhœa at home, and that a lactose placebo administered double-blind gives no relief.

In prophylactic trials it has been found that antimicrobial drugs can reduce the incidence of diarrhœa and its severity, but probably not its duration when it does occur.

Studies in travelling teams of athletes have been uncontrolled or imperfectly controlled. They are best summed up by a statement that U.S.A. athletes at the Pan-American Games "had good *luck*" with two Entero-Vioform tablets daily.

Prolonged prophylaxis should only be undertaken with drugs that do not alter the intestinal flora and have negligible toxicity. Clioquinol (Entero-Vioform) partially meets these criteria, and, on balance, clinical studies suggest that it is effective, though the dose should not exceed 7 g total over two weeks (followed by an interval of a month) because of the remote risk of CNS toxicity. In Britain high protein-bound iodine levels in blood for three months following the holiday season are liable to be due to clioquinol (which contains iodine) and not to disease.

Antimicrobials (streptomycin, neomycin and the less-absorbed sulphonamides) alone and in combination, can reduce incidence of disease but also have undesirable effects by altering bowel flora and function, causing rashes, promoting development of resistant organisms and hindering diagnosis of serious infection. These drugs are therefore only suitable for use as prophylactics on very special occasions and then only for less than three weeks. They are not suitable for the ordinary summer holiday.

Whether or not prophylaxis is to be used, travellers will often want something to take should they fall victim to this unpleasant disorder which, even in a mild form, can wreak social havoc in all but the most completely equipped holiday motor coach.

Antimicrobial drugs are not generally needed to treat travellers' diarrhœa which can ordinarily be controlled by one of the opium alkaloids that increase gut tone and reduce gut propulsion. Codeine phosphate tablets (30 mg) have not been superseded for both efficacy and convenience, and the patient can control his own dosage safely and within a wide range: diphenoxylate plus atropine (Lomotil) is an alternative. Other opium and kaolin preparations can be used, but many of these are liquids which are cumbersome to transport. These constipating drugs will also act quicker than an antimicrobial and the latter is ineffective where the cause is not bacterial.

If the symptomatic remedies fail, then the diarrhœa is fairly severe and the patient should consult a doctor, for the only alternative is to treat this fairly severe attack blind, assuming it to be infective. Patients are naturally reluctant to consult doctors when away from home for various obvious reasons, but it is generally undesirable to advise them to undertake a full therapeutic course of broad spectrum antimicrobial therapy, and to provide them with the wherewithal to do it.

Conclusion. A reasonable course for holiday travellers in Europe and the Mediterranean area is to take advice on hygiene and a symptomatic remedy, such as codeine phosphate, to be used at the start of diarrhœa, or, if some sort of prophylaxis against infection is thought to be essential, to use either clioquinol (Entero-Vioform) or phthalylsulphathiazole (1 g b.d.).

Ulcerative Colitis (*35, 36, 38, 40*)

The management of ulcerative colitis involves a lot more than giving drugs, e.g. correction of anœmia and dehydration.

The usefulness of drugs may be summarised.

For *symptomatic treatment of diarrhœa*, see above.

Severe attacks may be treated initially by an adrenal steroid (i.v. if necessary) (e.g. hydrocortisone 100 mg, or prednisolone 20 mg i.v., 2 or 3 times a day), or corticotrophin. Rectal hydrocortisone or prednisolone (12-hrly) may be used. After a few days of this intensive regimen, treatment may be as for moderate attacks (see below).

A well-designed clinical trial (*35*) has shown that corticotrophin (80 units of the gel i.m. daily) controls severe attacks of ulcerative colitis more effectively than cortisone (50 mg cortisone and 1 g potassium chloride orally 4 times a day) but only at the price of more complications and a higher relapse rate with the corticotrophin. It is therefore recommended that corticotrophin be used only in those who fail to respond to an adrenal steroid or in severe cases where the immediate benefits of more effective control outweigh the longer term risks.

The authors of this investigation point out a disadvantage of long-term therapeutic trials nowadays; that new remedies may be introduced whilst a trial is still in progress. In this particular case prednisone, prednisolone and triamcinolone were all introduced during the trial of cortisone and corticotrophin. It may be that these steroids are as effective as corticotrophin. Symptomless perforation of the bowel can occur in patients taking steroids. Surgery is often essential in very severe cases, and may be more hazardous in patients taking an adrenal steroid.

Moderate attacks may be treated by oral prednisolone (10 mg 6-hrly) and also rectally (12-hrly).

Mild attacks may be treated with prednisolone (5 mg 6-hrly) and a nightly retention enema: also sulphasalazine (orally 0·5–1 g 6-hrly).

Prevention of relapse. Systemic adrenal steroid (in doses that do not cause serious adverse effects) is ineffective in preventing relapse: retention enemas of an adrenal steroid (on most days) may help.

Sulphasalazine does usefully prevent relapse (0·5 g 6-hrly) and it may be continued indefinitely (or at least a year). At this dose adverse reactions are infrequent and generally mild.

Immunosuppressives (other than adrenal steroids which are also anti-inflammatory), e.g. azathioprine may be beneficial, but whether the risks of long-term treatment outweigh the benefits is still undecided. The risks include bone marrow depression, carcinogenesis and mutagenesis.

Idiopathic Proctitis

Prednisolone suppositories are effective. Acetarsol suppositories may be tried in resistant cases.

Guide to Further Reading

(Further references to the effects of anticholinergic drugs on the alimentary tract are given after Chap. 16)

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Chapter 22

HISTAMINE AND ANTIHISTAMINES

HISTAMINE

HISTAMINE is a naturally occurring amine of great interest to pharmacologists but with only a modest importance for physicians. It occurs naturally in an inactive bound form in most body tissues and pharmacologically active free histamine is released in response to injury, such as physical trauma of any kind or antigen-antibody reactions. There are also various chemicals which have power to release histamine. The more powerful of these (proteolytic enzymes and snake venoms) have no place in therapeutics, but a number of useful drugs, such as tubocurarine, morphine and even some antihistamines, also release histamine, although not usually enough to do more than transiently lower blood pressure or cause a local reaction. The **physiological role** of histamine is still not certain; one possible function is in the gastric mucosa, where the hormone gastrin may increase secretion by inducing histamine release. The actions of histamine which are clinically important are those on:

Gastric secretion. Histamine increases the acid and pepsin content of gastric juice. This effect is antagonised only trivially by atropine and not at all by some antihistamines. Histamine has been used to test the capacity of the gastric mucosa to secrete acid, but it has been replaced by pentagastrin which is selective for the stomach, unlike histamine.

Smooth muscle. In general histamine stimulates smooth muscle (excepting arterioles, but including the larger arteries) throughout the body. Stimulation of the pregnant human uterus is insignificant. A brisk attack of bronchospasm may be induced in subjects who have any allergy, particularly asthma, when it may occur even in the presence of an antihistamine.

Arterioles are dilated, with a consequent fall in blood pressure. The characteristic throbbing headache that occurs after histamine injections is due to stretching of pain-sensitive structures in the dura mater by the alterations in pressure in blood vessels and cerebrospinal fluid (*3*).

Capillaries dilate and their permeability to plasma increases, which responses comprise two parts (the local red response and the wheal) of the "triple response" described by Sir Thomas Lewis (*4*). The third part is arteriolar dilatation due to an axon reflex.

The suprarenal medulla is stimulated to release adrenaline and noradrenaline in amounts which are insignificant in normal subjects but which are sufficient to raise the blood pressure in patients with phæochromocytoma (which see) in whom i.v. injection of histamine is sometimes used as a diagnostic test.

Itch. Histamine release in the skin can cause itch.

General. Histamine is insignificantly absorbed from the alimentary tract and is largely metabolised in the body, although a little appears in the urine. After s.c. injection its unpleasant effects persist for about half an hour. True tolerance to histamine does not occur to any significant extent and there is no good evidence that courses of histamine injections to "desensitise" allergic subjects are of any value.

There is no important **clinical use** of histamine now that it is replaced by pentagastrin in gastric secretory tests. Attempts to utilise its vasodilator action in Ménière's syndrome and peripheral vascular disease have been given up. It has been used in migraine with dubious benefit; the placebo-effect of a substantial injection may be profound.

Unwanted effects of histamine are an extension of the actions described above, with, in addition, stimulation of the smooth muscle of the intestine which is not seen at ordinary doses. The main features are circulatory collapse and bronchoconstriction. The most rapidly effective antidote is adrenaline, and an antihistamine may be given as well, by injection in severe cases.

ANTIHISTAMINES

When it became clear that release of histamine by tissue injury had harmful effects it was evident that histamine antagonists might have therapeutic importance, especially in allergic conditions.

The effects of histamine can be opposed in four ways:—

1. By using a drug with opposite effects, e.g. histamine constricts bronchi, causes vasodilatation and increased capillary permeability. Adrenaline opposes these effects. This is physiological antagonism.

2. By preventing histamine from reaching its site of action, *e.g.* by competition, the antihistamines.

3. By accelerating the destruction of histamine in the body. Attempts have been made to use the enzyme histaminase (di-amine oxidase) for this purpose, but it has not proved effective.

4. By preventing the release of histamine; adrenal steroids and cromoglycate can suppress the effects on the tissues of antigen-antibody reactions.

The term antihistamine is confined to drugs which act by competition (group 2 above) although the formulæ of some differ completely from that of histamine.

Since the competitive antihistamines introduced in 1947 did not block some of the effects of histamine (e.g. gastric secretion, some of the blood pressure lowering effect) it seemed that there must be more than one kind of histamine receptor.

In 1964, based on the simple analogy with α-and β-adrenoceptors and their blockers, an investigation was begun into substances designed to block the histamine effects spared by existing antihistamines (*10*). About 700 compounds were synthesised and tested, and in 1972 burimamide was

given to man. *Metiamide* blocks the effect of histamine on gastric secretion and, when given with another antihistamine, completes the block of the hypotensive effect of histamine.

It seems that there are at least two types of histamine receptor:

H_2-receptor: effect on gastric secretion (and some effect on blood pressure).

H_1-receptor: the other effects of histamine (see above) including some on blood pressure.

The fact that burimamide also blocks the gastric secretion caused by gastrin (and pentagastrin) suggests that gastrin does indeed act by local histamine release.

Thus it seems that histamine antagonists (antihistamines) should be classified:

H_1-receptor blockers: see table and account below.

H_2-receptor blockers: burimamide: undergoing clinical trials for effects on gastric secretion, e.g. duodenal ulcer, Zollinger–Ellison syndrome.

H_1-receptor blockers. Substances capable of this effect were discovered in 1937, and by 1947 the antihistamines diphenhydramine and pyribenzamine were in clinical use. Since their introduction the number of antihistamines available has increased rapidly. This is both because they are relatively easy to make, and because they control some allergic conditions without curing them, so that they are in constant demand. A substantial proportion of the population, it is said as much as 10 to 15%, suffer allergic reactions at some time in their life, so that an effective antihistamine can be very profitable commercially even though only a minority of sufferers are benefited by the drugs.

The term antihistamine is unsatisfactory, for they have numerous other actions and are used as hypnotics, antiparkinsonian remedies, antitussives, expectorants and in motion sickness, actions which are not related to antihistamine effect. Although the drugs differ in various ways these are not of very great importance, except to an occasional individual patient, and so they can be conveniently discussed together. The ideal antihistamine, i.e. a drug which has no additional actions, has yet to be found.

Actions. Antihistamines (H_1-receptor) oppose all the effects of injected histamine except that on gastric secretion (H_2-receptor: see above). They also affect the central nervous system, usually to depress but sometimes to stimulate. They can occasionally make petit mal worse. They can be beneficial in Parkinsonism and motion sickness and this may be attributable to their anticholinergic effects. Some also have weak quinidine-like and local anæsthetic effects and modify responses to catecholamines.

Antihistamines are readily absorbed from the alimentary tract and are usually administered orally three or four times a day. They can also be

given i.m. or i.v. They are mostly metabolised in the liver, but **excretion** of enough in the milk to affect infants has been recorded.

Unwanted effects are common with antihistamines and can be very troublesome although persistence is worthwhile if a good therapeutic effect has been obtained, as tolerance to the side-effects sometimes develops. Some of the commonest effects are sedation, which is approximately proportional to antihistamine potency, dizziness, fatigue, insomnia, nervousness, tremors, gastro-intestinal disturbance and dry mouth. Dermatitis and agranulocytosis can occur. Severe poisoning due to overdose results in coma and sometimes in convulsions. If analeptics are needed they should be given cautiously because of the risk of causing convulsions. The administration of barbiturates for convulsions can lead to respiratory failure, but may be necessary. Hyperpyrexia can occur.

Uses. Histamine is released in many allergic states, but it is not the sole cause of symptoms. In urticaria histamine released in the epithelium has to diffuse to the blood vessels before producing its effects (extrinsic histamine effect) but in asthma the histamine is released in the bronchial muscle cells, *i.e.* at the site of action (intrinsic histamine effect). This may explain why antihistamines are effective therapy in urticaria but not in asthma, but it is probably a gross oversimplification.

Failure to respond is also due to the fact that active substances other than histamine are released in allergic states. In severe allergies adrenal steroids are very useful.

Acute urticaria (named after its similarity to the sting of a nettle, Urtica), and *angioneurotic œdema* usually respond well to antihistamines although severe cases are relieved more quickly by adrenaline (0·1 to 0·2 ml. Adrenaline, Inj., B.P., s.c.). Chronic urticaria responds less well.

Non-urticarial drug eruptions are not helped and may become worse.

Seasonal hay fever responds well, and nasal aerosols of vasoconstrictors, sodium cromoglycate or beclomethasone are also useful. Amphetamine, orally, may be needed to counter sedation in severe cases where relief can only be got with high doses. There may be a risk of drug dependence with such combinations. Any relief obtained from antihistamines in the *common cold* is due to a reduction of secretions and perhaps to control of any slight allergic element there may be in the response to infection. Reports that antihistamines aborted the common cold resulted from these effects, from failure to exclude patients with allergic rhinitis and from the therapeutic effect of suggestion. They provide a salutary lesson on observer bias, placebo-reactors, failure to appreciate that accurate diagnosis is an essential prelude to therapeutic experiment, and faulty presentation of results (*5*, *6*).

Perennial vasomotor rhinitis and non-urticarial rashes are less often helped.

Asthma responds poorly or not at all to antihistamines although the atropine-like effect on the bronchi may be useful. However, if tried, they should be stopped as soon as it is clear that they have provided no benefit

because it is known that they can increase bronchoconstriction, perhaps even by causing histamine release themselves (7).

Relief of *itching* is probably chiefly due to the sedative, or if applied locally, to the local anæsthetic effect. Prolonged local application is undesirable as the drugs are liable to cause allergic reactions. Antihistamines may be used prophylactically against serum or drug allergies on the rare occasions when these can be anticipated. They do not invariably give protection. They are useless against hæmolytic and pyrogenic reactions to blood transfusion.

They may be used systemically against *bee or wasp stings*, which both contain histamine and cause histamine release in the tissues, but are only worth giving to people who are known to react excessively. Administration needs to be very prompt to be useful.

Topical application is probably useless; indeed there are no indications for putting antihistamines on the skin where they are potent sensitisers.

The use of antihistamines as anti-emetics and in Parkinsonism is unrelated to their antihistamine activity.

DATA ON SOME ANTIHISTAMINES

Name (*Tablet size in mg.*)	*Oral dose* (*i.m. or i.v. dose*)	*Remarks*
mepyramine (Anthisan) (50)	100–200 mg. 3 or 4 times a day	A good general purpose drug.
diphenhydramine (Benadryl) (25, 50)	25–75 mg. 4 times a day (10–50 mg. i.m./i.v.)	Sedation and atropine-like effects marked. Also used in Parkinsonism and motion sickness.
promethazine HCl (Phenergan) (10, 25) promethazine theoclate (Avomine) (25)	25–75 mg. at night or twice a day (20–50 mg. i.m./i.v.)	A good general purpose drug. Acts for 20 hrs. Sedation marked. P. theoclate is especially used in motion sickness but is probably not superior to promethazine itself.
phenindamine (Thephorin) (25)	25–50 mg. 4 times a day	A good general purpose drug. More likely to cause cerebral stimulation than sedation. May be used in morning, after, say, promethazine at night.
chlorcyclizine (Histantin) (50)	50–200 mg. 2 or 3 times a day	Causes sedation.
dimenhydrinate (Dramamine) (50)	25–100 mg. up to 6 times a day (25–100 mg. i.m./i.v.)	Injection i.v. must be very slow. Chlorotheophyllinate of diphenhydramine. Sedation marked. Used in motion sickness, probably not superior to diphenhydramine.
chlorpheniramine (Piriton) (4)	4–16 mg. 3 or 4 times a day (10–20 mg. i.m./i.v.)	An alternative.

Preparations. The doses of some antihistamines are given in the table which includes more than any one physician will require. They are all about equally useful or useless, as the case may be. A generally satisfactory trio would be, promethazine, chlorcyclizine and phenindamine. When a useful therapeutic effect is marred by side-effects, usually drowsiness, it is worth trying other members, but any improvement may well be due to psychological factors. This was illustrated in a study where patients accustomed to chlorpheniramine developed symptoms when the colour of the capsule, but not its content, was changed (*12*).

Other available antihistamines include: cyclizine (Marzine), triprolidine (Actidil, Pro-Actidil), bromodiphenhydramine (Ambodryl), meclozine (Ancolan), pyrrobutamine (Co-pyronil), methdilazine (Dilosyn), diphenylpyraline* (Histryl), isothipendyl* (Nilergex), buclizine (Vibazine), tripelennamine (Pyribenzamine), antazoline (Antistin), dimethothiazine (Banistyl), deptropine (Brontina), brompheniramine (Dimotane), carbinoxamine (Extil), embramine (Mebryl), trimeprazine (Vallergan), cyproheptadine (Periactin), cinnarizine (Mitronal); they are mentioned solely for identification, there are others; most of them could be dispensed with, for, "there is such a thing as too many drugs" (W. Modell, 1961).

Guide to Further Reading

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* Even enthusiastic advocates of the exclusive use of non-proprietary names in prescribing must recognise that names such as these can never be widely used.

Chapter 23

VITAMIN K, ANTICOAGULANTS, FIBRINOLYSINS, HÆMOSTATICS, BLOOD-LIPID LOWERING AGENTS

ANTICOAGULANTS act on various components of the blood clotting mechanism, which may be simplified:

1. *Intrinsic system* (all factors in blood): damaged platelets + Anti-hæmophilic globulin + Christmas factor + Factor V + Factor VII + Ca'' → THROMBOPLASTIN

and at the same time,

Extrinsic system (requires non-blood, tissue/factor): damaged tissues + Factor V + Factor VII → THROMBOPLASTIN

2. *Then*, THROMBOPLASTIN + Ca'' + prothrombin → THROMBIN

Thrombin liberates more thromboplastin from the platelets and hence catalyses its own production.

3. *Then*, THROMBIN + fibrinogen → FIBRIN.

Vitamin K (*4*, *16*)

Vitamin K (fat-soluble) is necessary for the formation of prothrombin, factor VII and other clotting factors in the liver. It was discovered during feeding experiments on chicks in which it was found that deficiency of an ether-soluble substance caused a bleeding disease. At about the same time the bleeding tendency in obstructive jaundice was found to be due to prothrombin deficiency and that vitamin K was effective treatment. There are two naturally occurring vitamin K's. K_1 is widely distributed in plants and K_2 is synthesised in the alimentary tract by bacteria. Bile is required for vitamin K absorption. Metabolism and utilisation take place in the liver. Therefore vitamin K is less effective against hypoprothrombinæmia due to hepatic insufficiency. The response to vitamin K has been used as a liver function test in patients with prothrombin deficiency; failure of blood prothrombin to rise after administration indicates considerable liver damage. A bleeding tendency due to dietary vitamin K deficiency probably does not occur in man. However, **deficiency** may be due to:

1. Abnormal alimentary tract flora, e.g. in newborn infants and, rarely, after antimicrobials (e.g. sulphonamides, tetracyclines).

2. Bile failing to enter the intestine, e.g. obstructive jaundice: biliary fistula.

3. Certain malabsorption syndromes, e.g. sprue: after extensive small intestinal resections.

Vitamin K is a specific antagonist of the coumarin group of anticoagulants.

Vitamin K_1 (phytomenadione) (10 mg), the naturally occurring fat-soluble vitamin is the most rapidly effective vitamin K preparation, taking 3 to 5 hrs (sometimes longer) to act. A water-miscible solution (Konakion, Aquamephyton) is given by slow i.v. injection in emergency, otherwise i.m., s.c. or orally. If given orally in obstructive jaundice 2 g of bile salts should be given as well, or it will not be absorbed.

Dose. The parenteral dose in emergency for anticoagulant-induced prothrombin deficiency bleeding is 5–25 mg (rarely 50 mg) i.v.: if no emergency, 2·5–10 mg i.m. or s.c. or 10–20 mg orally. For oral use the range is 10–20 mg/day.

The synthetic vitamin K analogues are suitable for use on most occasions when a vitamin K effect is required, their main disadvantage is the longer time taken to act (24 hrs), and longer duration of action (several days).

Fat-soluble analogues are not absorbed from the intestine in the absence of bile, they include:

a. acetomenaphthone (5 mg) orally only, 5 to 20 mg daily.
b. menaphthone (menadione), 1 to 5 mg i.m., daily.

Water-soluble analogues can be given orally, s.c., i.m. or i.v., they include:

a. menadiol sodium diphosphate (Synkavit) (10 mg) 1 to 10 mg daily

Indications for vitamin K or its analogues are:

1. *Bleeding due to the coumarin or indandione anticoagulants.* Small doses given repeatedly, with simultaneous measurement of prothrombin times may be used in less urgent cases where anticoagulant therapy is to be continued. They avoid any risk of over-swing with thrombo-embolism which may exist if large doses are used.
2. *Hypoprothrombinæmia of the newborn and prematurity* (see below).
3. *Hypoprothrombinæmia in liver disease*, particularly for several days before and after surgery, but if liver-damage is substantial, vitamin K may not be synthesised to prothrombin.
4. *Hypoprothrombinæmia due to intestinal malabsorption syndromes.*
5. *Hypoprothrombinæmia due to antimicrobials, salicylates, phenylbutazone.*

Hypoprothrombinæmia of the newborn. The prothrombin level of newborn infants is low, and can be corrected by prophylactic administration of phytomenadione to the mother (5 to 10 mg) 4 to 24 hrs before delivery, or, for greater reliability, to the baby (0·5 to 1 mg, i.m. : 1 to 2 mg orally). A water-soluble analogue may be used instead.

Unwanted effects of vitamin K. Phytomenadione is not toxic in any reasonable dose, though the substances used to make the injection emulsion can cause local (i.m.) or systemic (i.v.) reactions.

Menaphthone and the water-soluble analogues cause hæmolysis in normals at high dose and in subjects deficient in erythrocyte glucose-6-phosphate dehydrogenase at low dose. Overdose of the newborn has caused hæmolysis, leading to hyperbilirubinæmia both because the liver of the newborn is offered a heavy bilirubin load and because the vitamin K analogue competes for the same conjugation path.

ANTICOAGULANTS

There are two sorts of anticoagulants:

1. *Direct acting*: **heparin, ancrod.** These are very rapidly effective, only act for a few hours and must be given parenterally. They are effective *in vitro* as well as *in vivo*.

2. *Indirect acting*: **coumarin and indandione group.** These take 16 to 72 hrs to become effective, act for several days, are given orally and can be antagonised, though comparatively slowly, by vitamin K. They are only effective *in vivo*.

The anticoagulants are compared in the table below.

Heparin

Heparin was discovered by a medical student* who, studying the clot-promoting activity of phosphatides, was surprised to find that a preparation from liver prolonged the clotting time. He investigated, and heparin was found. It is a mucopolysaccharide, occurs in mast cells and is prepared commercially from ox lung; it is standardised on animal blood. The sodium salt dissolved in physiological saline is used therapeutically.

Mode of action. Heparin is the strongest organic acid synthesised in the body and in solution carries a strong electronegative charge which is the cause of its interaction with basic proteins, i.e. the enzymes needed for clotting. In the presence of a plasma co-factor it is mainly active as an antithrombin and antithromboplastin, but it has been pointed out that the anticoagulant property of heparin is displayed on fresh whole blood rather than on any one particular part of the clotting system.

Heparin also reduces the lipæmia following a fatty meal by releasing an enzyme (lipoprotein lipase) that hydrolyses triglycerides to free fatty acids which pass into the tissues. It has been suggested, but is unproved that this action of heparin might influence atheroma and search is being made for heparin-like substances suitable for therapeutic trial.

Some believe that heparin is beneficial in arterial embolus, not only on account of its anticoagulant properties, but also by virtue of its slight vasodilator effect which may promote collateral circulation.

Although heparin has been found in the blood of dogs after anaphylactic shock and is released from mast cells by histamine liberators, it is not responsible for any of the bleeding diseases.

* J. McLean (1916). Johns Hopkins Medical School, U.S.A.

Dose. Heparin is ineffective by mouth. It is best given i.v. in a dose of 10,000–12,500 I.U. (100 mg = 10,000 I.U.). The maximum effect is *immediate* and rapidly wears off, little remaining after 6 hrs; the plasma half life is 50 min (low dose) to 150 min (high dose); it is partly excreted in the urine and partly destroyed in the liver. The injections should therefore be repeated at least 6-hrly; 4-hrly is the counsel of perfection. Injections given 8-hrly only provide intermittent effect. Injections i.m. and s.c. with and without hyaluronidase, and various depot preparations can be used and may give satisfactory delayed coagulation, but they are liable to cause painful hæmatomas. If long-term therapy is intended one of the coumarin group of drugs is started orally at the same time as the heparin. See also *interactions*.

Control of heparin therapy. The clotting time should be kept above 15 mins (normal 5 to 7 mins). The clotting time is the time required for blood to clot in glass and is easily measured at the bedside using capillary tubes. It should be measured before heparin therapy is started and at least once daily immediately before an injection is due.

Unwanted effects. Bleeding is the only serious complication of heparin therapy. It is not common, except after surgery. Transient alopecia and diarrhœa occur rarely: they are possibly due to interference with sulphonated mucopolysaccharide metabolism in the hair follicle and mucosa of the alimentary tract.

Heparin antagonists. Heparin effects wear off so rapidly that an antagonist is seldom required except after perfusion for open heart surgery. **Protamine,** a protein obtained from fish sperm, may be used to reverse the anticoagulant action of heparin. It is as strongly basic as heparin is acidic, which explains its antagonism to the heparin group of drugs. It is given by slow i.v. injection as protamine sulphate and neutralises an equal weight of heparin; but if the heparin was given above 30 mins previously, the dose must be scaled down by one half or more. Protamine itself has some anticoagulant effect and overdose must be avoided.

Ancrod (Arvin) is an enzyme preparation from the venom of the Malayan Pit Viper. Its anticoagulant effect is due to reduction of fibrinogen in the blood, probably by inducing microclots which quickly disappear (perhaps by the normal fibrinolytic system). This "controlled defibrination" by ancrod (i.v.) offers an alternative to heparin.

Coumarin and Indandione Anticoagulants

History. In the early 1920's, in North America, a new and mysterious cattle disease began to trouble farmers. There was hæmorrhage, often copious, which was sometimes spontaneous, but more often followed trauma; for example 21 out of 22 cows died after dehorning; 12 out of 25 young bulls died after castration. All had bled to death. Schofield, a veterinary pathologist who first described the disease, quotes a farmer who, "following the traditions of his elders, cut a slice of skin and cartilage from the ears of all his yearling cattle and then retired for the night. This

was to have had the mysterious effect of a blood tonic. The application of ligatures the following morning saved his cattle from immediate death, but due to a continuation of the feed they all succumbed" to hæmorrhage within a few weeks. It was found that bleeding only occurred in cattle which had eaten sweet clover, a new fodder crop.*

He observed that it was only mouldy sweet clover that was toxic and performed a simple experiment:

"Good clover stalks and damaged clover stalks were picked from the same hay mow. The good were fed to one rabbit and the damaged to another. The rabbit which ate the good remained well, while the rabbit which ate the bad died, showing typical (hæmorrhagic) lesions. This experiment was duplicated, using a different sample of clover hay. The results were the same.

This report, and the economic importance of the disease, led to a great deal of research, which after 20 years culminated in the isolation of the toxic agent, dicoumarol.

Coumarins are present in many plants and are important in the perfume industry; the smell of new mown hay and grass is due to a coumarin.

Coumarins: dicoumarol (bishydroxycoumarin): plasma $t_{\frac{1}{2}}$, 25–100 hrs.
warfarin (Marevan): plasma $t_{\frac{1}{2}}$, 44 hrs.
nicoumalone (acenocoumarin, Sinthrome): plasma $t_{\frac{1}{2}}$, 24 hrs.
phenoprocoumon (Marcoumar): plasma $t_{\frac{1}{2}}$, 150 hrs.
ethyl biscoumacetate (Tromexan): plasma $t_{\frac{1}{2}}$, 2 hrs.

Indandiones: phenindione (Dindevan): plasma $t_{\frac{1}{2}}$, 5 hrs.
anisindione (Miradon), diphenadione (Dipaxin).

Dicoumarol was identified in 1941 and soon became widely used in medicine. Its onset of action is slow but its effects are prolonged. Other drugs followed.

The principal differences between these drugs are pharmacokinetic rather than pharmacodynamic so they will be described together.

Mode of action. These compounds all prevent the formation of clotting factors, mainly factor VII and prothrombin (factor II), but also factors IX and X, from vitamin K in the liver.

Data on **two coumarins** are given in the table below. Their great **advantage** over heparin is that they can be given orally: their chief **disadvantage** is the time lag before they exert their effect due to their **indirect mode of action** in preventing replacement of normal body constituents.

Pharmacokinetics: the drugs are irregularly absorbed from the gut, are largely bound to plasma protein, and are partly metabolised in the liver. Clinically important interactions occur at each of these stages (see p. 23.7).

† SCHOFIELD, F. W. (1924). *J. Amer. vet. med. Ass.*, **64**, 553.

Management of oral anticoagulants. A loading dose is given and this is followed by maintenance doses which are eventually adjusted according to the results of prothrombin estimations.

The prothrombin level 40 hrs after the loading dose is important, as it generally coincides with the peak effect and the second dose will be large or small, given at once or delayed, accordingly.

There is greater individual variation in the duration of action of these drugs than there is in the time of onset of action, suggesting that individual rates of metabolism and excretion are the most important factors in determining dosage. Efficient laboratory control is vital. The clotting time, by methods practicable at the bedside, is unreliable for this purpose and Quick's one-stage "prothrombin time" is commonly used. It depends on the addition to citrated plasma of an excess of tissue thromboplastin and calcium ions and measurement of the time taken for it to clot. This procedure does not differentiate between a deficiency of factor VII or of prothrombin (factor II) but it is adequate for routine control of anticoagulant therapy. Results can be expressed in a confusing variety of ways (prothrombin time, ratio, index, concentration).

Satisfactory anticoagulant control is got with a *prothrombin time* (time for patient's blood to clot) of 2–3 times normal (normal about 12 sec), or a ratio of 1·8 to 3 (time taken for patient's blood to clot divided by time for control blood to clot). Owing to differences between reagents (particularly thromboplastin) and techniques, results are liable to vary within and between laboratories unless referred to a national standard thromboplastin.

The risk of bleeding is serious if the above limits are exceeded. Blood for prothrombin estimations should not be collected within 2 hrs of heparin administration, for it will not clot, and this estimation is not likely to be helpful until 16 hrs after starting oral therapy. Initially the prothrombin time should be measured daily or on alternate days until it is stable, when it may be checked about monthly.

Dosage note: because of the indirect mode of action and the long $t_{\frac{1}{2}}$, dosage should only be changed about every 5–7 days when a steady state may have been attained.

Unwanted effects. Bleeding is the commonest ill-effect and may occur at any site, but especially in the renal and alimentary tracts. In the latter a hæmatoma in the bowel wall can cause subacute obstruction. Subdural and intracerebral hæmatomas occur. Lumbar puncture or other needling procedure can cause substantial hæmatomas with local pressure symptoms. Patients with liver disease or vitamin K deficiency are exceptionally intolerant of these compounds.

Allergic effects (fever, blood, kidney) are more common with indandiones than with coumarins: the latter, e.g. warfarin, are preferred.

Withdrawal of oral anticoagulants. There is evidence that a higher incidence of thrombotic episodes occurs after withdrawal of anticoagulant therapy. The most likely explanation seems to be that this is a "catching-up"

SOME ANTICOAGULANTS COMPARED

Tablet size in mg →	*Heparin* —	*Dicoumarol* 100, 50 25	*Warfarin sodium* 1, 3, 5 10
Route of administration	i.v. (or i.m.)	oral	oral, i.v. or i.m.
Initial dose	50–150 mg 10,000–12,500 I.U.	600 mg	30–50 mg (50 mg i.v.)
Approx. maintenance dose	ditto 6–8 hrly	25–100 mg daily	3–10 mg daily
Onset of effect of single large dose	immediate	24 hrs	12–16 hrs
Peak of single large dose	immediate	40–72 hrs	32 hrs
Duration of effect	4–6 hrs	48–120 hrs	48–120 hrs
Antagonist	protamine	vitamin K_1	vitamin K_1

phenomenon, i.e. the patients now develop thromboses that they would have had earlier but for the anticoagulant therapy.

At one time it was thought that *sudden* withdrawal might be associated with a higher incidence of thromboembolism than gradual withdrawal due to a "rebound" hypercoagulable state. Withdrawal over several weeks was advocated. The prolonged effect of warfarin and dicoumarol (see table) means that sudden cessation of administration amounts to withdrawal of effect over several days. The balance of evidence is that sudden, as opposed to gradual, cessation of therapy does not add to the risk of thromboembolism.

Antagonists. Vitamin K_1, i.v., will reduce the prothrombin time to nearly normal in 3 to 5 hrs or, orally, in up to 12 hrs. If the larger doses are used anticoagulant effect with a coumarin drug (though not, of course, with heparin) will be impossible for up to 2 weeks. In the absence of bleeding an excessively long prothrombin times does not of itself demand treatment other than temporarily stopping the drug. Vitamin K analogues can be used if K_1 is not available, but they take longer to act.

Interactions (see chap. 6 for mechanisms).

Oral anticoagulant control requires to be precise for both safety and efficacy. Thus interference by other factors has only to be slight to have clinical importance. The effect of anticoagulants may be modified at several stages:

1. **Increase of anticoagulant effect.**

a. reduction of vit. K production by gut bacteria, e.g. with tetracycline therapy.

b. reduction of vit. K (fat-soluble) absorption, e.g. prolonged use of liquid paraffin.

c. increased level of free drug due to competition for plasma protein binding sites, e.g. chloral metabolite (trichloroethanol); antirheumatics, including aspirin; clofibrate; sulphonamides; probenecid, etc.

d. inhibition of enzymes that degrade warfarin by chloramphenicol or alcohol.

e. competition for same metabolic path, phenytoin, tolbutamide (both drugs are potentiated).

f. quinidine, clofibrate, thyroxine, anabolic steroids, phenformin potentiate drug either at receptor site or by altering other coagulation factors, e.g. fibrinolysis.

g. synergism of anticoagulant effect: aspirin, but not other salicylates, in high doses reduces prothrombin; paracetamol may have slight effect.

h. interference with platelet function: salicylates, phenylbutazone, chlorpromazine, diphenhydramine.

2. **Reduction of anticoagulant effect.**

a. binding of drug in gut (by cholestyramine).

b. increased hepatic metabolism of anticoagulant due to enzyme induction by hypnotics (but not most benzodiazepines, e.g. nitrazepam) antirheumatics, griseofulvin, etc.

c. increase in blood clotting factors due to oral contraceptives.

Conclusions: all concurrent drug therapy (including self-medication) must be carefully reviewed in patients taking anticoagulants.

Where unexpected fluctuation in anticoagulant control occurs, the possibility of a drug interaction should be considered.

Nitrazepam is the hypnotic of choice.

Aspirin should be avoided.

Choice of anticoagulant drug

For brief and immediate effect, heparin i.v. or i.m. (but ancrod may be tried).

For prolonged treatment (weeks or months) there is little to choose between the coumarins (warfarin, dicoumarol). Indandiones are more liable to cause allergic reactions.

Institution of anticoagulant therapy

From the above it is plain that anticoagulant therapy is ordinarily instituted by giving heparin i.v. plus an oral loading dose of, say, warfarin, followed by maintenance doses of both (see table).

The heparin provides immediate effect and is given 6 hrly until the oral agent takes effect in 24–40 hrs.

Details of control and long term use are given above.

Use of anticoagulants

(see also *fibrinolytic agents*)

Venous thromboembolism: anticoagulants are *useful in therapy and prophylaxis.*

Arterial thrombosis: anticoagulants are *less useful as therapy, and have only a limited place in prophylaxis.*

It is evident that there are important pathophysiological differences between venous and arterial thrombosis. This is because stasis is a major factor in the veins whereas it is not in the arteries. Arterial thrombus commonly has a local cause and platelets aggregate at the site (white thrombus) whereas venous clotting is predisposed to by slowing of blood flow (which is insignificant in arteries) and is formed by activation of the thromboplastin coagulation system (red thrombus).

Acute myocardial infarction. The majority of deaths from myocardial infarction occur within the first few hours and are due to arrhythmias and pump failure resulting from the initial episode and not to renewed arterial clotting that might be prevented by anticoagulant therapy. Benefits of therapy are probably the *prevention of venous thromboembolism* due to immobility, and sluggish venous circulation such as occurs in severe or "bad risk" patients (shock, arrhythmias, heart failure, intercurrent disease).

There is also evidence that younger patients (under 55 yrs) with a first infarct may benefit and some physicians would treat these too.

Duration of treatment is usually 2–4 weeks according to the patient's mobility.

Prevention of recurrence of myocardial infarction. The evidence suggests that in younger males (under 55 yrs) the two-year survival may be improved by about 7% (less in woman). It may be worth using an anticoagulant for one year (when most of the benefit is obtained) or two years in these males. In addition, some would use an anticoagulant indefinitely in patients who have had a recurrence within a few months.

Acute coronary insufficiency, where pain occurs at rest, but where it is uncertain that myocardial infarction has occurred, may perhaps benefit from indefinite anticoagulant prophylaxis.

Angina pectoris. There is now some evidence suggesting that myocardial infarction may be prevented by anticoagulants in patients with angina pectoris of less than 2 years duration, but it is not strong enough to advocate this as a routine.

Deep venous thrombosis or pulmonary embolism. Patients should receive at least 6 weeks anticoagulant therapy. Thromboembolism is an important cause of illness and death in injured and post-operative patients, especially those over 50 years old. This can be reliably prevented by anticoagulants, as has been shown in a study of 300 elderly patients with fractured hips (*9*). Of the half treated with phenindione there was no case of embolism whilst under treatment, and of the control half embolism occurred in 18% and fatal embolism in 10%. Clinical venous thrombosis occurred in 2·7% of treated cases and in 28·7% of controls.

It is clear that immobilised elderly patients benefit, as a group, from such prophylaxis, and this presents a social problem for, if the results of such trials lead to a decision that all should have anticoagulant prophylaxis, then expensive technical facilities must be provided.

A compromise at present might be that anyone considered to have any

special likelihood of developing thromboembolism should always have such prophylaxis if there are no contra-indications.

In general, prophylactic anticoagulant may be begun on the third day **after surgery,** for *embolism* is uncommon before this, and the increased risk of bleeding is substantial after many operations (see later). But *thrombosis* may begin immediately after surgery, and attempts to use low doses of heparin, starting before surgery to reduce the immediate post-surgical hypercoagulable state have shown some encouraging results. *Dextran 40* can also be used (to lower blood viscosity, to coat vessel walls and to reduce platelet adhesiveness) to prevent post-surgical venous thrombosis. It is given i.v. during and after surgery.

Anticoagulant therapy can be life-saving in *thrombo-embolic pulmonary hypertension.*

Retinal vein or artery thromboses are indications for an anticoagulant.

Arterial thrombosis and embolism (e.g. aorta, carotid). An anticoagulant may prevent the extension of the clot and possibly hasten recanalisation. Heparin has a reputation for being the drug of choice in arterial embolism. When an attempt is to be made to convert atrial fibrillation to normal rhythm anticoagulants may be indicated for they probably reduce both the likelihood of embolism and the damage that it causes. Recurrent embolism in cases of chronic atrial fibrillation also deserves anticoagulant therapy.

Cerebral vascular disease. There is inconclusive evidence that anticoagulant therapy is useful in recurrent *transient ischæmic attacks.* If it is used, it should last for at least one year. If, after slow withdrawal, another attack occurs, therapy should be resumed and continued indefinitely. Anticoagulants are dangerous (hæmorrhage) in established infarction, but these patients are immobile and are usually old, so that they are also liable to venous thrombosis and pulmonary embolism.

Surgery. In vascular surgery anticoagulants may be useful both during and after surgery. Heparin is commonly used, as its effects can be easily and quickly abolished. However the risk of bleeding is substantial in the first three postoperative days (see also above).

Long-term Anticoagulant Therapy

Long-term anticoagulant therapy may be desirable in any recurrent thrombotic or embolic disease where the likelihood of further episodes is considered to be substantial and serious. Its use in myocardial infarction is discussed above. Evidence is appearing that patients with any serious vascular insufficiency, e.g. angina pectoris, peripheral vascular insufficiency, live longer if given anticoagulant prophylaxis.

The decision to use long-term therapy in any one patient must take into account non-drug factors. Evidence of benefit has been obtained by physicians with a particular interest in the disease, who are both willing and able to provide what is probably an unusually high level of care.

Whether the marginal benefits will also be seen where the treatment is more of a dull routine and where laboratory control of therapy might fall below the highest standard, is uncertain. The admitted dangers (2% mortality in experienced hands) might then outweigh the possible benefits.

If adequate facilities for seeing the patient frequently and measuring his prothrombin time are not available, then long-term therapy should not be attempted. Stupidity or unconcern on the part of the patient (or the doctor) adds to the risks of therapy.

Another factor to be taken into account when deciding to use any long-term therapy that involves warnings of the risk (bleeding) and repeated blood examinations with dosage adjustment, is the emotional reactions of the patient to it.

It has been pointed out that patients who have suffered a life-threatening illness and are then placed on potentially hazardous therapy are prone to emotional disturbance. "A physician who undertakes anticoagulant therapy should recognise that he may be adding a psychological burden to a patient who has already suffered acute emotional stress from his basic disease" (*6*).

Patients should be stabilised on the chosen drug whilst ambulant in hospital and prothrombin should be measured weekly at first after leaving hospital. The patient must be told of the risk of hæmorrhage and of the signs of internal hæmorrhage into the alimentary or urinary tracts. When control has been good for some months the intervals between prothrombin estimations may be extended gradually even up to as long as 8 weeks. When therapy is well conducted the risk of hæmorrhage is about four times that in untreated patients.

Safety and good results are only obtainable by very close attention to detail. The dose may sometimes need repeated adjustment to maintain a steady effect, especially if the patient is alternately in bed and ambulant for substantial periods or has cardiac failure.

Contra-indications to Anticoagulant Therapy

These are mostly conditions in which there is a tendency to bleed (e.g. blood diseases, hæmorrhoids, ulcerative colitis, hepatic disease), and the contra-indication is relative rather than absolute, the dangers being balanced against the possible benefits.* Full doses of anticoagulant may be unwise immediately post-operatively (above), in the presence of active peptic ulceration, or severe indigestion, in severe renal disease (hæmaturia is more dangerous in previously damaged kidneys) and in the presence of any abnormality of vitamin K absorption or metabolism (e.g. in liver disease). Hypertension increases the risk of cerebral hæmorrhage. In bacterial endocarditis, embolism is not prevented and it may be accompanied by hæmorrhage, especially in the brain.

* This is sometimes described as taking a "calculated" risk, using the word to mean "deliberate", as in "calculated insult", and not meaning that the risk can be "reckoned by arithmetical processes", which it certainly cannot be.

Anticoagulants should be avoided, if possible, in the last three months of pregnancy as fetal death due to hæmorrhage may occur. Oral anticoagulants cross the placenta, but heparin does not significantly do so. Although the drugs are excreted in the milk, infants have been breast fed harmlessly. However, it might be prudent to give phytomenadione to the baby in the first few days of life whilst there is a physiological hypoprothrombinæmia.

Surgery in Patients Taking Anticoagulants

(see also *venous thrombosis*)

Capillary bleeding stops normally in the presence of coumarin anticoagulants if the prothrombin level is at the lower limit of therapeutic range, for immediate cessation depends on vessel retraction which gives extra time for the blood to clot. Therefore operations in which good control of larger vessels is assured may be safely performed if the prothrombin level is not unduly low. Neurosurgery and prostatectomy are particularly hazardous, and drainage tubes left in the body and "blind" needling procedures are liable to provoke bleeding by damaging small arteries.

For emergency surgery it has been proposed that the effect of prothrombinopenic drugs should be completely antagonised by vitamin K_1 20 to 50 mg i.v.). Oral therapy can be resumed 2 to 3 days later, depending on circumstances, though it may be blocked for up to 2 weeks. Heparin remains effective and may be used as necessary.

For elective surgery the anticoagulant may be withdrawn about 5 days before the operation and resumed about 3 days after if conditions seem appropriate. For dental extractions, omission of the drug for 1–2 days to adjust the prothrombin level to the lower limit of therapeutic range is adequate; it can be resumed the day after surgery.

Local and Systemic Hæmostatics and Hæmophilia

It is important to recognise that local measures for the arrest of bleeding must be such as do not interfere with healing, for until healing has occurred the risk of hæmorrhage persists. Bleeding in hæmophilia and Christmas disease can sometimes be stopped by pressure: edges of superficial wounds should be strapped, not stitched. Local applications, never injections, of thrombin or Russell's viper venom (Stypven) together with fibrin or gelatin are worth trying. Fresh blood or plasma transfusion in substantial amount restores the bleeding time even to normal for a few hours. In Christmas disease stored blood is effective and quite small amounts may suffice. Antihæmophilic globulin preparations are effective; cryoprecipitated human plasma provides a convenient source of anti-hæmophilic globulin ($t_{\frac{1}{2}}$ 12 hrs). Antiplasmins (which see) can be used to help clotting.

Many local hæmostatic preparations are available; most act by providing a network of fibres which promote coagulation. They are particularly effective on oozing surfaces, e.g. in tooth sockets.

Human or bovine thrombin is prepared as a powder; if a solution is required it must be freshly made; homologous serum hepatitis has been

transmitted by human thrombin. Thrombin is useful in hæmophilia and, together with fibrin, in neurosurgery and also when fixing skin grafts. It must never be injected.

Russell's viper venom (Stypven) acts as a strong thromboplastin. It can be useful in hæmophilia and must never be injected.

Fibrin foam is available as a dry mass of fibrils; it is usually used with thrombin. It is absorbed in the body.

Gelatin sponge, foam or film, is similar to fibrin, and is also absorbable. **Calcium alginate** is similar.

Oxidised cellulose (Oxycel) is not well absorbed; it is not used with thrombin on account of its acidity. It is suitable for surface hæmostasis, but should not be left on as a dressing as it interferes with repair of the epithelium.

Adrenaline or noradrenaline may be useful in epistaxis, stopping hæmorrhage by inducing local vasoconstriction when applied by packing the nostril with ribbon gauze soaked in Adrenaline Solution, B.P.

Antifibrinolysins (see *fibrinolysins* below).

Ethamsylate (Dicynene) and **naftazone** (Hæmostop) are claimed to reduce capillary bleeding when given systemically, e.g. in menorrhagia; the claims need confirmation.

Sclerosing Agents

A variety of chemicals is used to cause inflammation of and coagulation in varicose veins and bursæ so as to induce permanent obliteration. They include Ethanolamine Oleate Inj., B.P.C. (given i.v. for varicose veins) and Phenol Inj., Oily, B.P.C. (given submucously for hæmorrhoids). Local reactions and embolus can occur.

Citrate and Oxalate

Citrate prevents clotting by converting the calcium present to an unionised and therefore inactive form. Oxalate precipitates Ca but is too toxic for use in blood intended for transfusion. Sodium citrate (50 ml of a 4% solution to each pint of blood) is used routinely for this purpose. Massive transfusions may lead to citrate intoxication with cardiac depression and sometimes tetany, both due to reduction of ionised calcium. Calcium gluconate (10 ml of 10% solution) should be given i.v. for this.

FIBRINOLYTIC THERAPY AND ANTIFIBRINOLYTICS

For the preservation of an intact vascular system it is not only necessary that the blood should clot, but also that there should be a mechanism for removing blood clot when it has served its purpose of stopping a vascular leak, and repair of the blood vessel and its endothelial lining has occurred. The coagulation and fibrinolytic systems may be in a state of dynamic equilibrium (*27*).

The therapeutic potentialities of *fibrinolytic substances* are obvious. Anticoagulants may *prevent* thrombosis; fibrinolytics can *remove* formed thrombi and emboli. Any substance that dissolves clot or inactivates coagulation factors must also carry danger of hæmorrhage by preventing

clotting, so that close laboratory control of this sort of therapy is likely to be needed.

A detailed account of the fibrinolytic system will not be attempted here, for possibilities and techniques of therapy are still being explored and it should only be undertaken by people who make a special study of it.

The general approach is to infuse a *plasminogen activator*, e.g. *streptokinase* (Kabikinase) or *urokinase* (Actase, Thrombolysin). This converts plasminogen (an inert gamma globulin) in the blood into plasmin (fibrinolysin). Plasmin is a proteolytic enzyme (rather like trypsin), that dissolves fibrin and other proteins, including some coagulation factors (II, V, VIII). The infusion is given as near the clot or embolus as possible, for about 1 to 3 days. Angiograms are invaluable for determining just where the infusion should be placed. The principal risk is hæmorrhage, and an *antiplasmin* (antifibrinolytic), e.g. aminocaproic acid (Epsikapron) or tranexamic acid (Cyclokapron) should be kept at hand.

Obviously, therapy with fibrinolytics (streptokinase, urokinase) is likely to be most important in arterial occlusion by thrombosis or embolism and in those situations where tissue death distal to the block is slowest, giving time to institute therapy before permanent damage is done, and where the ideal site of infusion is anatomically accessible. The prospects are thus better for thrombosis or embolism in a limb rather than in the brain or heart.

Fibrinolytic therapy makes use of the normal body supply of plasminogen, and to prevent spontaneous thrombosis after therapy, heparin (initially) and a coumarin are given for 7 days to cover the period of restoration of plasminogen and physiological fibrinolytic function.

The *antiplasmins* (antifibrinolytics) (aminocaproic acid and tranexamic acid) can also be used in *hyperplasminæmic states* that occur due to disease, e.g. trauma, surgical or accidental, when tissues rich in plasminogen activator, e.g. lung, have been handled or damaged, or in some obstetric disorders (retained dead fetus, accidental hæmorrhage), menorrhagia or in hepatic cirrhosis. Attempts to use antiplasmins to encourage clotting in hæmophilia have shown some promise, particularly in dental extraction.

Aprotinin (Trasylol) is a polypeptide that is antifibrinolysin and also antitrypsin. Since release of trypsins into the blood may be responsible for death in acute pancreatitis, it is used for this. Obviously, controlled therapeutic trials in this serious disease are extremely difficult and the value of aprotinin remains uncertain.

Phenformin, orally, raises the level of natural plasminogen activator and is being studied in vascular occlusive disease; it is more effective when combined with the anabolic steroid ethylœstrenol.

Streptokinase-streptodornase mixtures (Varidase) are obtained by growing a special streptococcus in a special medium. They are used locally to liquefy clotted blood or pus, e.g. in empyemas and fistulæ. They do not dissolve living cells, but local inflammation is usual. They also cause fever, leucocytosis and anaphylaxis; albumin and casts may appear in the urine.

They should not be used if there has been recent hæmorrhage at the site of application.

Trypsin (Trypure-Novo) and **chymotrypsin** (Chymar) are pancreatic enzymes which have been used locally like streptokinase-streptodornase. They act on more proteins than the latter and also on mucin, so that they have been given by inhalation. Chymotrypsin is instilled locally to facilitate ocular cataract extraction. Given orally, both enzymes are probably useless for allaying inflammation, hæmatomas and bruising, though extensive claims are made. It is possible that oral chymotrypsin (Chymoral) may reduce sputum viscosity, though not in patients with abnormal mucus (mucoviscidosis). These enzymes can cause anaphylactic shock when given i.m.

BLOOD LIPID LOWERING AGENTS

These are used to prevent disease:

1. *Secondary prevention:* prophylaxis in hyperlipidæmic people who either have or have had clinical disease.

There is some evidence that reduction of hyperlipidæmia in patients with angina pectoris (before or after myocardial infarction) or with xanthomatosis, improves prognosis. This improvement has not been found after myocardial infarction alone.

2. *Primary prevention:* prophylaxis in hyperlipidæmic people who have no clinical disease. There is no conclusive evidence that drugs can prevent disease in these subjects.

Hyperlipidæmias differ in pattern according to whether cholesterol, triglyceride or lipoprotein is chiefly affected, and drugs should be chosen accordingly wherever possible. The distinction between the clinical varieties (there are five phenotypes) and therefore the choice of drug, is a specialised matter, and only a general outline is offered below. In the absence of detailed knowledge of the pattern of hyperlipidæmia, clofibrate is the drug of choice.

Clofibrate (Atromid-S) reduces plasma concentration of triglycerides, and to a lesser extent of lipoproteins and cholesterol. Its actions are complex; perhaps principally inhibition of hepatic lipid synthesis. Clofibrate is a relatively safe drug. It is largely bound to plasma protein and competes with oral anticoagulants (see interactions), and frusemide; adverse reactions (generally mild) are more frequent in nephrotic syndrome (low plasma albumin and so high free drug concentration).

Nicotinic acid reduces plasma lipoprotein, and perhaps cholesterol, synthesis. In the large doses needed it is liable to cause vasodilatation (flushing and hypotension).

D-thyroxine chiefly reduces plasma lipoprotein; it is chosen because it has less cardiac effect than L-thyroxine, but even so a β-adrenoceptor blocker is used with it to reduce tachycardia.

Neomycin reduces cholesterol absorption from the gut by disrupting

the intestinal micelles (polymolecular aggregates) necessary for its absorption. This action is unrelated to its antimicrobial effect.

Cholestyramine (which see) chiefly lowers plasma cholesterol and triglyceride.

Diet, ruthlessly applied, is effective in reducing hyperlipidæmia and reduction of obesity can have a substantial effect. But the patient may well rebel if the word gastronomy has any meaning for him, and drugs are likely to be needed.

Substitution of polyunsaturated fats (maize or corn oil, cottonseed oil) for saturated fats (butter, lard) can reduce cholesterol and triglyceride levels. Reduction of carbohydrate intake reduces triglyceride.

The spectacle of healthy young people, some of them doctors, who should know better, distorting their diets in the hope of living longer than their fellows, is unedifying, though males who are sufficiently determined may have less coronary heart disease (*34*).

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Chapter 24

PITUITARY AND SEX HORMONES : CONTRACEPTION : ERGOT : PROSTAGLANDINS

PITUITARY HORMONES

THOSE with application in medicine include:

ANTERIOR PITUITARY	POSTERIOR PITUITARY
1. growth hormone	1. vasopressin
2. gonadotrophic hormones	2. oxytocin
3. corticotrophin (see index)	
4. thyroid stimulating hormone (see index)	
5. prolactin	

Pituitary Growth Hormone (*1, 2, 11*)

Growth hormone preparations from animals have not been effective in treatment of human pituitary dwarfism. Hormone from human pituitaries is available (Crescormon) for use i.m. in accurately diagnosed cases of deficiency.

Gonadotrophic Hormones

Preparations are available from both animals and man. Animal preparations are unsatisfactory. Human chorionic gonadotrophin, obtained from the urine of pregnant women, can induce ovulation where ripe follicles are present and so can rectify some kinds of infertility. At other times follicle ripening must first be stimulated by follicle stimulating hormone (Humegon, Pergonal), obtained from post-mortem pituitaries or the urine of post-menopausal women, before giving the ovulation-dose of chorionic gonadotrophin. There is considerable risk of multiple pregnancy and of the hyperstimulation syndrome.

These preparations are useless in oligozoospermia.

The use of gonadotrophin in cryptorchidism is controversial, but is worth trying in boys aged 6 to 9 years provided the testis is not merely retracted and provided it is not ectopic and so incapable of descent without surgical help. The selection of suitable cases can be difficult. The reason why it is undesirable to wait until puberty before acting is that if the testis has not descended by then it may be too late to do anything to permit spermatogenesis to occur. Descent of the testis after chorionic gonadotrophin at age 6 to 9 years settles the point and failure to descend then means that surgery will be needed if the risk of a non-functioning testis is to be avoided. Some consider that testicular descent during or after such a course is purely coincidental.

Prolactin

Prolactin secretion is stimulated by phenothiazines, tricyclic antidepressants, reserpine and methyldopa; lactation may occur rarely.

Hypopituitarism

In hypopituitarism there is a deficiency of all the hormones secreted by the anterior lobe of the pituitary. The posterior lobe hormones may also be deficient in a few cases (e.g. when a tumour has destroyed the pituitary). Patients suffering from hypopituitarism may present in coma, in which case treatment is as for a severe acute adrenal insufficiency. Maintenance therapy is required, using adrenocortical and thyroid hormones. Sex hormones are not usually required, although androgens will help to establish a positive nitrogen balance in very wasted patients.

Posterior Pituitary Hormones (3-6, 11)

Pituitary (Post. Lobe) Inj. B.P.C. is an aqueous extract of the posterior lobe of animal glands. It contains antidiuretic and oxytocic hormones, both polypeptides. Since the different effects are never required at the same time, the extract has been replaced by separate preparations of the hormones, vasopressin and oxytocin. Synthetic forms are available; of oxytocin (Syntocinon) and of lysine-vasopressin, **lypressin** (Syntopressin); man secretes arginine-vasopressin. These synthetics are preferable, for natural preparations of each are always contaminated by some of the other.

Vasopressin (Pitressin) is the **antidiuretic hormone**. Its official name is most unfortunate, for only in high doses does it affect the vascular system and its chief use is to provide renal antidiuresis.

Vasopressin (antidiuretic hormone) increases permeability and so water reabsorption in the distal tubule. In its absence free water (i.e. water without electrolyte) excretion is increased.

Secretion of the antidiuretic hormone is stimulated by any increase in the osmotic pressure of the blood supplying the hypothalamus and by a variety of drugs, notably nicotine. Secretion is inhibited by a fall in blood osmotic pressure and by alcohol.

In large "unphysiological" or "pharmacological" doses vasopressin causes contraction of all smooth muscle, raising the blood pressure and causing intestinal colic. The smooth-muscle-stimulant effect provides an example of tachyphylaxis (frequently repeated doses give progressively less effect). It is not only inefficient when used to raise the blood pressure, but is also dangerous, since it causes constriction of the coronary arteries and sudden death has occurred following its use.

Uses. Vasopressin is used as replacement therapy in hypothalamic or pituitary **diabetes insipidus;** it is also used **to reduce portal venous pressure** in cases of hepatic cirrhosis with bleeding œsophageal varices (see below).

In **diabetes insipidus** a nasal spray of lypressin is the most convenient therapy (it is digested if swallowed). Dosage and frequency of administration (generally 3- to 5-hrly) are adjusted by the patient according to results. To begin with, it is convenient to use the spray whenever the bladder is emptied, it is then adjusted to individual needs. There is also a natural vasopressin snuff. Excessive use of these preparations can cause ulceration of the nasal mucosa due to extreme vasoconstriction, and allergic alveolitis. Vasopressin Tannate Inj., B.N.F. is a suspension in oil (shake the ampoule) that, given s.c. or i.m., lasts for 1 to 3 days. The initial dose is 2·5 I.U. It may be supplemented by the nasal spray. Longer acting vasopressins can be made, e.g. DDA vasopressin.

Vasopressin is effective in pituitary diabetes insipidus but, not surprisingly, ineffective in the nephrogenic form.

Aqueous solutions of vasopressin, when injected, act for a variable but brief time. They can be used in diagnosis of diabetes insipidus, and in the treatment of **bleeding œsophageal varices.** Vasopressin lowers portal venous pressure by constricting the splanchnic arterioles and so increasing the resistance to blood flow. Thus, the amount of blood entering the portal venous system is reduced, despite the concurrently induced rise in systemic arterial pressure due to generalised arteriolar constriction. It is hoped that during the period of reduced portal venous pressure (about 45 mins following 20 I.U., i.v. over 10 mins), a clot will form at the bleeding point. This is a dangerous treatment for a dangerous disease. It is contra-indicated if there is a history of angina pectoris or evidence of myocardial ischæmia. During it, the patient will become pale, arterial pressure will rise and abdominal colic and defæcation may occur.

Other drugs in diabetes insipidus. Thiazide diuretics (and other potent diuretics) have an antidiuretic effect in diabetes insipidus. That this is not due to Na depletion is suggested by the fact that the non-diuretic thiazide, diazoxide (which see) also has this effect. It is probable that changes in the proximal renal tubule result in increased reabsorption and in delivery of less Na and water to the distal tubule, but the mechanism remains incompletely elucidated.

Thiazides benefit some cases of the *nephrogenic* form which is not helped by vasopressin, and plainly this is their chief indication.

Chlorpropamide: in 1966 a patient with diabetes insipidus, wrongly believing himself to suffer from diabetes mellitus, "at his own discretion" took chlorpropamide*. His physician was suprised at the apparent therapeutic effect and tried the drug on other patients, confirming it.

Chlorpropamide is effective in pituitary diabetes insipidus and is ineffective in the nephrogenic form. It may act by potentiating the action of vasopressin. Some diabetics taking it develop hyponatraemia. Other sulphonylureas are ineffective. The biguanide, metformin, may also be effective, as may carbamazepine and clofibrate. None of these are drugs of first choice.

*ARDUINO, F. *et al.* (1966). *J. Clin. Endocrinol.* **26**, 1325.

Since vasopressin snuff can be unpleasant (rhinitis; cardiovascular and intestinal effects on smooth muscle) these drugs provide alternative or adjuvant therapy, though their other effects must be taken into account before prescribing them.

Oxytocin stimulates the contractions of the pregnant uterus, which becomes much more sensitive to it at term. The mechanisms governing the initiation of labour remain uncertain but oxytocin may play a part. However, patients with diabetes insipidus go into labour normally.

Oxytocin is reflexly released from the pituitary following suckling and causes contraction of the myo-epithelium of the breast; it has been used to discharge milk from engorged post-partum breasts. The only other clinically important effect is on the blood pressure, which may fall if an overdose is given.

Synthetic oxytocin (Syntocinon) is pure and is not contaminated with vasopressin as is the natural product. It is therefore safer if high doses must be given.

Oxytocin is now increasingly used in the **induction of labour,** and sometimes for uterine inertia, hæmorrhage or during abortion. It produces rhythmic contractions with relaxation between, i.e. it mimics normal uterine activity.

The decision to use it requires special knowledge of obstetrics. Oxytocin is ordinarily given by i.v. infusion. The buccal route is practicable, but dosage is less controllable due to irregular absorption and uterine rupture can occur.

Oxytocin has been supplanted by ergometrine in the treatment of post-partum hæmorrhage except when, as occasionally happens, there is no response to ergometrine. There are advantages in a mixture of oxytocin and ergometrine (Syntometrine, which see).

SEX HORMONES

Androgens

Testosterone is the natural androgen secreted by the interstitial cells of the testis; it is necessary for normal spermatogenesis, for the development of the male secondary sex characteristics, and for the growth, at puberty, of the sexual apparatus. It is probably converted by hydroxylation to the active dihydrotestosterone.

Protein anabolism is increased by androgens, that is, androgens increase the proportion of protein laid down as tissue, especially muscle. Growth of bone is promoted, but the rate of closure of the epiphyses is also hastened.

Indications for Androgen Therapy

Testicular failure may be primary, or secondary (due to lack of pituitary gonadotrophins). In either case replacement with androgens is often necessary. Unfortunately, sterility is seldom remedied, although

loss of libido and of secondary sex characteristics can be greatly improved. Impotence is helped unless, as is often the case, it is due to psychological causes. If androgens are given to a boy with delayed puberty a growth spurt and sexual development will occur. Such treatment is not usually indicated until the age of 16 years since up to that age natural delay in pituitary secretion may be responsible and normal development may yet occur. In **hepatic cirrhosis** degradation of œstrogens may be impaired, leading to raised blood levels of œstrogen with feminisation. Androgens may help such patients and also stop the **itching** of jaundice, but methyltestosterone should not be used as it can cause jaundice. Relatively small amounts of androgens can be used to increase the **formation of new tissue,** e.g. in osteoporosis (see below). The **œstrogen-dependent bony metastases** from carcinoma of the breast in premenopausal patients are sometimes made smaller and less painful by very large doses of androgens which will always cause marked masculinisation, and the patient may be helped by large doses of an adrenal steroid, especially if there is hypercalcæmia. Androgens may also help in **fibrocystic disease** of the breast and in some cases of **anæmia** due to bone marrow failure.

Preparations of Androgens

Testosterone is not given orally because, although well absorbed from the intestine, it is inactivated by the liver before reaching the systemic circulation. Pellets may be implanted s.c. at approximately 6-monthly intervals. **Methyltestosterone** (5, 10 mg) is given as sublingual tablets, 20 to 50 mg a day in divided doses, or about twice that dose if swallowed. **Testosterone propionate** is given i.m., 25 to 50 mg 2 or 3 times a week. **Testosterone œnanthate** is given i.m., 250 mg every 2 or 3 weeks which makes it more convenient than the propionate. **Fluoxymesterone** (5 mg) is active when swallowed (5 to 15 mg a day) and may be preferable to testosterone implants. There are various preparations. **Mesterolone** is a weak oral androgen.

Choice of androgen. For oral use fluoxymesterone, and by injection testosterone œnanthate, make a satisfactory pair for routine use.

Unwanted effects are mainly those to be expected of a male sex hormone, increased libido may lead to undesirable sexual activity, especially in mentally unstable patients, and virilisation is obviously undesired by most women. Androgens have a weak *salt and water retaining activity* which is not often clinically important. *Jaundice* can occur with methyltestosterone. It is dose-related and is not an allergy. In patients with malignant disease of bone, e.g. metastases from breast carcinoma, androgen administration may be followed by a rise in blood calcium sufficient to produce symptoms. The cause is uncertain. The less virilising androgens are used to promote anabolism and are discussed below.

Antiandrogens. Plainly œstrogens and progestagens are partial pharmacological antagonists to androgens. But compounds with selective antiandrogenic effect are being developed, and may find use in socially

disabling male hypersexuality and in disease characterised by androgen excess, acne, prostatic hypertrophy, etc.

Androgens used as protein anabolic agents

Androgens are effective protein anabolic agents, but their clinical use for this purpose is limited by the amount of virilisation that women* will tolerate. Partially successful attempts have been made to produce compounds with the desired anabolic action but without the other effects. These compounds can be used instead of the ordinary androgens in the treatment of **osteoporosis.** They can also prevent the calcium and nitrogen loss in the urine that occurs in patients bedridden for a long time and they have therefore been recommended in the treatment of some severe fractures. **Growth** in hypogonadal children is at first stimulated and the anabolic steroids may be worth using in some cases of dwarfism, but only if bone age is well below chronological age and corresponds with height age; methandienone (Dianabol) will serve. The chief risk of overdose is premature epiphyseal fusion, but this may be avoided by careful intermittent use.

Brief use in **acute renal failure** to reduce catabolism is rational and may yet prove to be effective in reducing the need for hæmodialysis.

The use of anabolic steriods in conditions of **general wasting** is justifiable in extreme cases, such as severe ulcerative colitis, and in the later stages of malignant disease they may make the patient feel and look less wretched. Their general use as tonics is scandalous as is their use in sport (which see).

The **itching of jaundice** may be relieved and these drugs are perhaps preferable to testosterone for the purpose. There is, however, a risk of increasing the degree of jaundice.

Attempts have been made to use anabolic steroids to counter the unwanted catabolic effects of adrenocortical hormones when the latter are used over long periods, but without notable success.

None of these substances can be assumed to be quite free from virilising properties in high doses; acne and greasy skin may be the early manifestation of virilisation. Salt and water retention may occur. Liver damage can occur, but it is usually mild and reversible. If used in carcinoma of the breast with bone metastases there may be hypercalcæmia, as with testosterone.

Œstrogens have only modest anabolic effect.

Administration should generally be intermittent in courses of 3 to 12 weeks with similar intervals, to reduce the occurrence of unwanted effects.

There is little to choose between the various available drugs clinically, and some are very expensive. One member should be chosen and used. An androgen (fluoxymesterone) will serve for men, and one of the following less virilising androgens for women: methandienone (Dianabol);

*In *adult* males androgens can be used as they do not cause hypermasculinisation.

nandrolone (Durabolin) orally, or Nandrolone Inj. B.N.F., once a week. Other members include methylandrostenediol (Stenediol); ethylestrenol (Orabolin); stanozolol (Stromba); stanolone (Anabolex); oxymetholone (Adroyd, Anapolon); norethandrolone (Nilevar); drostanolone (Masteril), etc.

Osteoporosis

Apart from treatment of the cause, androgens or œstrogens are given according to whether there are clinical suggestions of a lack of one or the other.

Some patients do better on a combination of androgen and œstrogen than on either given alone. It should be recalled that, when substantial œstrogen dosage is used in women administration should be cyclical, about 4 weeks on and one week off; there is likely to be withdrawal-bleeding, which some postmenopausal women find gratifying, but others objectionable. This can also worry gynæcologists because of the possibility of there being an underlying cancer.

In addition, fluoride, phosphate, vit D and calcium are used. Results are uncertain and choice of therapy is a matter for specialists.

Œstrogens

Œstrone and œstradiol are both natural œstrogens secreted by the ovary. Œstrogens are responsible for the normal development of the female genital tract, of the breast and of the female secondary sex characteristics. The pubertal growth spurt is less marked in females than in males, probably because œstrogens have very much less protein anabolic effect than do androgens, although they are as effective in promoting closure of epiphyses. Blood œstrogen levels must be above a critical level for the maintenance of both proliferative and (together with progesterone) secretory phases of the uterine endothelium. If the œstrogen level falls too low then the endothelium can no longer be maintained and uterine bleeding follows. Thus uterine bleeding may be stopped temporarily by giving large doses of œstrogens, or may start when they are withdrawn (œstrogen-withdrawal bleeding). Bleeding may occur despite a high blood œstrogen level if large doses are given for a long time, due to infarctions in the greatly hypertrophied endometrium. Œstrogens are necessary for the maintenance of normal pregnancy and for the accompanying breast hyperplasia. The vagina is more sensitive to œstrogens than is the endometrium.

Preparations of Œstrogens

Innumerable œstrogen preparations are available, but the following selection should cover all needs. The dose varies greatly according to whether replacement of physiological deficiencies is being carried out (replacement therapy) or whether œstrogens are being used as drugs to obtain certain effects by pharmacological force (pharmacotherapy). The

potency of œstrogens can be measured in women by a method using the occurrence of withdrawal-bleeding as an end point.

Œstradiol is a potent natural œstrogen. It is usually given i.m., 1 mg, 2 or 3 times a week (1 mg stilbœstrol = 0·5 mg. œstradiol monobenzoate). Œstradiol valerate is long-acting, 10 mg i.m. every 3 to 4 weeks generally being adequate.

Œstrone sulphate is probably the principal ingredient of the mixture of equine œstrogens, Premarin. Its advantage is that it has fewer toxic effects than other orally-active œstrogens. (1 mg stilbœstrol = 0·4 mg Premarin.)

Ethinylœstradiol (0·01, 0·02, 0·05 mg) is a potent orally-active semi-synthetic œstrogen. In equipotent doses it may not be less toxic than stilbœstrol although the contrary is claimed. (1 mg ethinylœstradiol = 25 mg stilbœstrol.)

Stilbœstrol (0·1, 0·5, 1, 5 mg) was the first synthetic œstrogen made and it is still most generally useful for efficacy and low price. However, if more than 1 mg a day is given, it is liable to cause nausea, vomiting and other abdominal disturbances, and headache.

Quinestradol (Pentovis) has very low activity and may be no more selective for the vagina than low doses of other œstrogens.

Other synthetic œstrogens. Hexœstrol and dienœstrol are not less toxic than stilbœstrol in equipotent doses (1 mg stilbœstrol = 4 mg dienœstrol = 20 mg hexœstrol). Other œstrogens are chlorotrianisene (TACE) and methallenœstril (Vallestril), mestranol (Ovastol).

Choice of œstrogen. Stilbœstrol remains a useful drug, and only expensive œstrone sulphate (Premarin) has been shown to be less toxic. However, individual patients may be intolerant of any one agent, when it is worth trying the others.

Indications for Œstrogen Therapy

Replacement therapy: in hypo-ovarian conditions. 1 to 1·5 mg stilbœstrol may be given orally, daily, for 20 days and repeated after a 10-day interval, or, if withdrawal bleeding occurs, on the fifth day of the cycle. Unless the cause of the hypo-ovarian state is primary ovarian failure, treatment should be stopped after every third cycle to see if spontaneous menstruation will occur.

For climacteric symptoms severe enough to demand treatment there are three rules that should be followed:

1. The minimal effective dose should be given.
2. Treatment must be in interrupted courses and not continuous.
3. Treatment should be stopped as soon as possible.

The aim is to allow the body gradually to accustom itself to the natural decline of œstrogens. Use of high doses will prevent this.

Stilbœstrol, 0·2 mg orally, daily, may be tried first for 4 weeks (ethinyl-œstradiol is an alternative). If menstruation is still occurring the œstrogen administration should be integrated with the periods and stopped when bleeding begins, as otherwise the bleeding may become prolonged. The

dose may be halved after 4 weeks and then gradually withdrawn. The patients' symptoms are the guide. Higher doses than the above may be needed but it is seldom necessary to give as much as 1 mg stilbœstrol/day (or equivalent); with this dose uterine bleeding may be expected.

Treatment may have to last anything from a few months to a few years.

For patients who fail to respond to the above regimen, who relapse repeatedly or have withdrawal-bleeds at low doses, œstrogen-androgen mixtures may be tried (e.g. Mepilin, Mixogen, and there are many others), according to the above time schedule, but unwelcome facial hair may appear.

Lifelong post-menopausal œstrogen replacement is advocated by some, but substantial evidence of its benefit versus risk must be obtained before it would be justifiable to consider recommending post-menopausal women to take an œstrogen for the rest of their lives.

Pharmacotherapy: Menstrual Disorders (see below).
Contraception (see below).

Vaginitis. Senile vaginitis usually responds to daily insertion of a stilbœstrol pessary (0·1 to 0·5 mg). Œstrogen ointment can be used in small girls with vaginitis.

Suppression of lactation. It is said that œstrogens prevent the engorgement and pain in a breast in which inhibition of lactation is occurring due to absence of suckling. They do not themselves actually suppress lactation, which will occur despite them if suckling is allowed. The œstrogen must therefore be given *early* after delivery.

Minimum doses should be used to reduce the risk of œstrogen-induced venous thromboembolism.

A usual technique is to give stilbœstrol thus:

5 mg	orally	three	times	daily	for	two	days
,,	,,	twice	,,	,,	,,	,,	,,
,,	,,	once		,,	,,	,,	,,
1 mg	,,	three	,,	,,	,,	,,	,,
,,	,,	twice		,,	,,	,,	,,
,,	,,	once		,,	,,	,,	,,

Equivalent doses of other œstrogens may be used.

This sometimes fails and a single injection of hexsestrol or of a long-acting œstrogen-androgen mixture (e.g. Primodian-Depôt) immediately after labour is claimed to give satisfactory results in most cases, but it has not yet undergone the stringent test of years of routine use that has been the lot of stilbœstrol.

An ergot derivative, bromo-ergocryptine, can suppress lactation by inhibiting pituitary secretion of prolactin.

Hormone-dependent carcinoma. High doses of œstrogens are used in prostatic carcinoma, which is an androgen-dependent neoplasm. Stilbœstrol, 10 to 15 mg a day, or more, reducing to 5 mg a day or even

less can be used. If the patient is intolerant other œstrogens can be tried. Feminisation is inevitable and the gynæcomastia is often painful.

Inoperable breast carcinoma in post-menopausal women may also sometimes be favourably influenced temporarily by œstrogens and by an adrenal steroid.

Post-menopausal osteoporosis may respond to œstrogen therapy.

To reduce sexual urge in men whose activities are qualitatively or quantitatively unacceptable to the community is an occasional indication for œstrogens. 1 to 2 mg stilbœstrol daily should be enough.

Blood lipid reduction can sometimes be achieved by œstrogens at sub-feminising doses in men, on the, at present, rare occasions when there is a definite indication to attempt it, but prolonged use causes uterine hæmorrhage in women.

Epistaxis: as a last resort in recurrent cases, e.g. telangiectasia.*

Atrophic rhinitis may benefit, as also may **peptic ulcer** and **acne.**

Unwanted effects consist chiefly in an excess of feminisation. Withdrawal-bleeding is common, but seldom prolonged. In men reduced libido, impotence and gynæcomastia which may be painful, occur, and there is sometimes salt and water retention with œdema. Both sexes may develop **thromboembolism.**

Oral administration is liable to cause nausea, vomiting and diarrhœa.

Œstrogens are known to be carcinogenic in certain experimental situations. But this does not mean that they are carcinogenic in clinical situations. A disturbing, though inconclusive, finding has been that mothers of girls with vaginal adenocarcinoma (aged 15-22 yrs) had been treated with high doses of œstrogens during pregnancy (8).

Antiœstrogens. Androgens are partial pharmacological antagonists to œstrogens. But compounds with selective antiœstrogenic effect are available, e.g. tamoxifen (Novaldex). They may be useful in œstrogen-dependent cancer and they might be contraceptives because œstrogen is required for implantation of the ovum. Some substances have both agonist and antagonist effect.

Progesterone and Progestagens

Progesterone is produced by the corpus luteum and converts the uterine epithelium from the proliferative to the secretory phase. It is thus necessary for implantation of the ovum, and is essential throughout pregnancy, in the last two-thirds of which it is secreted in large amounts by the placenta.

The production of powerful synthetic progestagens and knowledge of the amounts secreted in the body has led to the realisation that inadequate doses of progesterone have often been used in the past. The decision when to use progestagens is a skilled one, and therapeutic effects are uncertain. A detailed account of what can be attempted is beyond the scope of this book.

* BLACKBURN, E. K. (1963) *Brit. med. J.* **2**, 159.

The clinical uses of progestational agents are ill-defined; apart from *contraception* (which see), the principal indication is *threatened and habitual abortion.* There is, however, no proof that they are beneficial, although they probably are in cases of *true* progesterone insufficiency. Vigorous progestagen therapy during pregnancy occasionally virilises female fetuses seriously. This is probably least with hydroxyprogesterone caproate (Primolut Depôt) and with Enavid.

Other uses have included *menstrual disorders*, the *premenstrual syndrome*, *endometriosis*, and *dysmenorrhœa.*

The following **progestagen preparations** are available: progesterone given i.m. in an oily solution, as microcrystals or as pellets implanted i.m.: alternatively, ethisterone (Progestoral), allylestrenol (Gestanin), dimethisterone (Secrosteron), norethisterone (Primolut-N, Norlutin A), dydrogesterone (Duphaston), medroxyprogesterone (Provera) may be used orally. Hydroxyprogesterone caproate (Primolut-depôt), gestronal (Depostat), medroxyprogesterone acetate (Depo-Provera) can be given i.m. Megestrol, norethynodrel, ethynodiol and chlormadinone are used in oral contraception.

Antiprogestagens have been made. They may be effective as contraceptives.

Drugs and the Control of Conception

This subject will only be treated here in general terms. Any physician intending to prescribe oral contraceptives will need more extensive knowledge, at least of the preparation he intends to use.

The requirements of a successful oral contraceptive are stringent, for it will be used by millions of healthy people. It must therefore be extremely safe as well as highly efficient and its action must be quickly and completely reversible, even after years of continuous use. The fact that alternative methods are less reliable implies that their use will lead to more unwanted pregnancies with their attendant inconvenience, morbidity and mortality.

Possible sites of action include (20):

1. *direct inhibition of spermatogenesis*—this presents many problems including the lag in onset of effect due to storage of mature spermatozoa until they are ejaculated or die of old age.

2. *direct inhibition of spermatogenesis by suppression of pituitary activity*, which controls it, e.g. by œstrogens which also reduce male sexual drive, which is inacceptable to all men and to most women. Testosterone also inhibits spermatogenesis without impairing libido.

3. *immunological techniques*, to inactivate pituitary gonadotrophins, are theoretically possible, but no success has yet been achieved.

4. *inhibition of ovulation* presents a different problem. There is no need to suppress formation of the gametes, as in the male, but only to prevent their release from the ovary.

Either the pituitary gonadotrophin (luteinising hormone) may be inhibited, or the ovary may be made unresponsive to it.

5. *prevention of fertilisation*: no general progress has been made here, though the female genital tract may be made inhospitable to spermatozoa, e.g. by altering cervical mucus.

6. *antizygotic drugs*: compounds effective in the rat have been developed.

7. *inhibition of implantation*: implantation does not occur unless the endometrium is in the right state, and this depends on a delicate balance between œstrogen and progesterone. This balance can readily be disturbed.

Mice fail to become pregnant if, after mating, they are exposed to the smell of alien males (via a chemical communicator or pheromone). This approach does not yet seem to have been explored in man and "it would be rash indeed to suppose that a contraceptive perfume is on the way" (20).

Drugs used for oral contraception:

1. œstrogen+progestagen (combined administration)
2. œstrogen+progestagen (sequential administration)
3. progestagen alone:

Mode of action of currently used œstrogen-progestagen oral contraceptives. Oral contraceptives have been extensively used since 1956. The principal mechanism is inhibition of ovulation (4, above) by action on the hypothalamus inhibiting the release of substances that cause the pituitary to release gonadotrophins. In addition the endometrium is altered, so that implantation is less likely (7, above) and cervical mucus may become more viscous and impede the passage of the spermatozoa (5, above).

Œstrogens can inhibit ovulation, but they are not completely reliable.

Progestagens can inhibit ovulation but their principal contraceptive effect is on cervical mucus. There is liable to be break-through bleeding. They are less reliable than the mixture.

An appropriate dose of **œstrogen+progestagen** gives complete reliability with good menstrual cycle control.

The combination is started on the 5th day after the start of menstruation and continued for 20 days. Withdrawal bleeding usually begins 1 to 4 days later. It is begun again on the 5th day from the start of this, and so on. An alternative regimen is to take a tablet daily for 21 days and to commence again after an interval of 7 days, regardless of menstruation, i.e. to take a daily tablet 3 weeks out of 4. But packaging of numbered tablets (active and dummy) so that the woman takes a tablet each day without intermission may be best.

Another alternative technique, œstrogen for 15–21 days, accompanied by progestagen for the last 5–10 days of the 21-day course, the **sequential** method, is slightly less effective than the combined tablet but may give fewer side-effects in some patients.

Numerous field trials have shown that progestagen-œstrogen mixtures, if taken as directed, are the most reliable reversible contraceptives known.

(The only close competitors are the plastic intra-uterine mechanical devices.) Protection by œstrogen-progestagen mixture is not reliable until the second cycle in women with exceptionally short cycles.

Naturally the highest standards of acceptability to the patient, safety and recovery of function must be applied to such substances and a few of the more important aspects are discussed below (30–39).

Subsequent fertility. So far, the evidence points to a resumption of normal pituitary-ovarian function, with normal fertility, within two cycles of stopping the drug in almost all cases. But amenorrhœa of variable duration may occur. Permanent damage to fertility is rare.

Effect on an existing pregnancy. Although progestagens can masculinise the female fetus, e.g. when used in the hope of preventing habitual abortion, the doses for contraception are lower and the risk of harming an undiagnosed pregnancy is negligible.

Carcinogenesis. The possibility of genital cancer has been raised, but is without valid theoretical foundation, and is unsupported by present clinical experience. There remains the uncertainty of what will happen with longer experience. Data on breast tumours are reassuring (48).

Effect on menstruation is generally to regularise it, and often to diminish blood loss, but amenorrhœa can occur. In some women "break-through" intermenstrual bleeding occurs, especially at the outset, but this seldom persists for more than a few cycles. Recurrent "break-through" bleeding demands proper gynæcological investigation, as does its occurrence after months of trouble-free use.

Libido is not generally directly affected, but removal of fear of pregnancy may permit enthusiasm for the first time. But loss of libido can occur.

Drug metabolising capacity may be impaired by oral contraceptives, e.g. the $t\frac{1}{2}$ of phenazone (antipyrine) is increased by 30% (47) and this may apply to many other drugs.

Venous thromboembolism is probably about four times as frequent in women taking œstrogen-progestagen preparations as in those not taking them. The effect is due to the œstrogen. There has been considerable controversy over this matter, and increased risk is denied by some. But the balance of evidence is that there is risk. In addition there is the supporting evidence that œstrogen-containing contraceptives cause an increase in some blood coagulation factors. Arterial thrombosis is a much rarer disease and evidence is correspondingly harder to get, but the pattern may be the same.

Progestagen-only contraceptives do not cause thromboembolism but are less reliable.

Surgery in patients taking œstrogen-progestagen contraceptives: because of the added post-surgical risk of venous thrombœmbolism these oral contraceptives should be withdrawn if practicable, four weeks before surgery.

Decreased glucose tolerance occurs, perhaps due to a peripheral effect reducing the action of insulin.

Hepatic function as measured by bromsulphthalein retention may be impaired and cholestatic jaundice can occur.

Plasma lipoproteins may rise.

Plasma proteins: œstrogens cause an increase in proteins, particularly globulins that bind hydrocortisone, thyroxine and iron. As a result, the total plasma concentration of the bound substances is increased, though the concentration of free and active substance remains normal. This can be misleading in diagnostic tests. This effect on plasma proteins passes off about 6 weeks after cessation of the œstrogen.

Other unwanted effects, often most prominent at the outset and largely due to œstrogen include, nausea and, rarely, vomiting; breast discomfort; fluid retention; depression; headache; lethargy; abdominal discomfort; vaginal discharge; cervical erosion. A syndrome of lethargy and general "bitchiness" after about a year has been recognised, though causal attribution of this common phenomenon is naturally difficult.

Hypertension: there is a small but significantly measurable rise in systolic pressure. Rarely, a larger and pathologically important increase in both systolic and diastolic pressure occurs. The blood pressure usually returns to normal on stopping treatment, but may rise again if it is later resumed.

Contraindications: carcinoma of the breast or of the genital tract, past or present, is regarded as an absolute contraindication. In patients with a history of liver disease, they should only be used if liver function tests are normal. Diabetes may become more difficult to control or may be precipitated. Lactation may be reduced by mixtures but not by progestagens alone. Migraine, hypertension and facial nerve palsy may be associated with predisposition to cerebral vascular complications.

Duration of use. Whilst the effects of individual use for 20 years or more are unknown (see above), the most obvious problem at present is in women approaching the menopause. Because cyclic bleeding will continue to occur under the influence of the drugs even after the natural menopause, the only way of deciding whether contraception can be permanently abandoned is by abandoning it (and using another technique) for three months annually to see if natural menstruation is resumed.

Choice of oral contraceptive. There are no differences between the progestagen-œstrogen combinations sufficiently great or consistent to justify definite recommendations.

The principal progestagens used are norethynodrel, megestrol, lynestrenol and norethisterone and the principal œstrogens are mestranol and ethinyl-œstradiol. Available oral contraceptive mixtures include: Anovlar, Gynovlar, Norlestrin, Demulen, Minilyn, Noralen, Orlest, Ovanon, Ovulen, Conovid, Conovid-E, Volidan, Ortho-Novin and Lyndiol.

The above preparations require daily administration. The development of infrequent medication, say once a month, would be convenient. This can be achieved with i.m. slow-release formulations and choice will depend on circumstances. Quinestrol (an œstrogen), taken orally, is stored in body fat and is slowly released. It can be combined with quingestanol (a progestagen) which has similar pharmacokinetic properties, and once-a-month oral preparations are feasible.

Post-coital contraception. The probability of conception from one unprotected coitus is 1 in 25 to 1 in 50. It would obviously be a great convenience if an effective drug to be taken only after coitus were available. At present it is envisaged that an agent for routine use would be more likely to be taken at a particular time of the menstrual cycle to prevent implantation than to be taken after each act of coitus.

But œstrogens in large doses are effective postcoital agents in primates (they may disrupt ovum transport or implantation) and there is some evidence in women (from rape and volunteer cases) that oral stilbœstrol (50 mg/day) or ethinylœstradiol (5 mg/day) for 5 days is effective if begun within 48 hrs of coitus (40). But this dose can be unpleasant (vomiting) and is unsuitable for routine use (40).

Risk of oral contraception. Whether a drug should be prescribed involves an assessment of benefit to the patient versus risk to the patient. Even where there is a defined disease the decision can be difficult. It is even more so where the subject is healthy as is the case with most contraception. Reliable data on nature and incidence of adverse reactions is essential but all too often is not available.

It has been pointed out (32) that a woman having regular sexual intercourse faces a finite chance of death from pregnancy, childbirth or from measures to avoid or interrupt pregnancy. The general problem cannot be discussed here as it goes beyond the use of drugs.

But it is worth pointing out that, as well as the risks of unwanted pregnancy, the risks of oral contraceptives should be viewed in the context of the risks of everyday life, which are substantial.

The death rate from oral contraceptives is probably about the same magnitude as deaths from cricket and football (in Britain) and much less than those from swimming (1,000/annum in Britain). A car driver may expect, on average, to be admitted to hospital once in 20 yrs due to a road accident. A woman would have to use oral contraceptives for 2,000 yrs for a similar chance due to a thrombotic episode. It has been calculated that there is ten times the likelihood of a death in a family which has acquired an outboard motor boat than if an oral contraceptive is being used (32).

Any danger oral contraceptives may have for the individual must also be seen in relation to their benefits to the community (fewer self-induced and criminal abortions, fewer unwanted children, slowing down of the speed of increase of world population with less hunger and misery, etc.). Their merits will continue to be debated and new technical advances will

undoubtedly occur, probably concentrating on methods for use by women.

Vaginal preparations, to immobilise or kill spermatozoa, are used to add safety to various mechanical contraceptives. They are very unreliable and should only be used alone in an emergency.

Male contraception. Substances that depress spermatogenesis or maturation of sperms in the epididymis are known. Male contraception implies interference with the development of the reproductive cell itself, which is not the case with female contraception. Thus the risk of genetic damage (mutagenesis) to the sperm may be intrinsic to male contraception. This, as well as the ready availability of female contraception and the fact that males do not get pregnant, reduces the incentives to seek for contraceptives for the male.

Induction of Ovulation

Ovulation may be induced by gonadotrophins, by the antiœstrogen clomiphene and by cyclofenil. Multiple pregnancies are liable to occur and the treatment of infertility by these agents is a matter for specialists.

Menstrual Disorders

Only a note on the simpler uses of hormones in menstrual disorders is appropriate here.

A course for **secondary amenorrhœa or oligomenorrhœa** (after full diagnostic investigation) may consist of 1·5 to 2 mg stilbœstrol a day, orally, for 20 days. Cessation is followed by bleeding, and the œstrogen is begun again on the fifth day from the start of this.

For prolonged and irregular menstruation a 20-day course of an oral progestagen e.g. norethisterone (5 mg) 10 to 15 mg daily, beginning immediately, if the patient is in the middle of a bleeding episode, otherwise on the fifth day of the cycle, can be used.

If break-through bleeding occurs the progestagen should be stopped and started again 5 days later. Increased dosage may be needed. In some cases it is best to combine with the progestagen a dose of œstrogen, and then one of the oral contraceptives will serve.

Sometimes there are pressing social reasons for preventing menstruation at the normal time, but obviously this cannot be done if too short notice is given.

Menstruation can be postponed by giving norethisterone 10 mg orally, a day, from the 20th day of the cycle for up to 20 days; bleeding occurs on withdrawal. If started after the 20th day, then success becomes progressively less likely.

Menstruation can be advanced by giving a progestagen-œstrogen combination such as an oral contraceptive, for 14 days, when withdrawal will bring on bleeding. The shorter the time the mixture is given, the less likely becomes success.

Although there is no evidence that harm follows such manœuvres, it is obviously foolish to practise them too often.

Dysmenorrhœa is usual, in the absence of complicating disease, only in cycles in which ovulation occurs. Suppression of ovulation may prevent the pain and can be accomplished by an oral contraceptive (progestagen-œstrogen mixture).

Dydrogesterone (Duphaston) (5 mg), 5 to 20 mg a day total orally from cycle day 5 for 20 days will prevent dysmenorrhœa in 60 to 70% of cases without inhibiting ovulation.

Hormone treatment should be used only in severe cases. Non-narcotic analgesics, coupled with a suitable psychotherapeutic approach are usually sufficient.

The premenstrual syndrome may respond to:

1. Restriction of salt and fluid and a thiazide diuretic in the second half of the menstrual cycle.

2. Administration of a progestagen in the second half of the cycle, e.g. norethisterone 10 to 15 mg a day, orally may serve.

ERGOT (25–27, 43, 44)

"He gently prevails on his patient to try
The magic effects of the ergot of rye."
(attributed to Alfred, Lord Tennyson, 1809–1892)

Ergot is a fungus which preys on grasses, especially rye. For medical production the plant is artificially infected.

The history of ergot is infamous, for consumption of bread made from infected rye has cause epidemics of painful gangrene of the extremeties due to its vascular effects. The disease was called St. Anthony's Fire because sufferers obtained relief by visiting the saint's shrine, either because they had left the area where contaminated grain was being used or by supernatural intervention. Fits and mental disorder were also a feature of these epidemics, but it is not known whether these were partly due to concurrent nutritional deficiencies.

Ergotism is now very rare but an epidemic was reported in England in 1928* and in France in 1951†, although the genuineness of both these has been questioned.

The discovery of the chief alkaloids of ergot (ergotamine, ergotoxine, and ergometrine or ergonovine), all derivatives of lysergic acid, presents an interesting chapter in the history of both pharmacology and therapeutics. At the beginning of this century pharmacologists investigated ergot and found ergotamine, a principal alkaloid, ergotoxine, later found to be a mixture of three alkaloids, and histamine, acetylcholine and tyramine, amongst other things. Ergometrine was found in 1935.

Before 1935 some clinicians maintained that the uterine effect of ergot extracts was not all accounted for by the known constituents, and their

* Robertson, J., and Ashby, H. T. (1928). *Brit. med. J.*, **1**, 302.
† Gabbai *et al.* (1951). *Brit. med. J.*, **2**, 650 and editorial, *ibid.*, 596.

view was supported by the fact that the then current Pharmacopœial method of preparing the extracts effectively removed the known orally active substances. In 1932, a newly formed Pharmacopœial Committee decided that it was time that they either stopped the elimination of the active principles or else found out what unknown substance was rendering the extracts active, if indeed they were active. The Committee invited Dr. Chassar Moir to investigate the subject for them.

The hospital pharmacist prepared an extract according to Pharmacopœial regulations, i.e. it should, according to current knowledge, have been inert. He administered it to parturient patients and recorded the results with a balloon in the uterus attached to a manometer. "It was with the greatest surprise I found that, far from being inert, this preparation surpassed by great measure the activity of any drug which I had previously used in the same manner." He also observed that the rate of onset and type of contractions differed from those characteristic of ergotoxine and ergotamine. Moir could only suppose that the effects he observed were due to an entirely new constituent of ergot and that those "ergot alkaloids hitherto supposed to be all-important play in reality but subsidiary part in the clinical activity of the drug." Sir Henry Dale, whose early work on the analysis of the constituents of ergot is a pharmacological classic (43), commented on Moir's discovery. He wrote that another chapter had been opened "and probably one of great importance, in the already complicated story of ergot and its active principles. . . . Those acquainted with the present position, and its development during a quarter of a century, may be inclined to regard Dr. Moir's observations as a rebuke to the presumption of laboratory pharmacologists. They do, indeed, emphasise the danger of basing therapeutic conclusions on laboratory data, without direct clinical evidence. It is only fair to state, however, that the present position has arisen, not in spite of such evidence as Dr. Moir now supplied, but for lack of it. The need has been recognised and urged by some of us throughout the period in question; but, without such direct experimental guidance from the clinic, we could only search for the principles in ergot producing certain well-defined effects in the laboratory, and hope for the proper clinical trial of the substances so identified. . . . I have, indeed, on more than one occasion endeavoured to get a proper experimental comparison made in the clinic . . . . More than one eminent gynæcologist was willing to carry out a test; but only by handing the extracts to a resident officer or ward sister, with an instruction to administer them to alternate patients as a routine and to record impressions of their respective values. It can safely be stated that, so far from affording data for a quantitative comparison, such a method would not even give trustworthy information as to whether either extract was active at all." X . . . and Y . . . in the case of an extract of ergot "were content to show that the ward sister could not distinguish its action from that of a 'Marmite' solution, when both were given to alternate patients in the puerperium. The inference was that the liquid extract had no action, but Dr. Moir's experimental records show it

to contain what may well prove to be the most important substance in ergot from the point of view of practical therapeutics." This prediction was correct, for the substance was ergometrine.

Fortunately Moir's paper was published in a journal which has a correspondence column so that the subsequent clash of opinion between clinician and pharmacologist could take place in public.*

The Actions of Ergot

Ergotoxine is obsolete in therapeutics and so only ergotamine and ergometrine and some derivatives will be considered here. Their principal **uses** are, to stimulate the uterus and in migraine. They have the following actions:

Uterine effect. Ergometrine (ergonovine) is now the only ergot alkaloid used for stimulating uterine activity, as ergotamine is slow in acting even after i.v. injection, whereas ergometrine acts immediately when injected i.v. It is also relatively free from serious circulatory side-effects. The uterus is stimulated at all times, but is much more sensitive in late pregnancy.

Ergometrine and oxytocin differ in their actions on the uterus. In moderate doses oxytocin produces slow generalised contractions with full relaxation in between and ergometrine produces faster contractions superimposed on a tonic contraction. High doses of both substances produce sustained tonic contraction. It will be seen, therefore, that oxytocin is more suited to induction of labour and ergometrine to the prevention of post-partum hæmorrhage, the incidence of which is reduced by its routine use. An injection of ergometrine (0·3 to 0·5 mg) acts on the uterus for at least 3 hrs. It may be given i.m., with or without hyaluronidase, or i.v.

Since ergometrine is used to stop post-partum hæmorrhage the speed of onset of action is important. Given i.v. it acts at once, but in Britain a midwife may not give an i.v. injection, so that it is often given i.m., when it acts in 7 minutes. This is a long time to wait if a woman is bleeding, and hyaluronidase may be added to hasten absorption, when the ergometrine will act in 4 to 5 mins. But oxytocin given i.m. acts in 2 to 3 mins, though only briefly. It has therefore been mixed with ergometrine (Syntometrine: ergometrine 0·5 mg oxytocin 5 I.U.) to obtain the advantages of quick onset of action and prolonged effect.

When given during labour the timing of the injection is the subject of disagreement. It is commonly given when the anterior shoulder of the child is delivered, but some give it earlier at the crowning of the head (never before this) or later when the placenta has separated or has been delivered. Ergometrine tablets may be given orally (0·5 to 1 mg) twice a day in the early puerperium if bleeding occurs, or in incomplete abortion.

The occurrence of **hypertension,** lasting hours or even days after ergometrine has been belatedly recognised. The incidence of this effect may be less with methylergometrine (Methergin). It seems that in some

* Moir, C. (1932). *Brit. med. J.*, **1**, 1119, 1189, and **2**, 75.

patients the ergometrine is capable of inducing vascular effects of a magnitude similar to those of ergotamine. It is most likely to occur in toxæmic patients* and in cases where sympathomimetic vasoconstrictors have been used, e.g. with a local anæsthetic. It can be severe and complaints of headache post-partum should be taken seriously. The blood pressure can be reduced by chlorpromazine (10 to 15 mg) i.v. or i.m. and then larger doses orally, or by any other α-adrenoceptor blocking drug.

Vascular smooth muscle stimulation is the most prominent effect of ergotamine. Spasm of the arterioles occurs, with hypertension and reduced peripheral blood flow. The duration of action of a single dose may exceed 24 hrs so that if the drug is being given several times a day for, say, migraine there is a short-term cumulation which can be dangerous. Stimulation of other smooth muscle occurs but is of little clinical importance.

α-Adrenoceptor blocking effect, which is antagonistic to the vasoconstrictor effect mentioned above. It is negligible with ergometrine and moderate with ergotamine, although insufficient to prevent severe vasospasm. This action is increased by hydrogenation, which also reduces oxytocic and vasoconstrictor activity.

Hydrogenated alkaloids of ergotoxine are available (Hydergine, a mixture of dihydroergo-cryptine, -cristine and -cornine). Hydergine is given sublingually, 0·5 to 5 mg daily, in divided doses; or 0·3 to 1 mg, s.c., or i.m. It is occasionally used as a peripheral vasodilator but may be effective in some cases of migraine despite this.

Central nervous system effects are ill understood. There is a general depressant effect which includes the respiratory and vasomotor centres. Hypotension may occur. The vomiting centre is stimulated, probably via the nearby trigger zone. Cardiovascular reflexes are inhibited and this is perhaps more important as a cause of postural hypotension than is the α-adrenoceptor blocking effect.

Metabolism occurs in the liver.

Toxicity. Nausea and vomiting are prominent and often limit the use of ergot derivatives. Peripheral gangrene has frequently been reported from the excessive use of ergotamine in migraine, especially in cases of hepatic disease. This alkaloid is also dangerous in patients with obliterative vascular disease. Gangrene may not be entirely due to vasoconstriction but also to concurrent damage to the lining of small vessels with resulting thrombosis, as thrombophlebitis unrelated to the site of administration sometimes occurs after ergotamine. Angina pectoris may occur. The blood pressure may rise or fall. Patients complain of coldness and paræsthesiæ, weakness and muscular pain. Confusional states, depression, convulsions, hemiplegia and other neurological syndromes have been recorded following overdose.

* Synthetic oxytocin (Syntocin) is preferable in such patients.

Prostaglandins

Prostaglandins (which are modified hydroxyacids derived from prostanoic acid) were discovered in seminal plasma in the 1930s.

It was assumed that they derived from the prostate gland and so they were named prostaglandins. It was later discovered that they derived more from the seminal vesicles than from the prostate and that they are present in most, if not all, tissues including CNS, adrenals, liver, kidney, and gut.

Prostaglandins may be both humoural and neurotransmitters and mediators of inflammation. Some anti-inflammatory analgesics, e.g. aspirin, may act by reducing prostaglandin synthesis.

Prostaglandins have many actions that differ according to the particular prostaglandin used and to the physiological state of the organ. According to circumstance they can cause smooth muscle (vascular, uterine, bronchial) to contract or to relax.

There are at least 14 naturally occurring prostaglandins. They are named in a complex fashion dictated by their chemical structure. There are six "primary" natural prostaglandins (PGE_1, PGE_2, PGE_3, $PGF_{1\alpha}$, $PGF_{2\alpha}$, $PGF_{3\alpha}$) and eight other natural prostaglandins derived metabolically from them.

Prostaglandins can be synthesized.

Their use in medicine is being explored and, Karim* summarizes the present situation:

1. induction of abortion (i.v., intrauterine, vaginal routes): though effective orally, the high dose needed to stimulate the uterus in early pregnancy causes vomiting and diarrhœa. To avoid this they may be combined with oxytocin.

2. induction of labour (oral, i.v.): here prostaglandins must be shown equal to oxytocin before they can be accepted as safe.

3. contraception (intravaginal): by dislodging the fertilised ovum from the uterus by inducing vigorous contractions.

4. the function of prostaglandins in blood vessel and bronchial muscle and gastric secretion control are being explored.

Use of drugs and morality. Increasingly, drug use is providing moral as well as technical problems and this is particularly so in the field of reproduction (contraception and abortion).

Some doctors regard such uses as impermissible under any circumstances, as permissible under certain circumstances or as morally indifferent. In any case it is desirable that they should be *technically* informed if they are in any form of practice that may result in their meeting patients who may be taking or seeking such treatment.

Since pharmacological considerations are not fundamental to the moral decisions in this field the matter will not be discussed here.

* KARIM, S. M. M. (1971). *Brit. J. Hosp. Med.* p. 555.

Uterine Relaxants

β-adrenoceptor stimulants relax the uterus and have been used to inhibit premature labour (e.g. isoxsuprine, orciprenaline, ritodrine). Their benefits are uncertain and their use is complicated by the expected cardiovascular effects.

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Chapter 25

THYROID HORMONES AND ANTITHYROID DRUGS

THYROID HORMONES

L-thyroxine (L-tetra-iodothyronine, T_4) **liothyronine** (L-tri-iodothyronine, T_3) and dried thyroid are all iodine-containing compounds effective as replacement agents in the treatment of hypothyrodism (cretinism or myxœdema).

Thyroid hormone is stored in the gland as thyroglobulin from which thyroxine and liothyronine are released by enzymatic hydrolysis. For convenience, the term thyroid hormone is used to cover both liothyronine and L-thyroxine. It is probable that some of the L-thyroxine is converted into liothyronine in body tissues.

Pharmacokinetics: L-thyroxine (T_4) circulates in the blood 99·9% protein bound (chiefly to thyroxine-binding globulin). T_3 is less bound. For diagnostic purposes the thyroid hormone (T_4, T_3) in the blood is measured as protein-bound iodine (PBI) which has been found to parallel changes in the 0·1% of free and active hormone in the blood. This measurement gives satisfactory results except where there are changes in the amount of plasma protein or the patient has been taking iodine in any form. In these cases the PBI may vary though the free hormone level (controlled by the pituitary) remains normal. Diagnostic confusion results.

Thyroxine-binding plasma proteins are *increased* in pregnancy, with œstrogens (including doses in oral contraceptives), with clofibrate and with prolonged use of phenothiazine neuroleptics. The proteins are *decreased* in hypoproteinæmia (nephrotic syndrome, malnutrition), and with large doses of adrenocortical steroid or androgen (including anabolic steroids).

Phenytoin and salicylates compete for plasma protein binding sites and so lower the PBI concentration.

Administration of iodine-containing substances increases the PBI: clioquinol (Entero-Vioform) commonly causes difficulty in thyroid diagnosis for 3 months after a course: iodine-containing radiocontrast media may raise protein-bound iodine for days (intravenous pyelogram) or for years (bronchogram, myelogram). There are numerous iodide-containing cough mixtures on general sale to the public.

As an alternative to the PBI, plasma T_4 can be measured by displacement analysis. This is unaffected by iodine compounds but obviously the results will be modified by changes in carrier protein.

Plasma half-life ($t_{\frac{1}{2}}$) of thyroxine (T_4) is 7 days in normals (longer in hypothyroidism and shorter in hyperthyroidism): that of triiodothyronine

(T_3) is about 2 days. Thus, although it is convenient to administer thyroxine daily, it is not necessary to do so and the intervals between doses could be longer. Although there is less T_3 than T_4 in plasma, T_3 is more potent ($\times$ 5), and they may contribute about equally to biological effect.

The mode of action of thyroid hormone (T_4, T_3) is not precisely known. In its absence the synthesis of many intracellular enzymes is depressed. Thyroid hormone is necessary for growth, and all cells need it if they are to function properly.

Thyrotrophin-releasing hormone (TRH) is a tripeptide, formed in the hypothalamus (and controlled by free plasma T_4, T_3 concentration). It has been synthesised and can be used in diagnosis to test the capacity of the pituitary to release thyroid-stimulating hormone (TSH), e.g. to determine whether hypothyroidism is due to primary thyroid gland failure or is secondary to pituitary disease or to a hypothalamic lesion.

Thyroid stimulating hormone (TSH) **thyrotrophin,** a glycoprotein of the anterior pituitary controls the release of thyroid hormone and also the uptake of iodide by the thyroid gland. TSH secretion is inhibited (via the hypothalamus and TRH) by a high level of thyroid hormone in the blood and stimulated by a low level; thus there is a "feed-back" mechanism of control.

TSH is sometimes **used** in the differentiation of myxœdema due to thyroid disease from that due to hypopituitarism. The radioiodine uptake by the thyroid is measured after i.m. injection of TSH (Thytropar). If the myxœdema is due to primary thyroid disease there will be no change, but if the pituitary is responsible then the radioiodine uptake will increase except in some long-standing cases. TSH is also used to detect milder cases of hypothyroidism in which, though basal radioiodine uptake is normal, it fails to increase after an injection of TSH. Measurement of the patient's own TSH in the blood can, of course, give the required information, and this can be done by radio-immunoassay.

Antithyroid drugs, by reducing thyroid hormone production, cause increased formation of TSH, which is the cause of the thyroid enlargement that sometimes occurs during antithyroid drug therapy.

Long-acting thyroid stimulator (LATS) is probably a thyroid autoantibody that, curiously, has thyroid-stimulating effect. It may play a part in causing some cases of hyperthyrodism (it is not present in all cases) and in exophthalmos.

Eye signs of hyperthyroidism (lid retraction, lid lag, etc) are doubtfully due to thyroid hormone increasing catecholamine sensitivity. They are sometimes treatable by withdrawing sympathetic drive with an adrenergic-neurone blocking drug.

Exophthalmos. The cause is unknown. Antithyroid drugs do not help. TSH secretion is not responsible for exophthalmos (it is high in primary thyroid gland failure in which exophthalmos does not occur). There may be a special pituitary secretion that causes exophthalmos, and it has been named, needless to say, EPS or "exophthalmos-producing substance".

High systemic doses of an adrenocortical steroid may help, but in urgent cases surgery is necessary, i.e. orbital decompression.

The main indication for thyroid hormone is treatment of deficiency (cretinism, myxœdema). The adult requirement of hormone is remarkably constant, and dosage does not have to be altered once the optimum is found. Children naturally need more as they grow.

Early treatment of cretinous babies is important if permanent mental defect is to be avoided. It must be life-long.

Hypothyroidism due to panhypopituitarism requires replacement with adrenocortical as well as with thyroid hormones.

Small doses of thyroid in normal subjects merely depress TSH production and consequently reduce the output of thyroid hormone by an equivalent amount. Thus, L-thyroxine may be effective in reducing puberty goitre, which is presumably due to excess TSH. It is also effective in Hashimoto's disease and in goitre due to inborn thyroid enzyme defect or to iodine deficiency or to other drugs with incidental antithyroid effect (see end of chapter).

Thyroxine should never be used to treat simple obesity; if enough is given to "burn up" the excess fat, then other symptoms of hyperthyroidism are inevitable and appetite is stimulated; also it may lead to dependence on thyroid.

Preparations and dosage of thyroid hormones

Thyroid Tabs. B.P. are a preparation of the dried gland of ox, pig or sheep. Their potency varies because irrelevant standardisation procedures have been used. They are obsolete.

Thyroxine Tabs. B.P., (0·05, 0·1 mg) contain pure L-thyroxine sodium and should be used **to treat hypothyroidism.**

The initial oral dose may be 0·1 mg daily, but in the old and patients with heart disease or hypertension, this should be achieved gradually, starting with 0·05 mg daily for the first 2 to 4 weeks, and then 0·1 mg. The dose is then increased by 0·05 to 0·1 mg every fortnight until symptoms are relieved, usually at 0·2 mg daily. This is usually sufficient to reduce plasma TSH to normal levels. Patients who appear to need more are probably not taking their tablets consistently. The maximum effect of a dose is not reached for about 10 days and passes off over about 2 to 3 weeks. A cretinous baby should be given 0·025 mg daily at first and the dose increased by 0·025 mg fortnightly. The optimum dose is just below that which causes diarrhœa.

Tablets containing supposedly physiological mixtures of *thyroxine* and *liothyronine* are available but offer no advantage. Some exogenous thyroxine (T_4) is converted to liothyronine (T_3) in the body.

Hypothroid patients may be intolerant of drugs due to delayed metabolism. Digoxin plasma concentration is higher in hypothyroid patients after a standard dose than it is in normals.

D-thyroxine sodium, see blood lipid lowering agents.

Liothyronine Tabs. B.P. (5, 20, 25, micrograms). Liothyronine is the most rapidly effective thyroid hormone, a single dose giving maximum effect within 24 hours and passing off over about a week. Its main uses are in **myxœdema coma and psychosis,** both rare conditions. It is not used in routine treatment of hypothyroidism because the fast action can induce heart failure, but in the above conditions, particularly in coma where death is inevitable in the absence of treatment, the risk must be taken; L-thyroxine is too slow. The dose in myxœdema coma is up to 100 mcg, 12-hrly, according to the state of the patient. Hydrocortisone should be given in addition, because there is evidence that adrenocortical function is depressed in prolonged hypothyroidism.

Liothyronine is also useful in the diagnosis of doubtful cases of hyperthyroidism. In normals or in patients with non-toxic goitres, radioiodine uptake is suppressed by 120 mcg daily for 7 days, but this has no effect on uptake in hyperthyroid patients.

Unwanted effects of thyroid hormone parallel the increase in basal metabolic rate. The symptoms and signs are those of hyperthyroidism, minus exophthalmos. Angina pectoris or heart failure are liable to be provoked by too vigorous therapy; should they occur thyroxine must be discontinued for at least a week and begun again at lower dosage. Only slight overdose is needed to precipitate atrial fibrillation in patients over 60 years.

ANTITHYROID DRUGS AND RADIOIODINE

Drugs used for the treatment of hyperthyroidism include:

1. **Iodide,** an excess of which reduces the production of thyroid hormone *temporarily* by an unknown mechanism. It is also necessary for the formation of hormone.

2. **Thiourea derivatives and perchlorate,** which block the synthesis of thyroid hormone.

3. **Radioiodine,** which destroys the cells making thyroid hormone.

Iodide

Iodide is well **absorbed** from the intestine, is distributed like chloride or bromide in the body and is rapidly excreted by the kidney, unlike bromide. It is selectively taken up and concentrated by the thyroid, more in hyperthyroidism and less in myxœdema. A **deficiency** of iodide reduces the amount of thyroid hormone produced, and stimulates the pituitary to secrete TSH. The result is hyperplasia and increased vascularity of the thyroid, with eventual goitre formation.

Some foods, such as plants of the cabbage family, contain substances which block uptake of iodide by the thyroid or prevent its incorporation in thyroid hormone; these may be a factor in endemic goitre.

An **excess** of iodide has opposite effects to those of TSH on the thyroid; iodide promotes involution, making the gland in the hyperthyroid patient

firmer, and less vascular, so that surgery is easier. This is easy to understand where the hyperplasia is due to iodide deficiency (added iodide allows thyroid hormone synthesis, and "turns off" TSH), but how it works in hyperthyroidism is not known.

Excess of iodide can also cause goitre in subjects with normal thyroids, e.g. in parts of Japan where large amounts of seaweed are eaten; in asthmatics taking iodine-containing preparations (especially if these also contain phenazone, which has a synergistic effect, e.g. Felsol).

Iodide is **used** before operation on **thyrotoxic patients.** Even in a thyrotoxic patient **Potassium Iodide Tabs.** B.P.C. (60 mg) (180 mg a day) reduce the hyperplasia and vascularity of the gland; symptoms are also greatly improved. This effect is maximal after 10 days and then declines, so that symptoms recur in the absence of another antithyroid drug.

Prophylactic iodide (1 part in 100,000) should be added to all the salt or bread used where goitre is endemic. In Michigan, U.S.A., the incidence of goitre was inversely proportional to the iodide content of the water supply. In one county 42% of 3,645 schoolchildren had goitre in 1924. Four years later, after propaganda for prophylactic iodide, incidence of goitre among children in one town of that county dropped to 9%. Of the 900 children in the town who had used only *iodised* salt, one had a goitre; of 84 using mainly *ordinary* salt, 11 had goitres (*3*).

In primitive communities the best method of prophylaxis is to inject 4 ml of iodised oil i.m. every 3 yrs; given early enough to women, endemic cretinism can be prevented.

A small goitre presumed due to iodine deficiency (a presumption justifiable only in an area of endemic iodine deficiency), which is not producing symptoms, may involute if L-thyroxine in doses similar to those used in hypothyroidism are given, as well as iodide replacement, but nodularity or increase in size of the goitre is an indication for surgery.

Granulomatous lesions of late syphilis and actinomycosis used to be treated, with some benefit, with large doses of iodide. Antibiotics give better results.

As an antiseptic for use on the skin, Iodine Solution, Weak, B.P., is very effective. Allergic reactions occur.

Bronchial secretion. Iodide is concentrated in bronchial and salivary secretions. It acts as an expectorant in several ways (see *cough*), but is unpleasant because it must be given to the limits of tolerance. There is no point in including small amounts in cough mixtures.

Lugol's Solution is a traditional preparation which contains 5% iodine and 10% potassium iodide in water. The oral dose is 0·5 ml 8-hrly. Potassium iodide, 180 mg daily, orally, is just as effective for the iodine of Lugol's solution is converted into iodide before it is absorbed.

Organic compounds containing iodine are widely used as contrast media in radiology. Oily preparations are used, for example, in myelography, retrograde pyelography and bronchography; some solutions liberate iodine

so that it is essential to ask patients specifically whether they are allergic to it before they are used. A few radiographic preparations do not contain iodine. For intravenous pyelography water-soluble iodine compounds rapidly excreted by the kidney are used. The biliary system can be outlined by oral or i.v. administration of compounds excreted in the bile. The iodine in these water-soluble compounds is firmly bound, but patients are sometimes allergic to them. An i.v. test dose of 50 mcg ought to be given half an hour before the full i.v. dose, if there is history of any allergy. If there is any reaction repeated doses every half hour may be given, doubling the dose each time. See also below.

Adverse reactions. Patients vary enormously in their tolerance of iodine, some are intolerant or allergic to it both orally and when put on the skin. Symptoms of **iodism** are similar to those of bromism and include a metallic taste, excessive salivation with painful salivary glands, running eyes and nose, sore mouth and throat, a productive cough, diarrhœa, and various rashes which may mimic chicken-pox. The iodine solution used in antisepsis is caustic; it is sometimes drunk by suicidal patients: stomach washouts with solutions of starch are an antidote.

Goitre can occur (see above) with prolonged use of iodide-containing expectorants in bronchitics and asthmatics. Such therapy should therefore be intermittent.

Iodide intake above that in a normal diet will depress thyroid **uptake of administered radio-iodine,** because the two forms will compete. This may result in a normal response to the radio-iodine uptake test in a hyperthyroid patient who would ordinarily show increased uptake.

The most likely causes of this interference are increased dietary intake (*e.g.*, seaweed bread in South Wales), medication (iodide-containing cough medicines, *e.g.* Felsol, or diarrhœa prophylaxis with clioquinol Entero-Vioform) or use of radiodiagnostic agents.

In the case of diet, medication and water-soluble rediodiagnostic agents (pyelography, bronchography), interference will cease 2 to 4 weeks after stopping the source, but with those agents used for cholecystography it may last for 6 months or more and with iodised oil (Lipiodol) (bronchography) it may last for years (as long as the oil is visible radiographically).

Naturally, a high uptake remains significant, but a normal or low result may be false.

The combination of a low radioiodine uptake with a high blood protein-bound iodine (PBI) level is indicative of unusually high intake of iodine in some form.

Thiourea Derivatives

Mode of action. Thiourea derivatives do not block uptake of iodide by the thyroid but they do block the incorporation of iodine into organic precursors of thyroid hormone. The amount of hormone produced is thus reduced, and thyrotoxic patients correspondingly benefited. With overdose

the reduction in circulating thyroid hormone sometimes induces the pituitary to produce more TSH, which in turn causes thyroid enlargement (hyperplasia and increase in vascularity).

History. The association of endemic goitre with hypothyroidism had long been known and there was a supposition that the goitre might represent an attempt by the body to overcome a hormone deficit. It had also been suggested that any agent capable of causing this sort of goitre might be useful in the treatment of hyperthyroidism.

In 1932 it was suggested that a cyanide radical might be responsible for the goitre that had been shown to occur, a few years previously, in rabbits fed on cabbage. Ten years later it was noticed that patients treated with thiocyanates (for hypertension) developed goitre, and so thiocyanates were tried on some hyperthyroid patients, but without useful effect.

The discovery of the antithyroid activity of thiourea in the 1940's resulted from a variety of further observations. One group of research workers found that the goitrogenic factor in rape-seed was probably allylthiourea. Others, investigating the relationship between taste and toxicity in rats, happened to choose the bitter substance phenylthiourea, and found it to be goitrogenic. Yet others noted that workmen manufacturing sulphathiazole, and rats dosed with sulphaguanidine, developed goitres.

Inspired by these observations two independent groups simultaneously discovered that thiourea was a potent and relatively non-toxic goitrogenic substance. It was, with thioracil, soon given a clinical trial in hyperthyroidism and found effective (*1*). Numerous other drugs have followed it, some being substantially safer.

Drug (*Tablet size in mg*)	*Total oral daily dose* (*divided 8 hourly*)	
	Initial (*for about 8 weeks*)	*Minimum maintenance*
propylthiouracil (50)	200 mg	50 mg
methylthiouracil (50)	200 mg	50 mg
carbimazole (Neo-Mercazole) (5)	40 mg	5 mg
methimazole (Tapazole) (5)	40 mg	5 mg

Thiourea thus introduced in 1943 was in fact being re-introduced into medicine. Half a century previously it had been advocated and used to reduce lupus scars and in arthritis, leprosy and deafness. Its toxicity and therapeutic inefficacy for these purposes led to its abandonment 20 years later, with its ability to prevent thyroxine formation and to cause goitre still undetected.

Use (also below). It is probable that no patient is wholly refractory to these drugs. Failure to respond is likely to be due to the patient not taking the tablets or to wrong diagnosis.

Clinical improvement is noticeable in about a week, and the patient should be euthyroid after about 8 weeks. The dose is then reduced and adjusted according to the clinical picture. The best guides to therapy are the patient's feelings, his weight and pulse rate, though measurements of the latter can be misleadingly high in a well-controlled patient if he is only seen in a clinic. Measurement of the ankle reflex time is a useful guide to therapy in both hyper and hypothyroidism. Simple machines to record this are available.

Overtreatment leads to increased goitre due to increased thyrotrophin secretion from the pituitary.

Adverse reactions. These drugs are all liable to cause allergic effects: rashes, and most serious of all, leucopenia sometimes proceeding to agranulocytosis (0·5 to 1%) or aplastic anæmia. Blood disorders are most common in the first two months of treatment. Repeated leucocyte counts are often advocated, but agranulocytosis may be so acute that the counts give no warning; a leucocyte count should be done if the patient develops an infection, and any suggestion of anæmia should be investigated.

If a pregnant woman has hyperthyroidism she should be treated with the *smallest possible* amount of these drugs because they cross the placenta; with overtreatment fetal goitre occurs.

Antithyroid drugs should not be given to lactating women as they are concentrated in the milk.

Preparations and dosage (see table). Doses given are for the average hyperthyroid patient, but in a very severe case three times as much may be given initially.

Potassium Perchlorate

Because of the slightly greater risk of aplastic anæmia, perchlorate is only used in patients who are allergic to thiourea derivatives.

The thyroid gland concentrates iodide from the blood 20 to 30 times, for the normal blood iodide level provides too low a concentration for hormone synthesis to be accomplished. Perchlorate stops the gland from effecting the necessary concentration and thereby prevents synthesis of thyroid hormone. If substantial iodide dosage is given to a patient taking perchlorate, the blood iodide is raised sufficiently for the thyroid gland to synthesise hormone without the prior necessity for concentrating iodide, and the perchlorate effect is by-passed. This is why perchlorate is unsuitable for preparing hyperthyroid patients for surgery, see below.

The thioureas interfere directly with the hormone synthesis and so are unaffected by the presence of increased amounts of iodide.

Ill effects other than rashes are uncommon, but include aplastic anæmia.

Choice of antithyroid drug. When given in the above doses all are about equally effective in controlling hyperthyroidism. The choice should

therefore depend on their relative toxicity. Unfortunately this is not exactly known as medical practice is not adequately organised to produce figures on a sufficiently large scale, and reports from individual clinics leave the issue in doubt. Choice of drug is therefore a matter of opinion, but fear of aplastic anæmia with perchlorate has led many to abandon it, as this complication is probably more frequent than with the thioureas.

The need to measure accurately the relative toxicity of drugs of closely similar merit will grow as more diseases become treatable by drugs of low toxicity.

Control of Antithyroid Drug Therapy

The aim of drug therapy is to control thyroid function until a natural remission takes place. Unfortunately, though usual, remission is not invariable and there is no way of predicting which patients will not remit and who should therefore be offered surgery.

Radioiodine uptake tests are no guide to drug therapy, because hormone synthesis, and therefore iodine uptake, is suppressed.

Clinically, it is not possible to decide reliably when remission has occurred, although disappearance of bruit and reduction in gland size suggest it. Treatment should not be stopped whilst a bruit persists.

If there has never been a bruit, treatment may be stopped after the patient has been free from symptoms for 4 months on the minimum dose of drug. Lid retraction is the only eye sign that improves.

If spontaneous remission has not occurred, the patient will have relapsed within 2 to 4 months of stopping the drug.

Treatment is generally needed for 1–2 yrs.

Radioiodine uptake tests can be misleadingly high for some months after stopping drug therapy owing to the occurrence of a "rebound" phenomenon even where remission has occurred.

In pregnancy antithyroid drugs cause fetal goitre if overdose is given.

Preparation of a hyperthyroid patient for surgery can be satisfactorily achieved by making him euthyroid with one of the above drugs and *adding* iodide for 7 to 10 days to reduce the inconvenient vascularity of the gland. Perchlorate cannot be used instead for this purpose, as administration of the iodine to reduce vascularity would cause a relapse.

Thyroid crisis or storm is rare with modern methods of preparing hyperthyroid patients for surgery. It is probably due to liberation of large amounts of hormone into the circulation. Treatment is (1) to reduce production of hormone quickly (large doses of iodide, say 1–2 g/day of potassium iodide): (2) to reduce release of, or effect of catecholamines (reserpine, adrenoceptor blockers): (3) to control body temperature, heart failure, etc.*

Therapeutic hypothyroidism has been induced with antithyroid drugs (including ^{131}I) in cases of angina at rest or intractable heart failure.

* HARRISON, M. T. (1968). *Pharmacol. for Phys.* **2**, No. 1.

Gross myxœdema is required if the work done by the heart is to be usefully reduced.

Radioiodine (^{131}I and ^{132}I)

Both isotopes are treated by the body just like the ordinary non-radioactive isotope, so that when swallowed they are concentrated in the thyroid gland. They emit mainly β radiation (90%) which penetrates only 2 mm of tissue and thus allows therapeutic effect on the thyroid without damage to the surrounding structures, particularly the parathyroids. However, they also emit some γ rays, which are relatively penetrating and can be detected with a Geiger counter. These can be used in tests of thyroid function. After administration of radioiodine in hyperthyroidism the count over the thyroid is abnormally high, in hypothyroidism abnormally low. The percentage uptake at 24 hrs may be measured, or alternatively the count may be compared with that over an inert area, such as the thigh, and the result expressed as a ratio (neck/thigh ratio). This test will not detect mild hypothyroidism but is very sensitive in diagnosis of hyperthyroidism (see also *iodide* above). Abnormally situated thyroids can be located using radioiodine.

^{131}I has a physical half-life of 8 days, and even the small amount used for diagnostic purposes is enough to be an appreciable radiation hazard to children so that ^{132} I, which has a half-life of only a few hours, is preferable for all diagnostic purposes and especially during pregnancy and lactation. ^{125}I ($t_{\frac{1}{2}}$ 60 days) has a shorter range of radiation and may spare cell nuclei whilst damanging cell hormone synthesis; it is under trial in the hope it may cause less late hypothyroidism (see below).

^{131}I is used in the treatment of some cases of hyperthyroidism and in combination with surgery in some cases of thyroid carcinoma, especially those in which metastases are sufficiently differentiated to take up iodide selectively.

In hyperthyroidism the beneficial effects of a single dose may be felt in one month but its action is not maximal for 3 months. In severe cases antithyroid drugs (also antiadrenergics, see below) will be needed to render the patient comfortable whilst waiting.

In the event of inadvertent overdose, large doses of potassium iodide should be given to compete with the radioiodine for thyroid uptake and to hasten excretion by increasing iodide turnover (increased fluid intake and a diuretic are adjuvants). Radioiodine offers the advantages that treatment is simple and in no way unpleasant (the patient just drinks it) and it carries no immediate mortality. However, it is slow in acting and it is difficult to judge the dose, so that the patient may remain uncontrolled or permanent hypothyroidism may soon appear (some see no objection to this and would rather stabilise the patient on exogenous hormone than await a slowly-developing hypothyroidism).

Between 2–3% of patients become hypothyroid *annually* after treatment with radioiodine, perhaps because the capacity of thyroid cells to divide is

permanently abolished so that cell renewal ceases. Patients must therefore be followed up permanently after radioiodine treatment, for they are likely to need treatment for hypothyroidism sooner or later.

Experience has diminished, or even eliminated the fear that radioiodine might cause late carcinoma of the thyroid, and it is no longer mandatory to confine its use to those over 45 yrs. But children (and pregnant women) should never be treated with radioiodine, since it is known that irradiation of the thyroid in infancy can be carcinogenic.

There is a theoretical risk of germ cell mutagenic effect and patients should not reproduce for a few months after treatment. Larger doses of radioiodine are used for thyroid carcinoma than for hyperthyroidism, and there is an increased incidence of leukæmia in these patients.

Treatment of Hyperthyroidism

There are three possible lines of treatment, each with its special advantages and disadvantages:

1. Sub-total thyroidectomy, after preparation with antithyroid drugs
2. Antithyroid drugs alone
3. Radioiodine

Control of symptoms or signs that have been attributed to increased catecholamine sensitivity, but which may in fact be due to a direct action of thyroid hormones (*13*) can be achieved by reducing sympathetic drive to these organs, e.g. eye: guanethidine eye drops 5% (but not if there is any keratitis): tachycardia, palpitations, sweating, tremor, by a β-adrenoceptor blocker (say, propranolol 10-40 mg orally 6 hrly).

These drugs do not affect exophthalmos.

Surgery is indicated if obstruction of neck veins or trachea exists or is thought to be likely in the future, or if the thyroid is nodular or there are other grounds for fearing malignancy.

Antithyroid drugs are generally preferred for younger patients, provided the goitre is small and diffuse. A nodular goitre is generally large enough to be a source of complaint and it is best treated surgically. These drugs do not decrease thyroid size; it may even increase (see above).

Radioiodine is commonly used for older patients (over 45 yrs). It affects both diffuse and nodular goitre. The goitre becomes smaller. Thyrotoxicosis due to a single hyperfunctioning adenoma ("hot nodule") is particularly suitable for this treatment.

Drugs that Cause Unwanted Hypothyroidism

In addition to drugs used for their antithyroid effects, the following substances can cause hypothyroidism: PAS (for tuberculosis), phenylbutazone (antirheumatic), iodide (see above), cobalt salts (for anæmia), sulphonylureas (for diabetes), resorcinol (for leg ulcers), lithium (for depression).

Goitre may occur as the result of increased TSH secretion elicited by the decreased thyroid hormone synthesis.

Guide to Further Reading

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Chapter 26

INSULIN, ORAL HYPOGLYCÆMICS, DIABETES MELLITUS

Insulin (*1–8*) is synthesised and stored in the β-islet cells of the pancreas.

Daily secretion is about 25% of total pancreatic insulin content, so that most insulin is contained in the storage system from which it is released in response to changes in glucose concentration (also of amino, fatty and keto-acids) in the arterial blood supplying the pancreas.

Insulin is a polypeptide having two amino-acid chains (A chain 21, and B chain 30 aminoacids) linked by two disulphide bridges. The basic structure having metabolic activity is common to all species, but there are minor species differences which result in the development of antibodies in all patients treated with animal insulins. Most insulin used clinically in Britain is bovine, which differs from human insulin by 4 amino acids. Bovine is more antigenic than porcine which differs from human by only one amino acid. This is seldom clinically important.

Human insulin has been synthesised, but the process is at present too cumbersome and expensive to provide supplies for routine therapy.

Metabolic effects of insulin. There is no single action of insulin that accounts for all its effects. Insulin is localised and acts at cell membranes, especially muscle and adipose tissue; its actions include:

1. **Reduction in blood sugar** due to increased glucose uptake in the peripheral tissues (which make it into glycogen and fat), and reduction of hepatic output of glucose (diminished breakdown of glycogen and diminished gluconeogenesis). When the blood-glucose level falls below the renal threshold (180 mg/100 ml) glycosuria ceases in diabetes, as does the osmotic diuresis of water and electrolytes. Polyuria with dehydration and excessive thirst are thus alleviated. If the blood glucose falls much below normal levels appetite is stimulated.

2. **Other metabolic effects:** in addition to enabling glucose to pass across cell membranes, the transit of aminoacids and potassium into the cell is enhanced. The latter effect is used in treating hyperkalæmia.

Insulin regulates carbohydrate utilisation and energy production. It enhances protein synthesis.

An insulin deficient diabetic is dehydrated due to osmotic diuresis (see 1 above). He is ketotic because fats break down faster than the keto-acid metabolites can be utilized.

Indications for Insulin Therapy

The main indication is **diabetes mellitus.** Other uses are minor. Soluble insulin is sometimes given in small doses (10 I.U. 3 times a day,

half an hour before meals) to **stimulate appetite** and promote an increase in weight, e.g. in anorexia nervosa. Insulin promotes the passage of potassium simultaneously with glucose into cells, and this effect has been made use of in *hyperkalæmia* (which see).

Insulin hypoglycæmia can also be used as a test of anterior pituitary function (growth hormone and corticotrophin are released) and to test the results of vagotomy in reducing gastric secretion.

Pharmacokinetics. Insulin must be injected (s.c., i.m. or i.v.) as it is digested if swallowed. It is absorbed into the blood and is inactivated in the liver (about 40% in a single passage). About 10% appears in the urine. The plasma half-life ($t_{\frac{1}{2}}$) is 5 to 10 mins. This is convenient for an accurately controlled continuously functioning biological system, but it is not suitable for routine replacement in insulin deficiency. Therefore slow release preparations have been developed to provide the nearest approach to natural function compatible with convenience of daily living.

Preparations of Insulin

These are all sterile aqueous solutions or suspensions. Soluble insulin may be given s.c., i.m., or i.v. The depôt preparations are given only s.c.; given by i.m. injection they would have a different time-course of action and could not easily be self-administered. Dosage is measured in International Units (I.U.).

Soluble Insulin is an aqueous solution of insulin. It is simple to use, being given s.c. 2 or 3 times a day, 30 mins before meals. There is rela-

THE APPROXIMATE TIME RELATIONSHIP OF THE CHIEF INSULIN PREPARATIONS, GIVEN S.C.

Preparation	*Onset hrs*	*Max. Effect hrs*	*Duration hrs*
Soluble: Insulin Inj., B.P.	½	2—3	6—8
Semilente: Insulin Zinc Susp. (Amorphous), B.P.	1	6—10	12—16
Lente: Insulin Zinc Susp., B.P. (a mixture of semilente and ultralente, 3:7)	2—4	8—12	18—24
Isophane Insulin Inj., B.P.	similar to lente insulin		
Protamine Zinc Insulin Inj., B.P.	3—6	14—20	24—40

There is very great individual variation in response and big doses act for longer than small.

Soluble insulin is available in a solution containing 20 I.U./ml (single strength), 40 I.U./ml (double strength) and 80 I.U./ml (quadruple strength). The long-acting preparations are only available in strengths of 40 and 80 I.U./ml. More concentrated preparations can be provided to meet rare special cases.

tively little risk of hypoglycæmic reaction. If it is known that a meal must be delayed, then the insulin injection can be postponed. The dose can easily be adjusted according to the amount of glycosuria. For these reasons it is often used initially to balance diabetics needing insulin and always for the treatment of diabetic ketosis, when it may have to be given in very large amounts both i.v. and i.m. The biggest disadvantages of soluble insulin for long-term use are the need for frequent injections, and the occurrence of heavy glycosuria before breakfast.

Insulin Zinc Suspensions (the *lente* insulins: *semilente*, amorphous: *ultralente*, crystalline: *lente*, a mixture) are depôt preparations in which duration of action is controlled by modifying particle size. Soluble insulin can be mixed with them without altering the effect of either. **Isophane Insulin** is similar.

Protamine Zinc Insulin (P.Z.I.) was developed following the observation that the pancreas contained much zinc. It is a depôt preparation, the combination of insulin with protamine and zinc making it less soluble. If enough is given in a single early morning injection to abolish glycosuria throughout the 24 hrs, then hypoglycæmic reactions tend to occur at night or before breakfast. The dose of protamine zinc insulin may therefore have to be too low to give complete control, and small amounts of soluble insulin are often given in addition, usually before breakfast, but sometimes later in the day as well. Owing to the presence of excess protamine some of the soluble insulin is converted to P.Z.I. when the two are mixed so that the effect is different than if the two are given by separate syringes.

Globin Zinc Insulin is similar to isophane. Other short and long-acting insulins exist, e.g. Biphasic Insulin Inj. B.P. (crystals of bovine plus solution of porcine insulins).

Choice of insulin preparation. The choice of insulin depends on the patient's pattern of life and the amount of insulin he needs.

Most diabetics needing insulin can be managed satisfactorily on lente insulin (Insulin Zinc Susp., B.P.) in the morning, but if more than 48 I.U. are needed, control is likely to be better with a morning injection of the same total units of protamine zinc insulin plus soluble insulin in the proportion, say, 2 : 1. The two insulins are best injected through the same needle into the same site but from different syringes to avoid any risk of contaminating either insulin bottle with the other form.

An alternative is to use a mixture of isophane insulin with soluble insulin once or twice a day.

It is probable that young unstable diabetics are best controlled by two or three injections of soluble insulin a day.

It is clear that perfect control of the blood glucose level cannot be obtained by a single daily injection, for insulin requirements fluctuate during the day and all single dose regimens are a compromise.

In each diabetic it is necessary to find the most suitable insulin preparation by trial. Distribution of carbohydrate in the diet may have to be

adjusted to the type of insulin used. It is preferable to adjust therapy to suit the patient, rather than to adjust the patient to fit the physician's favourite routine.

Unwanted Effects of Insulin

Unwanted effects are mainly those of **excessive action.** Because the brain requires glucose as its source of energy, an adequate blood-glucose level is just as essential as an adequate supply of oxygen and hypoglycæmia may lead to coma, convulsions and even death.

It is usually easier to differentiate hypoglycæmia from severe diabetic ketosis than from other causes of coma, which are as likely in a diabetic as in anyone else. If there is doubt as to the ætiology in a comatose patient it is reasonable to give glucose i.v., but only after taking blood for a sugar estimation. If hypoglycæmia of short duration is responsible then a rapid improvement is usual; in any case a dose of glucose (see below) will do no harm.

Another adverse reaction to insulin is **atrophy of fat or lipomata** at the injection sites, after they have been used repeatedly. These are unsightly, but otherwise harmless. The site should not be used further, for absorption can be erratic, but the patient may be tempted to continue if local anæsthesia has developed, as it sometimes does. Generalised **allergic** reactions are very rare, but may occur to minute traces of extraneous animal protein in soluble insulin, to protamine or globin in the respective depôt preparations, or even to insulin itself. Change of brand of insulin may prevent the undesirable reactions. Hyposensitisation is sometimes possible. Local allergic reactions (itching weals) occur more commonly.

Treatment of a Hypoglycæmic Attack

Prevention depends very largely upon the education of diabetic patients taking insulin. In particular, they should never miss meals and must know the early symptoms of an attack. They should carry glucose sweets or lump sugar about with them and should carry a special card identifying them as diabetics. This card should request that if the bearer is found behaving strangely he should be given sugar. Treatment is always to give sugar, either by mouth if the patient can still swallow, or glucose i.v. (25–50 g). The response is usually dramatic, but if the patient does not respond within 30 mins, he may have cerebral œdema and will require treatment with i.v. dexamethasone and perhaps mannitol i.v. If the patient has been severely hypoglycæmic for hours, or if very large amounts of insulin have been taken, then large amounts of glucose may have to be given by i.v. infusion for several days. Very severe attacks sometimes damage the central nervous system permanently. See also adrenaline and glucagon below.

Insulin Resistance (*7, 25*)

Some established diabetics suddenly develop a need for huge doses of insulin, even as much as 5,000 I.U. a day. This can be due to the presence of antibodies (see above) and sensitivity may sometimes be restored by an adrenal steroid (prednisolone) which may act by suppressing antibody formation. Acidosis also reduces the effect of insulin on peripheral glucose utilisation.

Hormones which Tend to Raise the Blood Sugar

Adrenaline raises the blood sugar by mobilising liver and muscle glycogen; it does not antagonise the peripheral actions of insulin. Adrenaline (0·75 ml Adrenaline Inj, B.P. i.m.) was once recommended in the treatment of hypoglycæmia, but endogenous adrenaline is secreted reflexly before symptoms occur and glucose provides safer and more effective therapy. Glycosuria and diabetic symptoms may occur in patients with phæochromocytoma.

Glucagon is a polypeptide hormone from the α-islet cells of the pancreas. It is released in response to hypoglycæmia and so is a physiological regulator of insulin effect. It releases liver glycogen as glucose. It has been used to treat insulin hypolycæmia but in about 45 min from onset of coma the hepatic glycogen will be exhausted and glucagon will be useless. Its chief advantage would seem to be that, as it can be given s.c. or i.m. (1 mg) it can be used in hypoglycæmic coma by somebody, e.g. a member of the patient's family, who is unable to give an i.v. injection of glucose. If a comatose patient does not recover 15 mins after the second injection, i.v. glucose is essential. If he does recover, oral glucose will, of course, be needed. Glucagon is ineffective in marked hepatic insufficiency.

Glucagon has a positive cardiac inotropic effect; its use in cardiac disease is experimental.

Adrenal steroids, either endogenous or exogenous, antagonise the effects of insulin, although this effect is only slight with the primarily mineralocorticoid group: the adrenocortical hormones *increases* gluconeogenesis and reduce glucose uptake and utilisation by the tissues. Patients with Cushing's syndrome thus develop diabetes very readily and are resistant to insulin. Patients with Addison's disease are abnormally intolerant of insulin.

Oral contraceptives can impair carbohydrate tolerance.

Pituitary growth hormone antagonises the actions of insulin in the tissues. Acromegalic patients may develop insulin-resistant diabetes. Conversely patients suffering from hypopituitarism are abnormally sensitive to insulin.

Thyroid hormone increases the requirements for insulin.

Oral Hypoglycæmic Drugs (*9, 10, 12–14, 16, 18–22*)

Oral hypoglycæmic drugs are of two kinds, sulphonamide derivatives (sulphonylureas) and guanidine derivatives (biguanides).

Following the observation in 1918 that guanidine had a potent hypoglycæmic effect, guanides were tried in diabetes in 1926, but were abandoned a few years later for fear of hepatic toxicity.

In 1930 it was noted that sulphonamides could cause hypoglycæmia, and in 1942 severe hypoglycæmia was found in patients with typhoid fever during a therapeutic trial of a sulphonamide derivative. In the 1950's a similar observation was made during a chemotherapeutic trial in urinary infections. This was followed up and effective drugs soon resulted.

Mode of action: Sulphonylureas act by stimulating the β-islet cells of the pancreas to produce insulin. They are therefore ineffective in totally insulin-deficient patients and for successful therapy probably require about 30% of normal β-cell function to be present.

Biguanides reduce absorption of carbohydrates from the gut. They may also increase the uptake of glucose in peripheral tissues provided insulin is present, and they reduce hepatic gluconeogenesis.

Both groups of drugs are dependent on the presence of insulin. But biguanides, by their effect on gut absorption modify effects of injected insulin (sulphonylureas do not interact with injected insulin).

Drugs of the two groups may be used together.

The Principal Oral Hypoglycæmic Drugs

	Total daily dose (tablet size)	*Remarks*
Sulphonylureas tolbutamide (Rastinon)	0·5 to 3 g in 1-4 doses (0·5 g)	Relatively safe. Frequent administration. Less effective than chlorpropamide. Dose may be altered daily. Tolerance occurs.
chlorpropamide (Diabinese)	100-500 mg in 1 dose at breakfast (100, 250 mg)	Rather less safe than tolbutamide. May succeed where tolbutamide fails. Taken only once daily and dose only altered every 3-5 days.
Biguanides phenformin (Dibotin, D.B.I.)	50-200 mg in 2-4 doses (25 mg) or sustained release caps. 24 or 12 hrly (50 mg)	Capable of controlling some patients when used alone, but high incidence side effects. Chief use in supplementing a sulphonylurea (different mode of action) or insulin.

Individual Drugs

Absorption from the alimentary tract is good for all agents. If a patient fails to respond to one drug he may yet respond to another of the same group.

Sulphonylureas

Tolbutamide is rapidly metabolised by oxidation in the liver (half life, 5 hrs.) (1–4 doses a day) so that patients with hepatic disease should be treated with caution, as always. Troublesome effects are unlikely to

occur in more than 3% of patients. They usually consist of mild gastro-intestinal upsets, which may be mitigated by taking the drug after food or by antacids, and of rashes. Other ill-effects are very rare, but include blood disorders.

Sulphonamides, as expected, potentiate sulphonylureas. Phenylbutazone potentiates by plasma protein displacement.

Tolbutamide (1·0 g i.v.) is sometimes used in **diagnosis of insulinomas.** The blood glucose and, if possible, the plasma insulin, are measured over the succeeding 3 hrs. In insulinoma (and also severe hepatic insufficiency) the degree of hypoglycæmia is greater and more prolonged than normal.

Chlorpropamide is not metabolised and is dangerous in patients with poor renal function. It is longer acting than tolbutamide. Its half-life is 35 hrs (one morning dose) and it is longer in the elderly. Unwanted effects are about twice as frequent as with tolbutamide, gastro-intestinal upsets, rashes, vertigo, muscle weakness, headache, unpleasant taste, jaundice and blood disorders, but the latter are rare and seldom serious.

Alcohol intolerance (a reaction similar to that experienced with disulfiram) occurs in 10 to 30% of patients taking chlorpropamide. It is said to be less common with tolbutamide and glibenclamide and a change to another sulphonylurea is indicated if the patient wishes to take alcohol.

Other sulphonylureas: *acetohexamide* (Dimelor), *tolazamide* (Tolanase), *glibenclamide* (Daonil): *glymidine* (Gondafon) is a sulphapyrimidine.

Biguanides (diguanides)

Phenformin is taken in 2 to 4 doses a day. When used alone unpleasant effects occur in about 25% of patients, chiefly gastro-intestinal upsets, weakness and drowsiness. But, unwanted effects are less troublesome with slow-release formulations and with the low doses used when it is combined with other drugs. It is principally used in combination with a sulphonylurea when the latter alone has failed.

Phenformin enhances blood fibrinolytic activity (which see), but its utility in therapy of thrombotic disease has not yet been defined.

Metformin (Glucophage) is similar. Both drugs may cause malabsorption of vit B_{12}.

With biguanides ketonuria may occur in the presence of normal blood sugar. This is not generally severe and may be treated by reducing the dose; but persistence in overdose may lead to severe acidosis.

All patients on large doses of phenformin (>100 mg/day) have raised blood lactic acid levels, perhaps because of depression of aerobic glycolysis. Occasionally lactic acidosis develops, especially in peripheral circulatory failure, after alcohol and in renal insufficiency.

Hypoglycæmia may occur with all the oral drugs, but is less common than with insulin therapy. However it can be severe, prolonged for days and fatal, especially in the old. Because of its long $t_{\frac{1}{2}}$ chlorpropamide is not a drug of first choice in the old.

The Treatment of Diabetes Mellitus

Good control of diabetes always involves diet, and some patients need insulin or oral hypoglycæmics in addition.

The aim of treatment is to keep the blood sugar level within the normal range throughout the 24 hrs. Each patient must be assessed individually; only an outline of the general principles involved can be given here:—

Education. All diabetics should possess a book which contains general information about the treatment of the disease and detailed diets. Diabetics should understand that there is a possibility that proper control minimises the risk of serious complication such as blindness.

They should know how to give their injections and test their urine.

The introduction of simple testing methods has improved control by rendering patients less unwilling to do the tests.

Some tests are enzymic, employing glucose oxidase (Clinistix) and these are selective for glucose, though false negatives may occasionally occur.

Others measure reducing substances, e.g. employing copper sulphate and sodium hydroxide (Clinitest), or Benedict's or Fehling's Soln and may give a positive result with a variety of drugs and metabolites, but effects are often not consistent, e.g. nalidixic acid, cephaloridine, levodopa and methyldopa (perhaps), salicylates, nitrofurantoin, chloral.

It is important to stress that any **infection** or other pyrexial illness increases insulin need, which means that they should *increase* their insulin and take enough food or glucose to cover it. In patients taking oral antidiabetics trivial intercurrent illness does not generally upset control, for this group of patients is not liable to ketosis anyway; but there is great individual variation.

Diet. The patient should be allowed to follow his own preferences as far as is practicable, and his drugs should be adjusted to suit him. Some carbohydrate restriction is necessary, but the amount varies from patient to patient according to their total caloric requirements (100 to 300 g carbohydrate day generally) and whether weight increase or reduction is desired. The way in which carbohydrate is distributed through the day varies with the type of insulin taken.

In diabetics of normal weight protein and fat do not need control, and such patients' diets should not be needlessly complicated.

Weight. Elderly fat diabetics (maturity onset) form a group whose blood often contains much insulin but who are resistant to its action; they seldom develop ketosis. Glycosuria may cease when their weight is reduced. Biguanides particularly help weight reduction (see below).

Young patients with diabetes (growth onset) are often underweight and need insulin to restore normal weight. The blood of these young diabetics contains no insulin (they are sensitive to its action), and they readily become ketotic.

Assessment of drug therapy in diabetes (*20–22*)

As in other life-long diseases, e.g. hypertension, drugs are assessed

primarily for their capacity to modify favourably easily measurable features of the disease short-term. It tends to be assumed that if this is accomplished the desired objective (of controlling the disease until the patient dies of something else) must naturally follow. But this is not necessarily so.

In the case of diabetes mellitus, the effect of insulin in the young ketotic insulin deficient (growth onset) cases was dramatic and its immediate life-saving property was undisputed.

But in the case of the middle-aged non-ketotic, insulin resistant (maturity onset) case, the situation is very different. They have a substantial life expectancy and can often be controlled by diet alone.

With the advent of oral hypoglycæmics, in the 1950's the blood sugar of these patients could be controlled without insulin (to which they were often resistant) and the drugs became widely used. There was no evidence of their long term effects.

A number of studies of long term use of oral hypoglycæmics have now been done. Unfortunately the results are in disagreement. Such studies are hard to do in a way that is not open to serious objection. Evaluation is complicated by the fact that treated and control groups inevitably change in character and diminish in size with the years, and that mortality in all experimental groups must ultimately be 100%.

A large prospective study in 12 centres in the U.S.A. was set up to evaluate vascular complications of maturity onset non-insulin dependent diabetes. Patients received one of the following regimens: diet + placebo: diet + tolbutamide: diet + fixed insulin dose: diet + variable insulin dose (a study on phenformin has also been done). After 5–8 yrs follow up it was found that the tolbutamide treated group had a higher mortality from cardiovascular disease. The other groups (placebo and insulin) showed no significant differences. There has been much criticism of this study, selection of patients, allocation to treatment groups, etc., and so its results cannot be regarded as definitive, especially as they differ from those of other studies elsewhere.

The discussions centring on this study illustrate the enormous problems, including expense, of obtaining answers to apparently simple questions about the efficacy of treatment in complicated chronic disease.

The present situation is that maturity onset diabetes should be treated by diet. If this is inadequate there is disagreement as to whether an oral agent or insulin should be first chosen. But a short course of an oral agent to abolish glycosuria and relieve symptoms (e.g. polyuria and pruritus vulvæ) would seem justified as a temporary expedient until diet is effective.

In one diabetic clinic, 64 patients taking oral hypoglycæmics because they had failed to respond (normoglycæmia) to diet alone were transferred to placebo tablets; 31% did not relapse. Thus the use of oral hypoglycæmics, once started, need not be regarded as permanent (*26*).

Selection of therapy for diabetes

Diabetic ketoacidosis—insulin—urgent.

Glycosuria { Diet—especially if patient overweight,
or diet + oral hypoglycæmics,
or diet + insulin.

Very approximately, of **diabetics under 30 yrs,** almost all need insulin; **over 30 yrs** *one third* need **insulin**, *one third* **oral agents** and *one third* **diet alone.**

Oral hypoglyaæmics should only be used initially where there is no significant ketonuria. Oral drugs are useless if no insulin is present and are most useful in maturity onset cases. Careful therapeutic trial is the only sure way of deciding who can be maintained on oral therapy rather than on insulin.

Choice of oral hypoglycæmic agent. When it has been decided to use an oral agent, the choice should fall first on a **sulphonylurea,** for the biguanides, though capable of controlling some patients when used alone, carry too high an incidence of adverse effects, especially on the alimentary tract.

The **biguanides** are used: (1) *as a supplement to a sulphonylurea* where this is insufficient to give good control. (2) *in overweight diabetics*, especially those who find diet difficult; patients tend to lose their appetite and therefore to lose weight with a biguanide; the mode of action is uncertain. (3) *to smooth out the effect of insulin* in "brittle" insulin dependent diabetics and to reduce insulin requirement in some cases where insulin resistance is not due to antibodies.

Of the two principal sulphonylureas, tolbutamide is the safest, especially in the elderly, but has to be given up to 4 times a day. Chlorpropamide is slightly more toxic, but can succeed where tolbutamide fails and need only be given once a day. They thus each have their advantages and disadvantages and the choice in any patient is a matter of opinion.

To start a patient on a sulphonylurea, tolbutamide 0·5 g three times a day after food may be given, or chlorpropamide 250 mg in the morning. Dose is then adjusted according to the response, tolbutamide being altered daily by 0·25 to 0·5 g and chlorpropamide every 3 to 5 days by 50 to 100 mg.

If control is incomplete, phenformin may be added.

Failure of oral agents. If the post-prandial blood sugar does not fall below 250 to 300 mg/100 ml after four weeks, then other therapy is needed, for not only is this state unsatisfactory but, on the same treatment, control may worsen over succeeding weeks.

Also, unlike insulin, oral agents may fail after months of successful treatment. There may be many causes of this, for there can be little doubt that the mode of action of sulphonylureas is not as simple as has perhaps been implied above. One cause of late failure is progression of the diabetic state, i.e. the insulin-producing capacity falls.

In one study, the relapse rate for patients on tolbutamide was 44%,

on chlorpropamide 12% and on chlorpropamide and phenformin 13% Close supervision is clearly essential.

Changeover from insulin to a sulphonylurea. With the short-acting tolbutamide and acetohexamide it may be abrupt, but with the longer-acting chlorpropamide it should probably be made over several days.

If the stopping of insulin leads to ketosis before the sulphonylurea takes effect then the patient is unsuited to oral therapy. In any case insulin should be resumed immediately. Hypoglycæmia may also occur during the changeover.

Patients should be watched closely when changing over to oral therapy, with urine tests for sugar and ketones three times a day and blood sugar estimations before, and after, the drug.

Observation of patients taking these drugs should be at least as close as of those on insulin and probably closer. The patient must be disabused of any notion that substitution of tablets to swallow for the tiresome routine of self-injection carries any implication that his condition is less serious, or that diet can be relaxed.

Use of insulin. Diabetic ketosis is an absolute indication for insulin and admission to hospital, as is any severe acute illness in a diabetic. Other indications are weight loss in a thin diabetic or inadequate control of blood sugar and glycosuria with diet plus oral agents. If it is decided that insulin as well as diet is needed in a mild case then it is reasonable to start with a morning injection of lente insulin, 10 to 20 I.U. according to severity and to increase this by 4 I.U. on alternate days until the urine is sugar-free or hypoglycæmic symptoms appear. However, severe cases should be balanced with 2 or 3 injections of soluble insulin a day, preferably in hospital, and changed to a depôt preparation later if possible. When this is done the initial dose of the depôt preparation should approximately equal the previous daily total. If a patient needs more than 50 I.U. total per day, better control is usually got with 2 injections rather than a single morning injection of a single type of depôt insulin; the possibilities are numerous.

Muscular activity increases carbohydrate utilisation, so that hypoglycæmia is likely if a well-stabilised patient changes suddenly from an inactive hospital existence to a vigorous life outside. If this is likely to happen the diet may be increased by 250 to 500 calories or the dose of insulin reduced by up to one-third and then readjusted according to need. This is less marked in patients on oral agents.

Diabetic complications. It is uncertain to what extent complications may be prevented by meticulous control of the blood sugar, but the fact that they can occur in well-controlled patients is certain.

Peripheral vascular disease and its consequences receive the same treatment as in non-diabetics. Cramps in the legs are often helped by quinine. Improvement in peripheral neuritis has been attributed to administration of large amounts of thiamine or cyanocobalamin.

Some Factors Affecting Control of Diabetics

Intercurrent illnesses can cause fluctuations in the patients' metabolic needs. If these are marked it is prudent to use insulin rather than oral agents.

Surgery, see later.

Menstruation. Insulin needs may rise with menstruation.

In pregnancy close control of diabetes is of the first importance to avoid fetal loss. Insulin requirements are liable to increase steadily after the third month. During labour soluble insulin should be given 4-hrly with plenty of glucose orally. Substantially less insulin is likely to be needed immediately after delivery, when at least one injection of insulin should be omitted lest hypoglycæmia occur. Insulin need may increase again during lactation. Blood glucose estimations are necessary during the latter part of pregnancy, for glycosuria is not then a reliable guide because the renal threshold for glucose (also of lactose) falls, so that glycosuria and lactosuria may occur in the presence of a normal blood glucose. Some physicians advocate the admission to hospital of all diabetics after the 32nd week of pregnancy for careful control of the diabetes until after delivery.

Oral hypoglycæmic agents and pregnancy. There is increased fetal loss and they should not ordinarily be used.

Interactions

The subject is ill-documented, but whenever a diabetic under treatment takes other drugs it is prudent to be on the watch for disturbance of control, especially with drugs that are known to affect carbohydrate metabolism (adrenal steroids, salicylate).

The action of sulphonylureas may be expected to be intensified by heavy sulphonamide dosage and some sulphonamides increase tolbutamide blood levels, probably by competing for plasma protein binding sites.

Sympathetic block (e.g. with adrenergic neurone or β-adrenoceptor blockers) can prevent the symptoms of hypoglycæmia that are due to sympathetic discharge and the patient may go into coma without this useful warning. Sympathetic blocking drugs are not usually given in high enough doses, but they may be.

Monoamine oxidase inhibitors probably potentiate oral agents and perhaps also insulin. They can also reduce appetite and so upset control. Interaction may also occur with alcohol (hypoglycæmia), anticoagulants (competition for liver enzymes) etc.

These examples, all of which deserve further investigation, suffice to show that the possibility of interactions of practical clinical importance is a real one.

Effect of diabetes on pharmacokinetics. Obviously renal complications will affect excretion of drugs. But absorption of i.m. penicillin has been shown to be much slower in older diabetics than in control subjects (*27*). This results in lower peak plasma concentrations, which will

not usually be a matter for concern. The effect may be due to diabetic micro-angiopathy. It is likely to apply to other drugs.

Drug-induced diabetes

After the introduction of thiazide diuretics, it was soon found that their prolonged use increased hyperglycæmia in diabetics, and, later, that they could cause diabetes mellitus which is reversible, though it may be permanent in pre-diabetics.

About 30% of patients on long-term thiazide therapy develop impaired glucose tolerance. The mechanism of action is uncertain, but it may be associated with inadequate potassium supplement.

The risk of diabetes deserves special consideration when hypertensive patients with good life expectancy are treated with a thiazide lest they be made the victim of a second chronic disease.

Patients on long-term thiazide therapy should have their urine tested for glucose every few months, and development of polyuria should rouse suspicion of diabetes.

Thiazide-induced diabetes can be controlled by a sulphonylurea.

Research for better antihypertensive thiazides resulted in the discovery of a non-diuretic substance with antihypertensive effect **diazoxide** (Eudemine), but it proved unsatisfactory for routine use as it often caused diabetes. Diazoxide suppresses insulin secretion by the pancreatic β-islet cells. It is useful in treating hypoglycæmia due to islet-cell tumours. It is an effective antihypertensive (which see). The diabetic effect of diazoxide is reversible on withdrawal. Excess effect is amenable to a sulphonylurea.

An antibiotic (streptozotocin) is a β-islet cell toxin; its effects may be permanent. It has been used to treat functioning metastases from islet-cell tumours.

Adrenocortical steroids are also diabetogenic.

Diuretics for diabetics. In general a non-thiazide should be chosen. Frusemide and ethacrynic acid have only rarely precipitated diabetes.

Potassium conserving diuretics are particularly liable to cause hyperkalæmia if there is any diabetic nephropathy.

Diabetic Ketoacidosis*

Severe ketoacidosis. The condition is discussed in detail in medical texts and only the more pharmacological aspects will be dealt with here. The patient urgently needs insulin and i.v. fluid and electrolytes.

Soluble insulin (never a depôt form) should be given i.v. and i.m. By restoring normal carbohydrate metabolism it reduces production of ketoacids. An unconscious patient can need 200 I.U. (half i.v., half i.m.) at once.

One hr after the first dose, in the absence of improvement, 20–40 I.U.

* The doses suggested here are based on recommendations of: HOCKADAY, T. D. R. (1972). *Brit. J. Hosp. Med.*, p. 183: (1971). *Prescr. J.* **11**, 61.

(i.v.) should be injected. If there has been improvement, doses are adjusted in the light of clinical expertise assisted by laboratory measurements of blood glucose, ketones, arterial pH, pCO_2, pO_2. A third dose is likely to be needed at 5 hrs and then 4 hrly.

Usual requirements are 160 I.U. in the first 4 hrs and 240 I.U. over the first 12 hrs (i.v. and i.m.).

Large i.v. doses are rapidly destroyed in the liver and excreted by the kidney. Small frequent doses are more effective than large infrequent doses. Continuous i.v. infusion is practicable and the dose can be comparatively low due to increased efficacy.

Intravenous fluid and electrolytes. Initially 0·9% NaCl is needed (500 ml in first 20 min followed by 2 l in 90 min, then 1 l in 90 min, and 1 l in 120 min).

Bicarbonate i.v. should only be used in severe acidosis and should not be begun till after the first litre of saline; it should be given slowly (50–100 mEq sodium bicarbonate at 50 mEq per 15 min) because it causes potassium to enter cells rapidly. It will be needed in the infusion.

Success in treatment of diabetic coma and its complications (hypokalæmia, aspiration of stomach contents, infection, shock) attends on close constant, informed supervision.

Mild diabetic ketosis. If the patient is fully conscious and there has been no nausea or vomiting for at least 12 hrs, parenteral therapy is unnecessary. It is reasonable to give small doses of insulin 3 to 6 hrly with fluids by mouth.

Hyperosmolar diabetic coma is characterised by severe dehydration, a very high blood sugar (> 600 mg/100 ml) and lack of ketosis and acidosis. Treatment is with hypotonic saline (not glucose) and small doses of insulin. Many patients who recover do not require long-term insulin.

SURGERY IN DIABETIC PATIENTS

Principles:—

1. Insulin needs increase with surgery.
2. Avoid ketosis.
3. Avoid hypoglycæmia.
4. High blood glucose level matters little over short periods.

The programme for control should be agreed between anæsthetist and physician *whenever the diabetic must undergo general anæsthesia or modify his diet*. There are many different techniques that can give satisfactory results.

For major surgery the patient should be admitted 3 days before operation so that the control of the diabetes can be adjusted according to the results of urine tests and blood sugar analyses. It is better not to give glucose solutions, or anything else, by mouth for 4 hrs before operation as to do so increases the risk of vomiting during or after the anæsthetic and it is specially important to avoid post-anæsthetic vomiting.

There are three main groups of patients:—

1. Diabetics controlled by diet

To compensate for bed rest, alter the diabetic diet to one containing 250 to 500 Calories less than the patient's usual diet. If glycosuria of over 0·75% persists or the blood sugar is high then treat as in paragraph 2.

BEFORE OPERATION: No glucose by mouth and no insulin.

DURING OPERATION: No i.v. glucose and no insulin. For operations lasting more than 1 hour treat as in paragraph 3.

AFTER OPERATION: Manage as for a normal patient, but test urine for sugar and ketones every 3 hrs in the day time. If there is persistent glycosuria or ketosis give soluble insulin 4 to 6-hrly to control it.

2. Diabetics on diet plus oral hypoglycæmic drug

SMALL OPERATIONS: Omit drug on day of operation.

BIG OPERATIONS: Patient should be transferred to insulin, see 3.

The insulin requirement cannot be accurately predicted, but, as a rough guide, a patient on short-acting drugs may be given 12 I.U. soluble insulin 8 hrly; however, much more may be needed and the dose is adjusted according to the urine test results.

If the patient is taking the longer-acting oral preparations (chlorpropamide, sustained-release phenformin), less insulin will be needed in the 24 hrs after stopping them.

3. Diabetics dependent on insulin

Reduce the diet by 250–500 Calories and give only soluble insulin from the night before the operation. If the operation is on the following morning the patient may need no further insulin until after it. But if he is liable to ketosis he may be given 25 g glucose i.v. plus a little less than half his usual dose of soluble insulin 1 hr before surgery. If operation is on the following afternoon he will need a light breakfast preceded by about half the usual dose of insulin.

If the operation is prolonged i.v. glucose may be given during it.

After surgery insulin dose should be decided in the knowledge of the blood glucose.

4. Emergency Operations

When a surgical emergency is complicated by diabetic ketosis an attempt should be made to control the ketosis before the operation. Management during the operation will be similar to that described in 3 above, except that more insulin may be needed.

In other cases small doses of soluble insulin are given 2–4 hrly keeping the blood glucose between 150 and 300 mg/100 ml.

5. Minor Operations

For example, simple dental extractions and manipulations (for multiple extractions or when there is infection the patient should be admitted to hospital). A suitable post-operative diet of appropriate Calorie and carbohydrate content must be arranged. Plan the operation for between 12 noon and 5 p.m. Omit the usual dose of long-acting insulin on the morning of the operation and substitute soluble insulin, one-quarter of the usual total

daily dose, before a light breakfast 6 hrs preceding the operation. Take a light evening meal after the operation and soluble insulin, 10 to 30 I.U. s.c. according to the urine sugar tests. Return to the normal routine the next day.

Patients taking oral agents can continue them normally unless there is likely to be vomiting, when they should be changed to insulin.

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Chapter 27

IRON, VITAMIN B_{12} (COBALAMIN), FOLIC ACID

IRON (*3–17*)

IRON, which was the metal symbolising strength in magical systems, used to be given to people suffering from weakness, and no doubt many were benefited, some psychologically (placebo reactors) and others because they had anæmia. The rational use of iron could not begin until both the presence of iron in the "colouring matter" of the blood and the "defective nature of the colouring matter" in anæmia were recognised. Early in the 19th century Dr. Pierre Blaud recognised many of the important principles of iron therapy. He said that iron should be given in inorganic form, that small doses should be given at first and increased gradually to relatively high doses. He introduced his Pills, containing ferrous carbonate and sulphate. Unfortunately a number of eminent physicians towards the end of the last century considered, for purely theoretical reasons, that inorganic iron could not be absorbed, so that many expensive and relatively ineffective organic iron preparations were developed. Modern experiments have shown that Dr. Blaud was right.

Some facts and figures (*4*)

total body iron 2–5 g (male 50 mg/kg: female 35 mg/kg).
hæmoglobin comprises about 2/3 of total iron.
stores comprise about 1/3 (ferritin and hæmosiderin) in marrow, spleen and muscles.
most of the iron released from the 3×10^6 erythrocytes destroyed every sec. is reconverted to hæmoglobin.
6·3 g of hæmoglobin (21 mg iron) is cycled/24 hrs.
diet (average Western) contains 10–15 mg iron/day.
normal man absorbs up to 10% dietary iron (i.e. 1–1·5 mg/day).
anæmic man absorbs about 30% of dietary iron.
iron is lost from body mainly by desquamation from the gut.
total iron loss/day 0·5–1 mg.
menstrual loss averages 13·5 mg/period; menstruating woman therefore liable to be in negative balance.
pregnant woman needs 2·4 mg iron/day extra for fetus.

Iron absorption takes place chiefly in the upper part of the small intestine, where the acid medium enhances solubility but also throughout the gut, allowing slow release preparations to be used. Most iron in food is ferric. Ferrous iron is more readily absorbed than ferric and a reducing agent, such as ascorbic acid, greatly increases the amount of ferrous form;

however, substantial doses (200 mg 8 hrly with the iron) are needed to produce a useful clinical effect and combined formulations often do not contain enough. Succinic acid also enhances absorption.

The actual process of absorption involves active transport across the mucosal cells, and iron becomes bound to a plasma globulin, transferrin.

But iron that is not required by the body is bound inside the mucosal cell to a protein (apoferritin) to form ferritin which remains where it is and is eventually lost into the gut lumen when the cell is desquamated (intestinal cells are desquamated at an enormous rate).

Thus the body exercises some control over iron absorption by what has been called "the ferritin curtain" (*4*). But when iron is given in large doses, this system fails to sufficiently restrict absorption and eventually hæmosiderosis may result.

Abnormalities of the small intestine may interfere with either the absorption of iron, as in the malabsorption syndromes and cœliac disease, or possibly with the conversion of iron into a soluble and reduced form. Partial gastrectomy often leads to reduced iron absorption.

The formation of insoluble iron salts (such as phosphate and phytate) in the alkaline medium of most of the small intestine probably explains why much of the iron taken by mouth is not absorbed, even in severe iron deficiency.

It used to be thought that many forms of iron could not be utilised. However, using a radio-active isotope of iron (^{59}Fe) it has now been shown that a varying proportion of the iron in almost all iron compounds, ranging from steel filings to hæmoglobin, can be converted into a soluble ferrous form and absorbed.

Interaction. Iron and tetracycline bind together in the gut and impairment of absorption of both occurs to a clinically important extent.

Iron deficiency. The symptoms and signs of iron deficiency are mostly due to anæmia, which is usually microcytic and hypochromic, and is characterised by a low mean corpuscular volume (M.C.V.) and low mean corpuscular hæmoglobin concentration (M.C.H.C.). The sore tongue, atrophic skin and nail changes found in iron deficiency anæmia are possibly due to a reduction in the amount of iron-containing enzymes which are necessary for renewal of epithelial cells.

Iron therapy is only indicated for the prevention or cure of iron deficiency. 25 mg of iron per day must be available to the bone marrow if an iron deficiency anæmia is to respond with a rise of 1% of hæmoglobin (0·15 g Hb) per day.

When oral therapy is used it is reasonable to assume that about 30% of the iron will be absorbed and to give about 180 mg of elemental iron daily. However, such calculations are not necessary except when iron is given by injection.

Total i.v. iron required (mg)

4·4 × body wt in Kg × Hb deficit in g/100 ml blood. This formula allows about 0·5 g to replenish stores.

With iron dextran *i.v.* all the iron is available, but with iron *i.m.* it is not (*dextran*, due to binding in muscle: *sorbitol* due to renal excretion) 30 mg i.v. ≡ 40 mg i.m.; and this is taken into account when calculating an i.m. course.

In pregnancy 0·5–1 g may be added for fetal needs. Injectable preparations, Iron Dextran, and Iron Sorbitol contain 50 mg Fe/ml.

Iron stores are less easily restored by oral therapy than by injections, and oral therapy should be continued for several months after the hæmoglobin concentration has returned to normal.

It is illogical to give iron in hæmolytic anæmias unless there is also hæmoglobinuria, for the iron from the lysed cells remains in the body, and hæmosiderosis may ultimately occur.

Iron therapy is needed:—

1. *In iron deficiency due to chronic blood loss.*

2. *In pregnancy*. The fetus takes up to 600 mg of iron from the mother even if she is iron deficient, but the iron stores of a baby born to an iron deficient mother may be abnormally low. Dietary iron is seldom adequate and iron should be given to all pregnant women who should be particularly *warned not to let children get at the tablets*, which are usually attractively coloured and needlessly sugar-coated.

3. *In various abnormalities of the gastro-intestinal tract* where the proportion of dietary iron absorbed may be reduced (e.g. in malabsorption syndromes generally).

4. *In premature babies*, since they are born with low iron stores, and in babies weaned late. There is very little iron in human milk and even less in cow's milk.

5. *During the treatment of severe pernicious anæmia* with cyanocobalamin, as the iron stores occasionally become exhausted by the sudden increase in blood formation.

Oral iron preparations. There is an enormous variety of official and proprietary iron preparations. For each mg of elemental iron taken by mouth, ferrous sulphate is as effective and no more toxic than more expensive preparations. Solutions of iron salts are seldom used as they stain the teeth. It is particularly important to avoid initial overdosage with iron as the resulting symptoms may cause the patient to abandon therapy. A small dose is given at first and increased after a few days. If given on a full stomach iron causes less gastro-intestinal toxicity, but less is absorbed than if it is given between meals. Commonly used preparations, given in divided doses, include:—

Ferrous Sulphate Tabs, *B.P.* 200 to 600 mg daily. Each 200 mg tablet contains 60 mg of elemental iron.

Ferrous Gluconate Tabs, *B.P.* 300 to 1,200 mg daily. Each 300 mg tablet contains 35 mg of elemental iron.

Ferrous Fumarate Tabs, *B.P.* 200 to 600 mg daily. Each 200 mg tablet contains 65 mg of elemental iron.

Choice of oral iron preparation. Oral iron is widely used, both for therapy and for prophylaxis (pregnancy) of anæmia in people who are feeling little, if at all, ill. Because of this, the occurrence of gastro-intestinal upset is particularly important as it is liable to cause the patient to give up taking iron; in one study 32% of pregnant women were not taking the iron prescribed (*10*).

The evidence as to which preparation provides best iron absorption with least toxicity is conflicting. Unfortunately, many of the studies on which claims for rival preparations are made, are found, on close inspection, to be inadequate. There is little doubt that valid comparisons can only be made with doses of preparations containing equal amounts of elemental iron *and* under strict double-blind conditions. It has been shown that gastro-intestinal upsets can be greatly influenced by expectation.

The widespread use of iron preparations has stimulated many attempts to find formulations that may provide better therapy. This is a good thing.

Unfortunately, it has also stimulated some to make claims for their products that go beyond the evidence e.g. ignoring evidence against a preparation and quoting only evidence in its favour, regardless of the scientific quality of such evidence.

All the available iron preparations are not listed here, partly because the effort to find and classify them is just not worth making; there are more than 50 marketed in Britain.

The following course is suggested: Start a patient on ferrous sulphate. If this seems to cause gastro-intestinal upset, try ferrous gluconate, succinate or fumarate. Addition of adequate amounts of ascorbic or succinic acid increases the amount of iron absorbed and so may allow smaller amounts of iron to be given with a lower incidence of gastro-intestinal upset. If simple preparations are unsuccessful, and this is unlikely, then the pharmaceutically sophisticated, and expensive preparations may be tried, e.g. those that release iron slowly, and only after passing the pylorus from resins or plastic matrices (Slow-Fe, Sytron, Feospan etc).

The following mixtures are preferred to tablets by an occasional patient; some are available in less concentrated, flavoured solutions for infants.

Ferrous Sulphate Mixture, Pædiatric, *B.N.F.* 5–10 ml daily. 15 ml contains 55 mg of elemental iron.

Ferric Ammonium Citrate Mixture, *B.P.C.*, is prone to stain the teeth. 10 ml contains 400 mg of elemental iron. The dose is 10 ml daily; this large amount of iron is necessary because it is in the ferric form. It would seem particularly desirable to give ascorbic acid with this preparation, although it has been used without for many years.

Colloidal Ferric Hydroxide (Colliron) can be used. It is said to be relatively free from gastric side effects. Infants and young children are given 5 to 15 drops two or three times a day.

There are innumerable other iron preparations including the succinate, the glycine sulphate and chelated forms.

Slow release and **chelated** forms of iron can give fewer gut adverse effects and are also safer if consumed by a child.

Iron therapy blackens the fæces but does not generally interfere with tests for occult blood (commonly needed in investigation of anæmia), though it may give a false positive with the guaiac test.

Duration of therapy: in general a full dose (see above) should be given until the Hb level is normal and then continued at reduced dose for 4 months to replenish stores. Prolonged heavy dose can cause hæmosiderosis.

Parenteral iron administration may be required if iron cannot be absorbed from the intestine, if a certain response is essential in a severe iron deficiency anæmia, as in late pregnancy, or if, as sometimes happens for no known reason, oral iron therapy fails, or the patient cannot be relied on to take it.

The speed of response is not quicker than that with full doses of oral iron reliably taken and normally absorbed, for these provide as much iron as an active marrow can use. Response is substantial in 14 days.

The approximate total requirement can be calculated from the hæmoglobin level (see above).

The ionised salts of iron are extremely powerful protein precipitants which cannot be used parenterally and unionised iron complexes have been developed.

Intramuscular iron; Iron Sorbitol Inj., B.N.F. is satisfactory, though some prefer Iron Dextran Inj. (see below).

Intravenous iron: Iron Dextran is used (see below). There is no reason to give intermittent i.v. injections, so it is given by **total dose infusion** (enough iron to correct anæmia and to replenish stores on a single occasion). The technique has obvious advantages: it avoids the inconvenience and unpleasantness of repeated i.m. injections and of incomplete treatment by patient failure. The disadvantages are that the patient must arrange to attend hospital for several hours, that close supervision is necessary and that ill-effects, sometimes serious (collapse) and death, rarely, can occur. It should only be used where it is essential to do so.

Oral iron therapy should be stopped 2 days before injections begin; not only is it unnecessary, but it may promote adverse reactions to the injections by saturating the plasma protein (transferrin) binding sites so that the injection gives higher free iron plasma concentration than is safe. This is more likely to occur with iron sorbitol or iron dextrin than with iron dextran whose large molecule does not bind to transferrin.

Iron Sorbitol Inj., B.N.F. (Jectofer) (1 ml = 50 mg Fe) is an iron-sorbitol citric-acid complex of low molecular weight that is rapidly absorbed into the

blood from the site of injection (unlike iron-dextran). About 30% of a dose is excreted by the kidney in 24 hrs and the urine may turn black transiently at the time of peak iron excretion. It may also, though normal when passed, turn black on standing for some hours, probably due to formation of iron sulphide by bacterial action.

Iron sorbitol has been found to increase the urinary leucocyte excretion rate in patients with urinary tract infections or non-infective renal disease, and it should probably be avoided in such patients in whom iron dextran i.m. may be preferred.

Iron sorbitol is bound to the plasma globulin, transferrin, and is stored in the marrow and liver. It is not substantially taken up in the reticulo-endothelial system. Excess unbound iron is excreted in the urine. Iron sorbitol is unsuitable for total dose infusion, probably because, after rapid saturation of transferrin, there would be very high free (toxic) iron levels in the blood (compare with iron dextran below).

Iron sorbitol is given by deep i.m. injection which can be painful. It stains the skin, but this can be minimised by inserting the needle through the skin and then moving the skin and subcutaneous tissue laterally before entering the muscle so that the needle track becomes angulated when the needle is withdrawn. The dose is up to 1·5 mg/kg/day until the total amount of iron required has been given. The injections are usually painful and general reactions (headache, dizziness, disorientation, nausea, vomiting) occur and sometimes a metallic taste, up to 2 hrs after injection.

Iron Dextran Inj., B.P. (Imferon) (1 ml = 50 mg Fe) given i.m., has been widely used as the least toxic preparation of iron for parenteral use. After iron dextran had been in use for some years it was found that huge doses repeatedly injected into the same site in rats caused local sarcoma but there is no evidence that this occurs in man.

Iron dextran has a high molecular weight and is absorbed slowly from the injection site into the lymphatics. It is possible that the prolonged local residual concentration is relevant to carcinogenesis. Iron sorbitol injection, however, has a low molecular weight and is rapidly absorbed into the blood, and is not carcinogenic in animals, so that, for i.m. use, it may be preferable. However, iron sorbitol probably causes more immediate reactions than iron dextran. The immediate ill-effects of iron dextran i.m. are similar in kind to those of iron sorbitol.

Iron dextran is not bound to transferrin and is stored in the reticulo-endothelial system (unlike iron sorbitol, see above) and this may be why the total requirements to correct anæmia and to replenish stores can be given in a single slow infusion.

Iron Dextrin Inj., (Astrafer) is an alternative injectable form.

Folic acid deficiency may be unmasked by effective iron therapy. Where there is a deficiency of both iron and folic acid, the deficiency of the latter may not be obvious because hæmopoiesis is held back by lack of iron. If iron is supplied there will be an increased formation of red cells and the folic acid deficiency will be uncovered. This is liable to happen in pregnancy and so folic acid is commonly given to all pregnant patients with anæmia (see below); it also occurs in malabsorption syndromes.

Iron toxicity. Some unwanted effects of therapeutic doses are mentioned above.

Ordinary doses of iron preparations sometimes, and slight overdoses very frequently, cause mild gastro-intestinal disturbances. These are minimised if the initial dose is small and then cautiously increased. Nausea, abdominal pain, and either constipation or diarrhœa, may occur. Gossip in clinics leads expectant mothers to anticipate being upset by iron tablets, and one blind controlled trial has shown that nausea, heartburn, flushes, constipation and diarrhœa were just as common in the control group receiving dummy tablets as in the group taking adequate amounts of iron.

High doses of iron salts by mouth can cause severe gastro-intestinal irritation and even necrosis of the mucous membrane. Large amounts are absorbed and cardiovascular collapse occurs. Autopsy has shown severe damage to brain and liver. Tablets of most iron preparations are attractive to children because they are senselessly highly coloured and sugar-coated. Death may occur if an infant swallows a quantity of these "sweets" whose danger is not sufficiently recognised. Slow release forms are safer.

Cautionary tale: ". . ..a girl aged 19 months was found vomiting after taking 15 or 16 ferrous sulphate tablets. She was taken to hospital and there given salt and water and she vomited again. The mother was told that there were no beds available and she was sent to another hospital. Here she was told that the tablets were not poisonous and would do the child no harm. The child was retching now but not vomiting and the mother was told to take her home and give her plenty of milk to drink. The mother was not satisfied and took the child to another doctor on the way home. He told her to give the child orange juice to drink and she would be all right. The mother then took the child home, put her in her cot, and went to make some orange juice. When she returned the child was dead . . . about four hours after the child had taken the tablets."*

The clinical course of a typical case of acute iron poisoning has four phases.†

First, ½ to 1 hr after ingestion: abdominal pain, vomiting, bloody diarrhœa, acidosis and cardiovascular collapse, with coma and death in 4 to 6 hrs in 20% of cases.

Second, in 80% of cases, a period of improvement lasting 8 to 16 hrs which may be permanent or which may pass into—

Third, cardiovascular collapse, convulsions, coma and sometimes death about 24 hrs after ingestion.

Fourth, 1 to 2 months later, gastro-intestinal obstruction from scarring.

Treatment of acute iron poisoning is urgent and immediate efforts

* SPENCER, I. O. B. (1951). *Brit. med. J.*, **2**, 1112.

† ALDRICH, R. A. (1958). In iron in Clinical Medicine. Eds. Wallerstein, R. O., and Mettier, S. R. Univ. of California Press.

to chelate iron in the blood and in the intestine must be made. Raw egg and milk help to bind iron until a chelating agent is available.

The first step should be to give desferrioxamine 1–2 g i.m. (and to repeat it 12 hrly in severe cases) (see below).

Only after this should gastric lavage or emesis (which see) be performed. If lavage is used, the solution should be 1% sodium bicarbonate to render the iron salts less soluble. After emptying the stomach, 5 to 10 g desferrioxamine in 100 ml water should be put down the tube or swallowed.

After this, an i.v. infusion should be set up both to correct abnormalities of electrolyte and water balance. Desferrioxamine may also be given i.v. at up to 15 mg/kg/hr with a maximum dose of 80 mg/kg in 24 hrs.

Where anuria occurs exchange transfusion should be considered, for the toxicity of large amounts of ferrioxamine is unknown.

Desferrioxamine (Desferal) is an iron-chelating agent (see *chelating agents*). During a systematic investigation of Actinomycete metabolites, iron-containing substances (sideramines) were discovered; they probably play a part in incorporating iron into porphyrin systems. One of these substances was ferrioxamine. The iron in this can be removed chemically, leaving desferrioxamine. This provides an example of the drug industry at its best.

When desferrioxamine comes into contact with ferric iron, its straight-chain molecule twines around it and forms a non-toxic complex of great stability (ferrioxamine) which is excreted in the urine. It has a negligible affinity for other metals and seems to have no important unwanted effects.

Desferrioxamine has been shown to be effective in the therapy of acute iron poisoning and in the treatment and perhaps the diagnosis of diseases associated with chronic iron accumulation. An eye ointment is available for ocular siderosis.

Diethylene triamine pentacetate is an alternative iron chelating agent.

Chronic iron overload. The body is unable to excrete any excess of iron so that, if there is uncontrolled iron absorption, it accumulates in the body. Grossly excessive parenteral iron therapy, or a hundred or more blood transfusions, can lead to hæmosiderosis. Oral iron therapy has also been reported to cause it over many years.

In treatment of chronic iron overload (e.g. hæmochromatosis, hæmolytic anæmias, thalassæmia) desferrioxamine is an adjuvant, and venesection remains the most effective way of removing iron. However, sometimes there is anæmia and venesection is then unsuitable.

Desferrioxamine, by daily injection, can remove about 20 mg iron/day, but this may not be maintained for long. A single venesection of 500 ml blood, in the absence of anæmia, removes 200 mg iron and can be repeated weekly. But induction of mild hæmolysis (by phenylhydrazine) can render more iron available for chelation.

Unfortunately, desferrioxamine given orally only chelates inorganic iron. It does not usefully reduce iron absorption from the ordinary diet where it is present chiefly in meat (hæmoglobin and muscle).

Diagnostic use of desferrioxamine in iron storage disease is specialised and still experimental. The amount of iron excreted in the urine after i.m. injection is measured.

Deficiencies of other metals

Copper, cobalt, molybdenum and manganese deficiencies have all been postulated as rare causes of otherwise unexplained anæmias. The evidence is seldom convincing and they have no place in therapeutics at present. Goitre and nephritis have occasionally followed the use of cobalt in anæmia.

EXTRINSIC AND INTRINSIC FACTORS IN PERNICIOUS ANÆMIA

In 1925 Castle performed classical experiments demonstrating that two factors were required to cure pernicious anæmia. He showed that beef muscle and normal human gastric juice were ineffective when given separately by mouth, but that when they were given *together* a good reticulocyte response was obtained. "Consequently it was assumed that some unknown but essential interaction between beef muscle as an extrinsic (food) factor and normal human gastric juice as an intrinsic factor appeared to be required for the restoration of normal hæmatopoiesis in the patient with pernicious anæmia" (*1*). During the succeeding 20 years many successful attempts were made to isolate both the extrinsic and intrinsic factors from various sources. Soon after crystalline cyanocobalamin (vitamin B_{12}) was isolated in 1948 it was generally accepted to be the extrinsic factor. Intrinsic factor (secreted by the gastric mucosa) is a glycoprotein and relatively crude preparations from animal stomachs are used in the oral therapy of pernicious anæmia. Intrinsic factor acts solely as a vehicle for carrying the important extrinsic factor into the body, but if large oral doses of cobalamins are given they are absorbed independently of intrinsic factor.

VITAMIN B_{12} (THE COBALAMINS)

The cellular coenzyme B_{12} is formed in the body from cobalamins (different forms of vitamin B_{12}). Those in clinical use are cyanocobalamin and hydroxocobalamin.

Pure crystalline cyanocobalamin was prepared from liver simultaneously and independently in the U.S.A. and in England in 1948, 22 years after Minot and Murphy first demonstrated the effectiveness of oral liver therapy in pernicious anæmia. The delay was mainly due to the great difficulties of assay of the vitamin. Assay of different fractions is obviously essential during any purification procedure, and for many years the production of a reticulocyte response in patients with pernicious anæmia was the only method. Research has been greatly helped by the discovery that some micro-organisms (Lactobacillus casei, Euglena gracilis) require vitamin B_{12} as a growth factor, and this has been used to develop a relatively simple microbiological assay which will be interfered with if the patient is taking

antimicrobials. Vitamin B_{12}, as prepared, was soon shown to contain cobalt and a cyanide radicle and so was given the chemical name cyanocobalamin, which is now the official name. Its structural formula has been elucidated by crystallographic analysis. Cyanocobalamin is now made from cultures of streptomyces.

Function. A deficiency of vitamin B_{12} in the body leads to:—

1. A megaloblastic anæmia (Addisonian, or pernicious, anæmia).
2. Degeneration of the brain, spinal cord and peripheral nerves (subacute combined degeneration): symptoms may be psychiatric or physical.
3. Abnormalities of epithelial tissue, particularly of the alimentary tract (e.g. sore tongue and malabsorption).

The mechanism of changes 2 and 3 is not known, but it seems that synthesis of desoxyribosenucleic acid (DNA) is interfered with at a later stage than in deficiency of folic acid. If cells are to divide the amount of DNA present has to be doubled and it is possible that megaloblasts may be cells unable to synthesise enough DNA for cell division to proceed. Prevention of sufficiently rapid cell division could not account for 2 above, of course. For 1 above, see folic acid.

Requirements of cyanocobalamin are about 1 mcg daily. Absorption takes place mainly in the ileum. After absorption it is carried in plasma bound to proteins (transcorrins). Excretion is in the bile (there is enterohepatic circulation) and via the kidney. Several years' supply are normally stored throughout the body; in the liver the half-life of cyanocobalamin is about a year. Most animals cannot synthesise cobalamin and so are directly or indirectly dependent upon micro-organisms for it. Man gets most of his cobalamin from meat; organisms in the human colon synthesise it but it is not absorbed from this part of the intestine.

Cobalamin does not occur in plants (except in legumes in which it is made by bacteria in root nodules) and **dietary deficiency** occurs amongst people who have not enough money to buy meat as well as amongst the Vegans, who are a sect of particularly uncompromising vegetarians.* A rare form of dietary deficiency is due to Scandinavian fish tapeworms which live in the gut and take up all the cobalamin before the host has a chance to absorb it.

The fate of cobalamin has been studied by labelling it with radioactive cobalt.

Indications for vit B_{12}

Indications for administration are the prevention and cure of conditions due to its deficiency, which commonly presents as megaloblastic anæmia, though psychiatric disorder (without anæmia) can occur.

In **pernicious** (**Addisonian**) **anæmia** the gastric mucosa is unable to produce intrinsic factor and so vit B_{12} deficiency occurs. A histamine-fast

* SMITH, A. D. M. (1962). *Brit. med. J.*, **1**, 1655.

achlorhydria is invariably present. Despite its name, the prognosis of a patient with uncomplicated pernicious anæmia, properly treated, is little different from that of the rest of the population. The neurological complications, particularly spasticity, are often permanent, although there may be considerable improvement under treatment. Total removal of the stomach, or atrophy of the mucous membrane in a post-gastrectomy remnant may, after several years, lead to a similar anæmia.

Malabsorption syndromes. In cœliac disease and idiopathic steatorrhœa vitamin B_{12} and folic acid deficiency is common although megaloblastic anæmia occurs only relatively late.

Deprivation of vitamin B_{12} by abnormal bowel flora occurs in tropical sprue, multiple jejunal diverticula, bowel fistulæ and blind-loop syndrome. This can be remedied by a broad-spectrum antibiotic, e.g. tetracycline.

Cyanocobalamin has been tried empirically, sometimes in enormous doses, without striking success, in a variety of **neurological conditions.** In some types of peripheral neuritis, especially the diabetic, it has been thought to give benefit, but controlled trials are lacking. Hydroxocobalamin is worth giving in tobacco amblyopia where it is possible there is an element of cyanide intoxication from the tobacco, and cyanocobalamin may be formed.

Diagnostic use. Large doses of cyanocobalamin may induce an incomplete response in pure folic acid deficiency, but response to a tiny dose (2 to 4 mcg) is diagnostic of cobalamin deficiency.

In addition, the *Schilling test* of vit B_{12} absorption may be used. A small *oral* dose of radioactive vit B_{12} is given (plus a large flushing *injected* dose of non-radioactive vit B_{12}) and excretion of radioactivity in the urine is measured. In pernicious anæmia absorption and therefore urinary excretion is negligible. If the test is repeated plus oral intrinsic factor, and the patient has pernicious anæmia, absorption will occur and urinary excretion of radioactivity will rise. The test remains positive even if the patient has been given vit B_{12} (unlike the bone marrow).

Contraindication: *undiagnosed anæmia*; therapy of pernicious anæmia must be both adequate and life-long, so that accurate diagnosis is essential. Even a single dose interferes with diagnosis for weeks. Inclusion of small amounts of cyanocobalamin in oral tonics is probably harmless but implies an irresponsible attitude in both promoter and prescriber. It is a bad thing that a patient's health should ever depend on his not absorbing his physician's therapy.

Preparations and dosage: hydroxocobalamin (Neo-Cytamen) is bound to plasma protein to a greater extent than **cyanocobalamin,** with the result that there is less free to be excreted in the urine after an injection so that rather lower doses at longer intervals are adequate. This is why it is preferred to cyanocobalamin.

The initial dose in cobalamin deficiency anæmias, including uncomplicated pernicious anæmia, is hydroxocobalamin, 100 mcg, i.m. every 3 days for 7–10 doses (single large doses are mostly lost in the urine) to

induce remission and to replenish stores. Maintenance may be 1,000 mcg 2–4 monthly, but some prefer higher doses for increased assurance. Higher doses should probably be used in renal and hepatic disease (*21*) (due to defects in conversion to the active coenzyme and excretion).

The stimulation of hæmoglobin synthesis often depletes the *iron* and *folate* stores and supplements of these are needed. **Hypokalaemia** may occur at the height of the erythrocyte response in severe cases. It is attributed to uptake of K by the rapidly increasing erythrocyte mass. Oral K should be given.

Failure to respond implies inaccurate diagnosis, or the presence of other disease such as carcinoma, hypothyroidism or chronic infection. If neurological complications have occurred the dosage can be doubled, though this probably does no good, but some would give all cases milligram doses initially as hydroxocobalamin is non-toxic.

Because of increased urinary excretion where high blood levels are achieved, inadequate response should be treated by increased frequency of injections as well as increased amount.

Depôt preparations have been shown to be capable of controlling pernicious anæmia with less frequent injections, but are not yet judged completely reliable. Hæmoglobin estimations are necessary at least every 6 months to check that enough is being given. Hydroxocobalamin is effective when given as a snuff, or in an aerosol, in doses not much larger than by injection, though these preparations are potentially less reliable than injection.

Ill-effects do not occur, but its use as a "tonic" is an abuse of a powerful remedy for it may make the diagnosis of pernicious anæmia almost impossible, which is a matter of great importance in a disease requiring life-long therapy, and prone to serious neurological complications.

Oral treatment of pernicious anæmia is only used where injections are refused or are not practicable. It can be done with enormous doses of cyanocobalamin, for then some is absorbed by diffusion without intervention of intrinsic factor, but this is unreliable as well as wasteful. More satisfactory are combinations of vitamin B_{12} with animal stomach intrinsic factor preparations, e.g. Biopar Forte, although patients tend to relapse, probably because they develop an immunological reaction to the animal ingredients; and a B_{12}-peptide complex.

It is doubtful whether several tablets daily is preferable to one injection at 1–4 monthly intervals.

Liver extracts contain folic acid and cyanocobalamin. The introduction of cobalamins has made them obsolete. They were the mainstay of therapy for pernicious anæmia for about 20 years.

In pernicious anæmia folic acid is incomplete therapy and must not be used. Although it will improve the anæmia it allows progression of subacute combined degeneration of the nervous system. A patient with pernicious anæmia who has been given folic acid is in a dangerous situation.

There are oral preparations containing a miscellany of substances

necessary for blood formation, including iron, folic acid, cyanocobalamin and other vitamins, liver, stomach extracts, etc, generally in doses insufficient to cure anæmias, but sufficient to interfere with diagnosis.

They are promoted to preserve the aged in health, for anæmia and as tonics.

Both their indiscriminate promotion by commercial interests and their use by physicians in undiagnosed cases shows a disregard for patients' interests that is inconsiderate at best and callous at worst.

As well as involving needless expense, they can have catastrophic effects, as the following report shows:—

An anæmic patient was given a proprietary preparation of iron, which was later found also to contain thiamine, extract of raw liver and folic acid. " . . . her general condition improved greatly. Her appetite returned to normal and her weight increased but the stiffness of her legs began to worsen rapidly . . . she fell and was admitted to hospital for treatment of an infected hæmatoma. After 10 days in bed she was found to be unable to rise to walk . . . the patient was found to have a spastic paraplegia with great muscular weakness, bilateral extensor plantar responses and complete loss of posterior column sensation in both legs. . . Histamine-fast achlorhydria was demonstrated."* There was a moderate macrocytic anæmia. A diagnosis of subacute combined degeneration of the cord was made and the patient fortunately responded well to vitamin B_{12}. But this mishap need never have occurred.

FOLIC ACID (PTEROYLGLUTAMIC ACID)

Folic acid was so named because it was discovered as a bacterial growth factor present in spinach leaves (folium = a leaf). It is one of the B group of vitamins and was soon shown to be the same substance as that present in yeast and liver which cured a nutritional macrocytic anæmia in Indian women, a similar experimental anæmia in monkeys, an anæmia and growth failure in chicks, and to be a growth factor for a variety of micro-organisms.

Functions. Folic acid is itself inactive. It is converted into the biologically active coenzyme tetrahydrofolic acid which is important in the biosynthesis of amino and nucleic acids, and therefore in cell division. The formyl derivative of tetrahydrofolic acid is folinic acid or citrovorum factor (Leucovorin) and this can be used where the body fails to effect the conversion of folic acid (see folic acid antagonists).

Ascorbic acid protects the active tetrahydrofolic acid from oxidation, and the anæmia of scurvy, although usually normoblastic may be megaloblastic due to deficiency of tetrahydrofolic acid.

Deficiency of folic acid leads to a megaloblastic anæmia probably because it is necessary for the production of the purines and pyrimidines which are essential precursors of desoxyribosenucleic acid (DNA). The megaloblastic marrow of cobalamin deficiency is due to interference with

* LOWTHER, C. P. (1954). *Brit. med. J.*, **1**, 564.

folic acid utilisation since the morphological changes of such deficiency can be reversed by folic acid. However it is vital to realise that folic acid is not proper treatment for pernicious anæmia. Folic acid antagonists (which see) are sometimes used in treatment of acute leukæmias.

Occurrence and requirements. Folic acid is widely distributed, especially in green vegetables, yeast and liver. It is present in food mostly in a conjugated form (polyglutamates). Many body tissues contain an enzyme which releases the folic acid from the conjugates. Daily requirement is about 50 mcg and a diet containing 200 mcg polyglutamates will provide this. It is synthesised by bacteria in the large intestine, but as the sole site of absorption is the jejunum, this is irrelevant. Body stores are adequate for several months only.

Indications are the prevention and cure of the megaloblastic anæmia due to deficiency of folic acid:—

Dietary deficiency. There is just enough folic acid in an ordinary Western diet for normal people, but its deficiency plays some part in the complex nutritional macrocytic anæmias which are common in the economically underdeveloped areas of the world. A rare megaloblastic anæmia of infancy has been caused by dietary deficiency of folic acid which was absent from certain brands of dried milk.

In malabsorption syndromes, particularly steatorrhœa and sprue, poor absorption of folic acid from the small intestine often leads to a megaloblastic anæmia.

In pregnancy, folate requirement is increased to about 400 mcg/day and mild deficiency is common, with a minority of cases developing severe megaloblastic anæmia. For this reason, many now consider that routine folic acid administration should be added to the routine iron administration. The dose needed is small, about 100 mcg a day. This is insufficient to alter the blood picture of pernicious anæmia and so there is no risk of masking that disease, which is also very rare in women of reproductive age and is probably incompatible with a successful pregnancy. A large number of preparations of iron with folic acid from 100 mcg to 5 mg are available, e.g. Ferfolic, Fefol, Pregamal, etc. They are only suitable for this purpose. Larger doses may be used in therapy of the anæmia; it will remit spontaneously some weeks after delivery. Vigorous iron therapy in pregnancy may unmask a folic acid deficiency.

In chronic hæmolytic states folic acid requirement is increased.

Anticonvulsant drugs, particularly phenytoin, primidone and phenobarbitone, occasionally cause a macrocytic anæmia which responds to folic acid. This may be due to enzyme induction by the anticonvulsants increasing need for folate to perform hydroxylations (see under *epilepsy*) but other factors may be involved. Some **antimalarials** (e.g. pyrimethamine) may interfere with conversion of folates to the active tetrahydrofolic acid, causing macrocytic anæmia, as may nitrofurantoin.

Diagnostic use is similar to that of cyanocobalamin.

Preparations and dosage. Synthetic folic acid (5 mg) is taken orally;

10 to 30 mg daily are usually given. The sodium salt is available for injection and it is reasonable to start treatment of a severe deficiency with it. After the first few doses oral supplements are adequate even in the malabsorption syndromes. There is no advantage in giving folinic instead of folic acid, except in the treatment of the toxic effects of folic acid antagonists in order to by-pass the site of metabolic block.

For dose in pregnancy, see above.

Adverse reactions: allergy occurs rarely.

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Chapter 28

VITAMINS, CALCIUM, BONE

VITAMINS are substances which are essential for normal metabolism and which must be chiefly supplied in the diet.

Man cannot synthesise any vitamins in his body except some vitamin D in the skin, and nicotinamide from tryptophan. Lack of a particular vitamin may lead to a specific deficiency syndrome. This may be primary (inadequate diet), or secondary, due to failure of absorption (intestinal abnormality or chronic diarrhœa), or to increased metabolic need (growth, pregnancy, lactation, thyrotoxicosis, fever).

Vitamin deficiences are commonly multiple and complex clinical pictures occur. There are numerous multivitamin preparations, e.g. Vitamin Caps, B.P.C. (A, B, C, D) to provide therapy. Detailed clinical descriptions may be found in any textbook of medicine.

It has often been suggested, but never proved, that subclinical vitamin deficiences are a cause of much chronic ill-health and liability to infections. This idea has led to enormous consumption of vitamin preparations which probably have no more than placebo value. Fortunately most of the vitamins are comparatively non-toxic, but prolonged administration of vitamins A and D can have serious ill-effects.

Vitamins fall into two groups:—

The water-soluble vitamins: the B group and C.
The fat-soluble vitamins: A, D, K and E.

VITAMIN A

Vit A exists in a variety of forms: carotene = provitamin A: retinol = vit A_1: 3-dehydroretinol = vit A_2. Deficiency leads to defective vision in dim light and to metaplasia and hyperkeratosis of epithelia throughout the body, which is especially serious on the cornea, leading to xerophthalmia and keratomalacia.

Functions. Vit A forms part of the light-sensitive protein, rhodopsin, present in the rods of the retina. The part played by this vitamin in the maintenance of epithelia is unknown. Since epithelia damaged by vitamin A deficiency are vulnerable to infection the reputation of vitamin A to be the "anti-infectious" vitamin has some basis of fact, but there is no evidence that it protects normal people against infection.

Sources. Carotene is converted into vitamin A in the intestinal wall. Green vegetables and carrots are satisfactory diet sources, and so are milk, cheese, butter, eggs and liver, Margarine has vitamin A added to it. Fish liver oils are recommended for babies on account of their vitamin D content, but they are also very rich sources of vitamin A.

Requirements are about 3,000 International Units a day for an adult, increased to 4,000 I.U. during pregnancy and lactation. A normal Western European diet contains adequate amounts of vitamin A or carotene, but deficiencies are relatively common in Asia. Vitamin A is stored in the liver, which, in normal individuals, contains enough to last for 1 to 2 years.

Indications for vitamin A therapy are the prevention and cure of deficiency. There is no convincing evidence that it prevents sunburn as is claimed. A derivative retinoic acid, used topically may be of benefit in some diseases characterised by epidermal hyperplasia (e.g. psoriasis). Vitamin A is fat-souble and so is poorly absorbed in steatorrhœa and similar conditions. Once a deficiency has been diagnosed, 30,000 units of vitamin A should be given daily by mouth, and should be continued until the patient recovers. Capsules of the pure vitamin and of fish-liver oil are available, e.g. Halibut-liver Oil Caps. B.P. (about 5,000 I.U. per capsule).

Toxic effects occur if very large amounts are taken (in children 50,000 to 500,000 I.U. daily). A diagnostic sign of chronic poisoning is the presence of painful tender swellings over the bones. Anorexia, skin lesions, hepatosplenomegaly and general malaise also occur. Vitamin A is very cumulative and effects take weeks to wear off. Most cases of vitamin A poisoning have been due to mothers administering large amounts of fish-liver oils to their children in the belief that it was good for them, but travellers have been made ill by eating the livers of arctic carnivores.

"Eskimos never eat polar-bear liver, knowing it to be toxic, and husky dogs, with instinctive wisdom, also avoid it. . . . Those who pooh-pooh the Eskimos' fears or the husky dogs' instincts and are tempted to enjoy a man's portion of polar-bear liver—appetites get sharp near the North Pole—will consume anything up to 10,000,000 I.U. of vitamin A. This is too much of a good thing, and the diner will probably soon find himself drowsy, then overcome by headache and vomiting, and finally losing the outer layer of his skin. These are, it is believed, signs of acute poisoning with Vitamin A" (*6*).

THE VITAMIN B COMPLEX

The name "Vitamin B" was originally given to a dietary factor which was necessary for the growth of rats. It was soon shown not to be a single compound. A number of widely differing substances are now, for convenience, included in the vitamin B complex:—

Thiamine (B_1), *riboflavine* (B_2), *nicotinamide* (B_7) and *pyridoxine* (B_6) are discussed here; for *folic acid* and *cyanocobalamin* (B_{12}) see previous chapter.

Pantothenic acid, *inositol*, *biotin*, and *para-aminobenzoic acid* are not known to be of practical clinical importance as recognisable deficiency states do not occur in man. *Choline* is usually included in the B group of vitamins, although it can be synthesised in the body if sufficient methyl groups are available (e.g. from methionine). Choline deficiency in animals

leads to accumulation of fat in the liver, and it has been given to patients with Laënnec's hepatic cirrhosis, but a good diet contains enough.

The B group vitamins are all soluble in water and many of them are concerned in essential oxidation-reduction reactions; yeast and liver are rich sources of most and they are synthesised to a variable extent by bacteria normally present in the colon.

Secondary deficiency may occur as a result of inadequate absorption due to diarrhœa, including that due to antimicrobials that alter colonic flora. It may also be due to increased need (thyrotoxicosis, fever) or to defective utilisation (hepatic disease).

Patients maintained by intravenous feeding for more than 2 days need the B vitamins. There are a large number of proprietary preparations of the B group vitamins as well as those in the B.N.F.

Vit B Cpd. Tabs, B.P.C: for prophylaxis. Thiamine, 1 mg; riboflavine, 1 mg; nicotinamide, 15 mg.

Dose: one or two tablets daily.

Vit B Cpd Tabs Strong, B.P.C: for treatment of deficiency. Thiamine, 5 mg; riboflavin, 2 mg; nicotinamide, 20 mg; pyridoxine, 2 mg.

Dose: one or two tablets, thrice daily.

Thiamine (Vit B_1)

Gross deficiency of thiamine leads to beri-beri which is characterised by peripheral neuritis, high-output cardiac failure, œdema and, rarely, demyelination of the central nervous system (Wernicke's encephalopathy).

History. Beri-beri is largely a man-made disease; it became common in the East only when steam mills were developed in the mid-19th century and polished rice (i.e. rice without its inner husk) replaced brown rice as the staple diet. Beri-beri occurred in up to 40% of Japanese naval ratings, but was almost abolished by the introduction of a more varied diet. In 1909 an experiment was performed on 300 healthy Javanese labourers building a railway in Malaya. They all preferred polished rice, for its superior taste, and chose it even though it was explained that they might get beri-beri. Half of them, chosen at random, were given polished rice, and the remainder brown rice. After 3 months beri-beri developed only in the group eating polished rice. The groups were switched after 6 months and beri-beri immediately improved when the victims ate the brown rice. Correspondingly, the previously unaffected group began to develop beri-beri now that they were eating polished rice. In all, 20 cases of beri-beri developed on the polished rice diet, as compared with none amonst those eating brown rice. It was soon realised that the anti-beri-beri factor and the "vitamin B" necessary for growth in rats were similar. Thiamine was synthesised in 1936.

Function. Thiamine is the co-enzyme of carboxylase, and is required for normal carbohydrate metabolism. In its absence the substrates of

carboxylase (pyruvic and other α keto-acids) cannot be normally metabolised, and so they accumulate. Despite detailed knowledge about its function as a co-enzyme, it is still not known how a deficiency of thiamine leads to the characteristic symptoms of beri-beri.

The pyruvate metabolism test for thiamine deficiency is performed by measuring blood pyruvate before and after taking glucose by mouth. An abnormal rise in the blood pyruvate usually indicates thiamine deficiency, but may also occur in heavy-metal poisoning.

Sources and requirements. Thiamine is very widely distributed in plants and animals. The outer coats of grain kernels are rich in it, but these are removed in the preparation of white flour of polished rice. Requirements of thiamine vary directly with the amount of carbohydrate consumed, but 0·5 mg. thiamine for every 1,000 Calories is about enough.

Indications. Vitamin deficiencies are almost always multiple and although beri-beri is primarily due to a deficiency of thiamine, diets are generally also deficient in riboflavine, nicotinamide, pyridoxine, vitamins A and D and protein. Thus a general improvement in diet is desirable in addition to the specific treatment with thiamine. In Western countries where beri-beri is rare and often atypical, it is due either to a bizarre diet or to malabsorption from the gut, e.g. in chronic diarrhœa. Thiamine is destroyed readily in an alkaline medium and hence deficiency is particularly likely to occur in achlorhydric patients. Thiamine deficiency should always be considered as a possible cause of obscure peripheral neuritis or high-output cardiac failure. Alcoholic polyneuritis sometimes responds to large doses of vitamin B complex; spirit-drinking alcoholics who take most of their calories in the form of alcohol (which requires thiamine for its metabolism) and do not eat enough thiamine-containing food, may develop beri-beri heart failure.

For severe beri-beri 25 mg of thiamine should be given daily i.m. or i.v. For prophylaxis, 2 mg daily by mouth is adequate.

Ill-effects are very rare, but occasionally a patient shows allergy.

Riboflavine (Vitamin B_2)

Deficiency of riboflavine leads to angular stomatitis, ulceration of mucous membranes, "magenta" tongue, vascularisation of the cornea and seborrhœic dermatitis, especially of the face. It is very rare in Britain, but occurs in areas where chronic malnutrition is widespread. It usually accompanies other deficiency diseases, such as beri-beri, pellagra and kwashiorkor. Riboflavine deficiency predisposes to snow-blindness.

Riboflavine is an essential component of certain oxidative enzyme systems. It is present in milk, yeast and green vegetables.

Daily requirement is about 2 mg. If a deficiency of riboflavine is suspected a therapeutic test may be performed; improvement of the lesions within a week of giving riboflavine in the absence of other therapy suggests that the lesions were in fact due to its deficiency.

The usual therapeutic dose is 5 to 10 mg a day orally, but parenteral preparations are available. Toxic effects do not occur.

Nicotinamide (Nicotinic Acid Amide, Niacinamide), Nicotinic Acid (Niacin)

Deficiency of nicotinamide leads to pellagra, which is a generalised disease affecting especially the whole gastrointestinal tract (diarrhœa, red inflamed tongue, gastritis), the central nervous system (dementia), the skin, especially where it is exposed to light (dermatitis). It occurs in underfed populations, particularly where maize is a staple food.

Nicotinamide is an essential part of co-dehydrogenases I and II, and so it is present in every living cell. Tryptophan, which is present in good quality protein, can be converted into nicotinamide, and consequently will substitute for it in the diet. Maize protein is conspicuously lacking in tryptophan. Nicotinamide is also synthesised in the bowel, by bacteria, so that daily needs (about 20 mg) are difficult to measure accurately.

Pellagra is not usually a pure nicotinamide deficiency, so the other B vitamins and ascorbic acid should be given too. The dose is 250 to 500 mg orally daily in divided doses. Parenteral preparations are available.

Toxic effects do not occur with nicotinamide. Nicotinic acid, which is converted into nicotinamide, causes peripheral vasodilatation accompanied by an unpleasant flushing and itching, and the patient may faint.

Pyridoxine (Vitamin B_6)

Pyridoxine, converted to pyridoxal phosphate, is a coenzyme for transamination and is concerned with many metabolic processes. It is present in liver, yeast and cereals.

Pure pyridoxine deficiency is very rare. It occurs chiefly in children on peculiar artificial foods. Familial pyridoxine resistance is also known. The children present with convulsions and dermatitis. 5 to 25 mg pyridoxine orally or parenterally daily should suffice for treatment.

Adults develop an anæmia (hypochromic, microcytic with high serum iron), due to defective hæmoglobin synthesis, that may respond to big doses of pyridoxine (0·5 to 1 g a day). That such big doses are needed suggests that it is not a simple pyridoxine deficiency.

Normal adult dietary requirements are 1 to 2 mg pyridoxine a day, and the therapeutic dose for suspected deficiency is about 100 mg per day orally or parenterally.

Isoniazid interferes with pyridoxine (there are structural resemblances) and causes a peripheral neuritis that can be prevented by adding pyridoxine.

Pyridoxine, even in small doses, can block the therapeutic effect of levodopa in Parkinsonism.

It is also advocated in vomiting of pregnancy and radiation sickness, though unequivocal evidence is lacking.

Some cases of homocystinuria (an inborn error of aminoacid metabolism with mental defect and thrombosis) respond to pyridoxine. The defect is

in an enzyme (cystathionine synthetase) that converts homocystine to cystathionine. This enzyme is activated by pryidoxine, thus lessening the metabolic block.

ASCORBIC ACID, VITAMIN C

Deficiency of ascorbic acid leads to scurvy, which is characterised by petechial hæmorrhages, hæmatomas, bleeding gums (if teeth are present), anæmia and, in children, cessation of ossification in the growing-ends of bone.

History. Scurvy had been a scourge for thousands of years. In the Middle Ages it was treated with a great variety of preparations, among them citrus fruit and fresh vegetables. In 1753 Dr. James Lind performed a simple therapeutic trial on twelve sailors with advanced scurvy. They were all on the same basic diet and were living in the same quarters on board ship at sea. He divided them into pairs and dosed each pair differently. The respective daily treatments were:—

1. cyder
2. sulphuric acid
3. vinegar
4. sea-water
5. a concoction of garlic, mustard, balsam and myrrh
6. two oranges and a lemon

The pair receiving the oranges and lemon recovered and were back on duty within a week; of the others, only the pair taking cyder were slightly improved. Lind also recognised the antiscorbutic properties of green vegetables and salads. The efficiency of oranges and lemons in the prevention and cure of scurvy was repeatedly confirmed; but 40 years were to pass before any attention was paid and a regular daily allowance of lemon juice provided in the Navy. Unfortunately lime juice was soon substituted for lemon juice because it could be had cheaply in the West Indian Colonies. Lime juice contains only about a third as much ascorbic acid as lemon juice and failed to prevent scurvy completely. Synthetic ascorbic acid has been available since the 1930's.

Function. Ascorbic acid is a powerful reducing agent and probably plays a part in intracellular oxidation-reduction systems. In scurvy there is a general breakdown of collagenous connective tissue, which explains the mains symptoms. Ascorbic acid is also needed to prevent oxidation of tetrahydrofolic acid (which see). It is present in high concentration in the adrenal cortex and it may be involved in steroid synthesis. Only man, monkeys and guinea-pigs get scurvy, other animals are able to synthesise ascorbic acid for themselves.

Detection of deficiency. Ascorbic acid saturation tests are difficult to interpret as the range of normal response is wide. A more reliable test for ascorbic acid deficiency is to measure the leucocyte ascorbic acid content.

Sources are mainly fresh fruit and vegetables; meat and milk contain a little. Ascorbic acid is rapidly oxidised and destroyed by heating in the

presence of air, hence deep-fried potatoes contain more than do boiled. Properly canned fruit and vegetables retain a high proportion of their ascorbic acid. Vitamin C supplements are commonly given to babies (orange juice).

The requirement of ascorbic acid is about 30 mg daily for an adult. Maintenance of full saturation requires more than 75 mg a day, but there is no certainty that full saturation is necessary. Pregnancy, lactation, active growth or severe disease increase utilisation of the vitamin. Human milk contains 3 to 4 times as much ascorbic acid as cows' milk, in which the amount is also reduced by heat, including pasteurisation. Hence scurvy can occur with prolonged bottle-feeding of babies unless a supplement of ascorbic acid is added. It also occurs among elderly widowers living alone on bread, bacon, cheese, margarine and tea. Old-fashioned diets for patients with peptic ulcer were liable to be deficient in ascorbic acid. Wound healing is delayed in scurvy, hence ascorbic acid supplements may be desirable in surgical patients who are decrepit or who have been eating abnormal diets.

Indications for ascorbic acid are:—

The prevention and cure of scurvy. Urinary acidification.

Methæmoglobinæmia, for its properties as a reducing agent (see below).

It is possible that large daily doses (1 g/day) of ascorbic acid may reduce the incidence and severity of coryza. Reliable trials in this disease are difficult and the results are not, so far, conclusive. To justify prolonged prophylactic use of such doses in populations, the benefit must be shown to be clinically, as well as statistically significant.

Dose of Ascorbic Acid Tabs. B.P. (25 mg) for scurvy is 1 g orally, daily. 100 mg daily is enough to prevent it. Parenteral preparations are available.

Ill-effects do not occur at ordinary doses.

Methæmoglobinæmia

A reducing substance is needed to convert the methæmoglobin (ferric iron) back to oxyhæmoglobin (ferrous iron) whenever enough has formed seriously to impair the oxygen carrying capacity of the blood. Ascorbic acid is non-toxic, but is less effective than methylene blue. Both can be given orally, i.v. or i.m. Excessive doses of methylene blue can *cause* methæmoglobinæmia.

Methæmoglobinæmia may be drug-induced (phenacetin, sulphonamides, bismuth subnitrate, nitrites, nitrates (may occur in well-water), pamaquin, primaquine, sulfones, pyridium, acetanilide, phenazone, chlorates, aniline and nitrobenzene). In the rare instance of there being urgency, methylene blue 1–2 mg/kg slowly i.v. benefits within 30 min. In the congenital form oral methylene blue (3 to 6 mg/kg/day in divided doses) with or without ascorbic acid (0·5 g/day) gives benefit in days to weeks.

Methylene blue turns the urine blue and high concentrations can irritate the urinary tract, so that fluid intake should be high when big doses are used.

Sulphæmoglobinæmia cannot be treated by drugs. It can be caused by phenacetin, acetanilide, sulphonamides, pyridium.

VITAMIN D, CALCIUM, PARATHORMONE, CALCITONIN

Deficiency of vitamin D leads to rickets in growing children and to osteomalacia in adults.

Calcium. The skeleton contains about 1,200 g of calcium (all the rest of the body contains only about 12 g), and provides a reserve which is drawn upon to maintain the plasma calcium around the normal level of 10 mg/100 ml; about half of this is normally in the ionised form. Calcium is incompletely (about 20%) absorbed from the small intestine, the amount absorbed being particularly dependent on vitamin D. Calcium is lost from the body in the fæces (fæcal calcium is mostly the non-absorbed fraction from the food, but some is excreted into the intestine) and to a lesser extent in the urine. Calcium metabolism may be represented:—

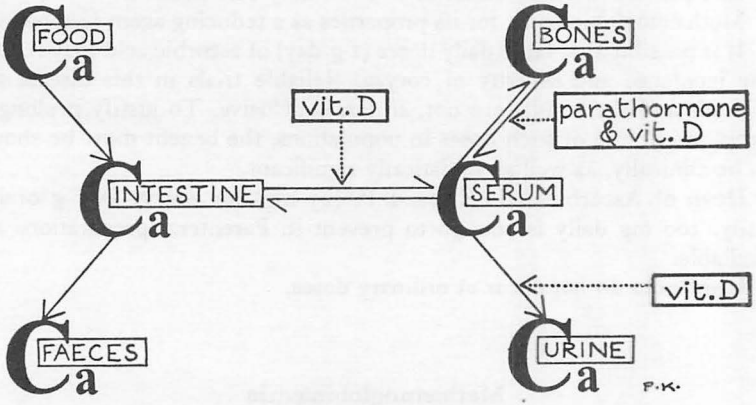

FIG. 22.

A daily intake of 1 g of calcium is normally adequate but this should be doubled in pregnancy and lactation, and during the treatment of rickets and osteomalacia.

Parathyroid hormone maintains a normal plasma calcium concentration.

Its chief effect is on mobilisation and deposition of Ca in bone, but it also affects Ca absorption from the gut and its excretion (urine, fæces). It increases renal excretion of phosphate. It also probably affects the formation of the most biologically active form of vit D.

Impure parathyroid preparations are available and may be useful for the treatment of acute hypocalcæmic tetany in order to avoid repeated injections of calcium gluconate, but immunological resistance soon occurs and

they do not provide long-term replacement therapy in parathyroid deficiency. The D vitamins are both more reliable and more effective in chronic hypoparathyroidism. Owing to the slow action of the vit D acute hypoparathyroidism is better treated by i.v. injections of calcium (see *tetany*) and dihydrotachysterol.

Calcitonin occurs in the thyroid in man and other animals. It is a 32 aminoacid polypeptide; it has been synthesized; it must be injected. Its chief physiological action is to regulate the calcium in bone. It also lowers plasma calcium concentration and has been used in treating hypercalcæmia, especially where it is due to mobilisation of Ca from bone. It is being tried in osteoporosis and in Paget's disease.

History of vitamin D. In the early 1920's there were two theories about rickets, the older that lack of sunlight caused the disease, the other that it was due to a dietary deficiency. Both were correct and were reconciled when it was shown that irradiation of food increased its antirachitic activity. The increased sensitivity to rickets of negroes living in temperate climates may be partly due to their skin pigment preventing the comparatively small amount of sunlight that they receive from activating ergosterol in the skin. There are a large number of chemically related compounds with vitamin D-like activity. Those therapeutically important are:—

- D_2 (calciferol ergocalciferol), made by ultraviolet irradiation of ergosterol
- D_3 (cholecalciferol), made by ultraviolet irradiation of 7-dehydrocholesterol. It is also the form that occurs in natural foods and is formed in the skin.

} Vitamin D

- Dihydrotachysterol (A.T. 10).

Pharmacokinetics. Vit D_2 and D_3 are absorbed in the upper gut. Being fat soluble, bile is necessary for absorption. Large doses of liquid paraffin may reduce absorption.

Although the vitamin has some biological activity, it is metabolised in the liver to a number of substances including the more active 25- hydroxycholecalciferol which is converted in the kidney to the even more active 1,25-dihydroxycholecalciferol.

Actions are complex. Vit D promotes absorption of Ca from the gut, mobilisation of Ca to and from bone and increased urinary Ca excretion. The plasma Ca rises. After a dose there is a lag in action of about 12 hrs and this is probably due to the time needed for its metabolic conversion and also for its action on a protein cellular carrier mechanism for Ca absorption.

A large single dose has biological effects for as long as 6 months (because of metabolism and storage, knowledge of the plasma half-life is of no practical importance). Thus the drug is cumulative and overdose by a mother anxious that her child shall have strong bones can cause serious toxicity.

If there is a deficiency of vit D, growing metaphysial cartilage and osteoid tissue does not become calcified, and rickets results. An adult, who is not growing, needs much less vit D than a child, but a chronic deficiency over many years leads to skeletal decalcification, i.e. osteomalacia. Women kept indoors on inadequate diets, and who bore many children, used to suffer from osteomalacia (the fetus and infant being parasitic upon the mother for both vit D and calcium). Nowadays, except in poorly fed populations, osteomalacia usually follows metabolic disorders which appear to produce an increased requirement for vit D, for instance steatorrhea, renal failure, and certain inherited diseases.

Enzyme induction due to antiepileptics (which see) can cause rickets in children and osteomalacia in adults due to increased metabolism of vit D.

Sources and requirements. Milk, liver and egg-yolk are the best sources, but an ordinary diet may not provide enough vitamin D for a growing child, unless he is exposed to much sunlight. 400 I.U. (10 mcg) per day of vitamin D are normally adequate for children; most baby-foods have enough vitamin D added to them by the manufacturers. Fish-liver oil is a usual source for children, some of whom appear not to dislike it. Premature babies require at least 800 I.U. daily as they are particularly liable to rickets. Adults do not normally need more than 100 I.U. daily, and this will generally be formed in the skin if it is not present in the diet. Pregnant and lactating women should take about 800 I.U. daily.

Indications are the prevention and cure of **rickets** and **osteomalacia** and the symptomatic treatment of some cases of **hypoparathyroidism.**

In osteomalacia secondary to steatorrhœa or renal disease there is defective absorption of calcium from the gut and large amounts of vitamin D are often needed.

Dosage. The therapeutic dose for primary, diet-deficiency, rickets is 3,000 to 5,000 I.U. per day, but much more may be needed in malabsorption syndromes and dosage must then be carefully controlled by measuring plasma calcium levels (a rise in total calcium above 11 mg/100 ml is dangerous).

The prophylactic dose in diet-deficient people should be about 1,000 I.U./day for a few months.

The maximum anti-rachitic effect of vitamin D is delayed for 1 to 2 months (dihydrotachysterol acts rather quicker) and the plasma calcium level reflects the dosage of weeks ago. Frequent changes of dose are pointless and confuse the picture.

Preparations are many and the choice is not critical.

It is important to recognise that, because of the need for very big doses in certain vitamin D resistant cases, there is an *unusually wide range of dosage in single tablets* available, for example, Calcium with Vitamin D Tabs. B.P.C. each contain 500 I.U. (12·5 mcg calciferol) whereas Calciferol Tabs. B.P. contain 100 times as much. The latter tablets are only for use in exceptional circumstances, e.g. hypoparathyroidism, or metabolic rickets; their inadvertant administration to children can lead to disaster.

Dihydrotachysterol is an alternative to calciferol that is used chiefly in metabolic rickets. It acts more quickly, i.e. in days rather than in weeks.

Toxicity is due mainly to the excessive rise in plasma calcium which is provoked. General effects include malaise, drowsiness, nausea, abdominal pain, thirst, constipation and loss of appetite. Other long-term effects include ectopic calcification almost anywhere in the body, renal damage and an increased calcium output in the urine (giving a strongly positive Sulkowitch test); renal calculi may be formed. It is dangerous to exceed 10,000 I.U. daily of vitamin D for more than about 12 weeks.

Patients with sarcoidosis are intolerant of vitamin D, possibly even to the tiny amount present in a normal diet, and to that synthesised on their skin by sunlight.

Adrenal steroids antagonise vitamin D by an unknown mechanism and have been suggested in the treatment of hypercalcæmic sarcoidosis and of severe hypervitaminosis D.

Idiopathic hypercalcæmia of infants, presenting as failure to thrive with vomiting and constipation is related to vitamin D intake. Government action has been taken to limit indiscriminate "fortifying" with vitamins, of children's foods, but much vitamin D toxicity is due to well-meaning, but needless, administration by parents. The U.S.A. Food and Drug Administration warn that intake of fortified supplements should not exceed 400 I.U. a day.

Treatment of acute hypercalcæmia may be needed whether or no the cause can be removed. Sodium phosphate i.v. binds the Ca as $CaHPO_4$ and is effective quickly; but the $CaHPO_4$ can cause renal damage.

Disodium edetate i.v. chelates Ca and is rapidly effective.

Hydrocortisone reduces intestinal Ca absorption and is useful in vit D intoxication and sarcoid, but it has no effect in hyperparathyroidism.

Calcitonin is effective in a few hrs where the Ca is at least partly mobilised from bone (hyperparathyroidism, vit D intoxication).

Hypercalcæmia due to cancer may be reduced by intermittent doses of drugs that inhibit osteoclastic activity, e.g. mithramycin.

Cellulose phosphate binds calcium in the intestine and prevents absorption: it is used for renal stone formation (due to hypercalciuria) in patients who overabsorb dietary calcium.

Tetany

A low plasma ionised calcium increases the irritability of the nervous system generally.

Alkalosis (e.g. from vomiting in pyloric stenosis) causes tetany partly by lowering the proportion of ionised calcium in the extracellular fluid. The commonest cause of tetany is probably hysterical overbreathing, leading to respiratory alkalosis; rebreathing from a bag or administration of 10% carbon dioxide in oxygen will help in such a case. Sedation may be necessary to stop the overbreathing. Calcium gluconate is given slowly i.v. in the acute case of tetany following removal of, or damage to,

the parathyroid glands or removal of a parathyroid tumour, or associated with very severe rickets or osteomalacia. Aluminium hydroxide binds phosphate in the gut, causing hypophosphatæmia which stimulates production of 1,25-dihydroxycholecalciferol in the kidney; increased Ca absorption from the gut and Ca mobilisation from bones occurs and urinary Ca excretion increases; (osteomalacia can occur with prolonged high doses of aluminium hydroxide). Dihydrotachysterol is also used to increase Ca absorption. It acts quicker than vit D_2 or D_3. Dietary Ca is increased by giving Ca gluconate (an effervescent tab is available) or lactate, and this and vit D (in high dose) may be needed long-term.

Calcium Gluconate Inj. B.P. is given i.v. as a 10% solution, 10 to 20 ml being given at the rate of about 2 ml per minute and repeated as necessary (every few hrs). It must not be given i.m. as it is painful and causes necrosis.

Toxic effects of intravenous calcium may be very dangerous. An early sign is tingling in the mouth and a feeling of warmth spreading over the body. Serious effects are those on the heart, which mimic and synergise with digitalis; fatal cardiac arrest may occur in digitalised animals and it would seem advisable to avoid i.v. calcium in any patient on digitalis; indeed, reduction of ionised calcium by a chelating agent, has been successful in treating digitalis arrhythmia. The effect of calcium on the heart is antagonised by potassium and similarly the toxic effects of a high serum potassium in acute renal failure may be to some extent counteracted with calcium.

VITAMIN E (THE TOCOPHEROLS)

Vitamin E is an antisterility vitamin in rats; a corresponding deficiency disease does not occur in man. It has been used with doubtful benefit in many diseases, including peripheral vascular disease.

PAGET'S DISEASE OF BONE

This disease is characterised by bone resorption and formation (bone turnover) increased as much as 50 times normal. Some therapeutic success has been found with *calcitonin* (which inhibits bone resorption), with *cytotoxic agents* that inhibit osteoclasts (mithramycin, actinomycin D), and with *diphosphonates* (e.g. disodium etidronate) which inhibit crystal formation, growth and dissolution, such as must occur in bone mineralisation and demineralisation.

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Chapter 29

THE CHEMOTHERAPY* OF MALIGNANT DISEASE AND IMMUNOSUPPRESSIVES†

MALIGNANT disease is of immense variety. Prevention, by drugs, of the genetic change, whether spontaneous, or induced by chemicals or viruses, that converts a normal cell to an invasive malignant cell is not in sight. However, some cancers can be prevented, wholly, or in part, by protecting people from exposure to known carcinogens (industrial cancers, bronchial cancer).

Chemotherapy depends on developing drugs that are selective for the tumour cells and leave those of the host unharmed. Development is greatly assisted if models of the human disease can be set up in the laboratory. Unfortunately this is a great difficulty with cancer; as well as animal tumours, tissue cultures of human tumours are used.

The comparative success of antimicrobial chemotherapy is due to the fact that the metabolism of the parasite differs qualitatively from that of host cells. But cancer cells are host cells that differ from normal cells quantitatively rather than qualitatively.

In addition, the immune system of the body commonly responds vigorously to an invading organism and cytostatic (as well as cytocidal) agents provide effective therapy. But in cancer, the immune response is slight and cytostatic agents are less useful.

Thus in cancer the cells are relatively closely allied to the normal cells and must be killed by treatment. Whereas in **infections** the cells are markedly different from the normal host cells and generally a treatment that arrests growth is sufficient.

Despite this, some differences between normal and malignant cells have been found and can be exploited.

It used to be thought that cancer cells divided more rapidly than normal cells so that drugs that interfered with mitosis would affect them selectively. But this is now known not to be so; the increase in tumour size can be due to decreased cell loss. This explains why antimitotic drugs are not as useful as had been hoped. The normal cells that divide more rapidly than cancers are those in the gut mucosa and the bone marrow. They are greatly affected by antimitotic drugs and toxicity to gut and marrow are limiting factors to use of these agents.

* Although not in strict accord with the definition in ch. 7, the word chemotherapy is in general use in this connection and it would be pedantic to avoid it. It arose because some malignant cells can be cultured and the disease transmitted by inoculation as with bacteria.

† I am particularly indebted to Dr. A. S. D. Spiers for this chaper. D.R.L.

One known metabolic difference is that some malignant cells cannot synthesize the amino acid L-asparagine (necessary for formation of DNA and RNA) and are dependent on its presence in their growth medium. Injected lymphoma cells fail to survive in the guinea pig because guinea pig plasma contains the enzyme L-asparaginase which deprives the cells of the essential asparagine. The enzyme can be obtained from *E. coli* and other micro-organisms (colaspase): it is used in leukæmia.

Apart from discovering biochemical mechanisms and developing drugs that are selectively toxic, much can also be done by attention to detail in exploiting existing drugs. Dosage schedules and combinations can be devised that increase their efficacy. This requires knowledge, skill and persistence, but it has been shown that children with leukæmia known to have been treated by physicians specialising in its treatment survive considerably longer than others (*17*). *Other effects* of antineoplastic drugs include:

sterility; teratogenesis; carcinogenesis; mutagenesis; immunosuppression.

Other approaches to malignant disease include:

Hormone therapy: some tumours are greatly affected by sex hormone balance, e.g. carcinoma of prostate, breast; anti-œstrogens, e.g. tamoxifen (Novaldex) and anti-androgens are being developed. Others are affected by adrenocortical hormones (e.g. leukæmia) which may also reduce hæmolysis and thrombocytopenia that occurs with some malignant diseases.

Immunotherapy is still experimental.

Radiotherapy and surgery play an essential part in many cases, but will not be discussed here.

Treatment of malignant disease

A malignant growth may be:

1. *cut out* (surgery)
2. *burnt out* (radiotherapy)
3. *poisoned* (chemotherapy)

The selection and combination of these approaches is sometimes self-evident, but more often requires skill and experience.

Generally the objective is to eliminate all malignant cells, but as there may be some host resistance, this is not always essential for cure.

Indications for chemotherapy

1. No better form of treatment available.
2. Benefit likely to justify risk: cure or palliation.
3. Existence of a measureable factor, a symptom, sign, laboratory factor, that can be followed and allow progress to be assessed.

Contraindications

1. Drug likely to be ineffective.
2. Other approach superior.
3. Very advanced disease: fatal toxicity likely.
4. No means of assessing progress.

5. Existing bone marrow depression.
6. Presence of active infection.

Adverse effects are largely the result of the intrinsic properties of drugs. They are cytotoxic, and specially attack the more rapidly dividing tissues:

bone marrow—anæmia, hæmorrhage, infection.
gut mucosa—stomatitis, diarrhœa, hæmorrhage, septicæmia.
lymphoreticular tissue—immunosuppression, infection.
wound healing—interfere with.
hair follicle—alopecia.
testis—sterility—mutations.
fetus—teratogenesis, abortion.

Other adverse effects include nausea and vomiting (especially alkylating agents), cystitis (cyclophosphamide), etc.

Response to Chemotherapy

Group A. Tumours in which *striking response and significant benefit are common.*

Childhood acute leukæmia	Choriocarcinoma
Chronic granulocytic leukæmia	Wilms' tumour
Chronic lymphocytic leukæmia	Ewing's sarcoma
Hodgkin's disease	Seminoma
Follicular lymphoma	Prostatic carcinoma
Lymphosarcoma	Breast carcinoma
Ovarian carcinoma	Burkitt's tumour

Group B. Tumours in which chemotherapy is *less effective.*

Acute leukæmia in adults	Gastrointestinal carcinoma
Multiple myeloma	Corpus uteri carcinoma
Reticulum cell sarcoma	Hepatoma
Bronchogenic carcinoma	Cholangiocarcinoma

Group C. Tumours in which chemotherapy is *usually ineffective*, or effective only when special techniques of administration are employed.

Cervix uteri carcinoma	Cerebral gliomata
Renal carcinoma	Oropharyngeal carcinomas
Melanoma	Carcinoma of paranasal sinuses
Osteogenic sarcoma	

(Modified from W.H.O. Technical Report No. 232).

General principles of treatment

Drugs do not yet cure predictably except in chorioncarcinomas but they often prolong life and have an important place in making it more comfortable even in cases where it is not prolonged.

Hopes have recently risen of achieving total cure by completely eradicating all malignant cells from the body, especially in early cases of leukæmia before infiltration of the central nervous system, where drugs do not readily penetrate, has occurred.

Wherever cure is felt to be a practical, even if a remote possibility, *intensive treatment* by combinations of drugs to the limits of tolerance is given. To stop the patient being killed along with the malignant cells, supportive therapy to replace blood leucocytes and platelets and to prevent superinfection is used.

In other cases, drugs are used in two principal ways (*a*) *continuous suppressive therapy*, or (*b*) by *intermittent courses* when relapse occurs. Bone marrow failure is anyway liable to occur in blood diseases and it is possible that continuous therapy hastens its onset. Choice is based on experience in large therapeutic trials.

Administration. The drugs are given in initial arbitrary doses, usually until bone marrow depression is seen, when dosage is reduced or spaced out. Generally the dose is controlled by blood picture and physical size of deposits or of liver and spleen. If toxic effects occur, the drug is stopped until they disappear. Some drugs (busulphan, chlorambucil) have a latent period before maximal effect, which means that the dose should be reduced before the ideal response is achieved.

The oral route is used wherever practicable, but some drugs must be given i.v. In addition, to improve the therapeutic ratio, regional therapy e.g. intrathecal or by local perfusion is used.

Drugs used*

Alkylating agents were developed from war gases that were observed to depress bone marrow. They interact with DNA. They include the nitrogen mustards (mustine, mannomustine, uramustine, chlorambucil, cyclophosphamide, melphalan), busulphan, ethoglucid, triaziquone, thiotepa, mitobronitol.

Antimetabolites. These are analogues of normal metabolites and act by competition. They interfere with nucleic acid synthesis. They include *folic acid antagonists* (methotrexate): *purine antagonists* (mercaptopurine, azathioprine, thioguanine) and *pyrimidine antagonists* (fluorouracil, floxuridine, cytarabine).

Alkaloids act on nuclei in mitosis. They include demecolcine, vinblastine, vincristine.

Antibiotics act on nuclear function in a variety of ways. They include actinomycins C and D, daunorubicin (rubidomycin), mithramycin, mitomycin.

Miscellaneous: colaspase (L-asparaginase), procarbazine, urethane, hydroxyurea.

Radio-phosphorus (^{32}P, sodium radiophosphate)

Phosphorus is concentrated in bone and in cells which are dividing rapidly, so that the bone marrow, receives most of the β irradiation when

* The terminology of drugs is not generally agreed. The terms *cytostatic* and *cytotoxic* are often used to refer to all antineoplastic drugs (except hormones).
The term *antimitotic* agent generally includes the drugs that are classified in this book as antimetabolites and cytotoxic agents.

^{32}P is given. The effects are similar to those of whole-body irradiation and in **polycythæmia vera** ^{32}P is now a treatment of choice. The maximum effect on the blood count does not occur for 1 to 2 months after the dose. In polycythæmia, yearly treatments often give good control. Excessive depression of the bone marrow is the main unwanted effect.

Radio-gold (^{198}Au) is concentrated in the liver and has been used in various abdominal neoplasms.

Steroid hormones

Adrenal steroids are chiefly useful in blood diseases. In leukæmia they are used for two purposes, first to influence the primary disease process, this only occurring with the lymphocytic forms; and second, to reduce complications, particularly hæmolytic anæmia and thrombocytopenia. Resistance occurs. High doses are used, up to 200 mg prednisolone a day.

In other neoplasms they are probably useless, but if they are tried, lower doses (prednisolone, 30 mg a day) will give any benefit there may be.

Adrenal steroids are also useful in controlling hypercalcæmia due to bone metastases, e.g. from breast or prostate.

Œstrogens are used in prostatic carcinoma and in metastatic breast carcinoma in later postmenopausal women (in premenopausal and recent postmenopausal women they may stimulate the growth).

Androgens are sometimes useful in metastatic breast cancer in premenopausal women.

Progestagens are useful in some cases of endometrial cancer.

Anti-œstrogens and **anti-androgens** are being developed.

Drug resistance

The position is comparable to that with some micro-organisms; some malignant cells have a *primary* or *natural* resistance to various drugs, others develop a *secondary* or *acquired* resistance during therapy.

Acquired resistance is a serious clinical problem. It may be due to *adaptation* of the cell to an alternative metabolic path, or to *mutation.*

Natural (primary) resistance can only be overcome by development of new drugs.

Acquired (secondary) resistance can be combated by vigorous initial treatment and by the use of drug combinations (from different chemical groups).

Choice of Drugs

The table sets out the drugs of first and second choice in a number of neoplasms but it gives a general indication only.

Immunosuppression

Immunosuppression is a specialised technique. The following notes provide a little background.

Disease	*Drugs of 1st choice*	*Drugs of 2nd choice*
Acute leukæmia	prednisolone, mercaptopurine vincristine, methotrexate cyclophosphamide, rubidomycin cytarabine L-asparaginase	carmustine* methyl-GAG*
Chronic granulocytic leukæmia	busulphan	6-mercaptopurine cyclophosphamide
Chronic lymphocytic leukæmia	chlorambucil, prednisolone	cyclophosphamide fluoxymesterone
Multiple myeloma	melphalan, cyclophosphamide	urethane; prednisolone for hypercalcæmia
Hodgkin's disease	cyclophosphamide or other alkylating agent; vinblastine	procarbazine, prednisolone vincristine.
Lymphosarcoma and follicular lymphoma	alkylating agents; vincristine	procarbazine, prednisolone vinblastine.
Reticulum cell sarcoma	vincristine, alkylating agents	prednisolone, methotrexate vinblastine
Breast carcinoma	fluoxymesterone, stilbœstrol	progestogens, prednisolone cyclophosphamide
Prostatic carcinoma	stilbœstrol	alkylating agents
Ovarian carcinoma	chlorambucil	vinblastine
Bronchogenic carcinoma	vinblastine	alkylating agents
Gastrointestinal carcinoma	fluorouracil	vinblastine alkylating agents
Choriocarcinoma	methotrexate	vinblastine actinomycin D cyclophosphamide
Ewing's tumour	cyclophosphamide	vincristine
Wilms' tumour	actinomycin D	vincristine
Neuroblastoma	vincristine	rubidomycin

* These drugs are not marketed (1972).

1. Immune responses in man may be antibody-mediated or cell-mediated.
2. Both derive from cells in lymphoid tissue.
3. Rejection of grafts and delayed allergic reactions are cell mediated.
4. Suppression of damaging immune response is useful in allergic and autoimmune diseases and in tissue or organ grafting.
5. Effective drugs (on both types of response) act on lymphoid tissue or on lymphocytes: they include:

(*a*) *adrenal steroids.*
(*b*) *cytotoxic agents and antimetabolites.*
(*c*) *antilymphocytic globulin.*

They suppress development of immune response more readily than established immunity.

6. The above are all non-specific immunosuppressives so that the general defences of the body against infection are impaired: infections should be treated by *bactericidal* drugs.

7. *Adrenal steroids* destroy lymphocytes and reduce inflammation.

8. *Cytotoxic agents and antimetabolites* destroy immunologically competent cells: azathioprine (Imuran), a purine antagonist, is commonly used.

9. *Antilymphocytic globulin* is made by preparing antisera to human lymphocytes in animals (horses): allergic reactions are common.

10. *Hazards of immunosuppression:* (*a*) those of long term adrenal steroid therapy (which see): (*b*) impaired immune responses (see 6 above): (*c*) bone marrow depression (cytotoxics): (*d*) carcinogenicity by cytotoxics and antilymphocytic serum: it has been suggested that an "immunological surveillance" by which antigenically unusual cells arising in the body are eliminated may be suppressed. (*e*) mutagenicity and teratogenicity: patients should not reproduce whilst taking a potent immunosuppressive regimen.

11. Whilst the hazards are relatively acceptable for treating grave life-endangering disease, they give more cause for concern when immunosuppressive regimens are used in younger patients with less serious disease e.g. rheumatoid arthritis, ulcerative colitis.

12. Treat all infection early and vigorously: use human gamma globulin to protect if there is exposure to virus infections, e.g. measles, varicella.

13. *Diseases in which immunosuppression may be useful include*: ulcerative colitis, regional ileitis, rheumatoid arthritis, chronic active hepatitis, systemic lupus erythematosus, glomerulonephritis, nephrotic syndrome, some hæmolytic anæmias or thrombocytopenias, tissue transplantations.

14. *Active immunisation during immunosuppressive therapy*. Response to non-living antigens (tetanus, typhoid, poliomyelitis) is diminished and 1 or 2 extra doses may be wise. With living vaccines (small pox) there is a risk of serious generalised disease. If vaccination *must* be performed, reduce or stop the immunosuppressive therapy and vaccinate lightly. If a severe reaction occurs use methisazone (which see) or human antivaccinial gammaglobulin.

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Chapter 30

DRUGS ACTING ON THE SKIN

In this chapter some general aspects of the use of drugs in dermatology will be discussed, but an outline of treatment of a number of afflictions is also given in a table.

It is well-established that the skin may react to emotion, e.g. in eczema or psoriasis, and sedatives or tranquillisers may be useful in therapy of skin diseases. To avoid repetition from earlier chapters, the following account is confined to therapy directed primarily at the skin.

It is easy to do more harm than good with potent drugs, and this is particularly true in skin diseases; also, many skin lesions are in fact caused by systemic or local use of drugs. In patients prone to any allergy it is very easy to provoke further reactions during treatment.

Local treatment of skin lesions appears to offer a unique opportunity for the trial of different treatments on similar lesions in the same individual at the same time, but substances applied locally are sometimes absorbed and may exert effects on the body as a whole, also, the healing of a lesion at one site, may, for no known reason, produce improvement in similar lesions elsewhere. Conversely, to provoke a flare-up at one site often makes all the other lesions worse as well. Thus the "control" treatment may at first appear to have caused healing or exacerbation that is in fact due to the effects of the more active substance applied elsewhere.

Substances that are well **absorbed** from intact skin are usually soluble in both water and fats or combine with skin fatty acids, e.g. heavy metals; those completely insoluble in either are not absorbed. Fats and oils enter the skin partly through the hair follicles and sebaceous glands. From pathologically affected areas most substances are probably absorbed to some extent. Systemic toxicity can occur.

The manner in which drugs are **applied** to the skin is often important and depends upon the nature of the drug and the desired physical effect; for instance, this may be to cool, to reduce evaporation or friction, or to protect.

In general, acutely inflamed lesions are readily aggravated by drugs and so simple soothing applications should be used.

Intensification of effect can be got by covering the area to which a drug has been applied by a sheet of impermeable polythene (occlusive dressing). Substantial absorption with systemic effects can occur when this is done.

Vehicles in which drugs or inert substances are formulated for application, are important. Whether a drug is offered in a lotion, cream or ointment depends on the drug, the condition and site of the diseased skin and the objectives of the prescriber, which are rational either on an empirical

basis or from knowledge of the pathophysiology of the disease. Those who do not make a special study of dermatology are advised to follow well trodden paths.

Lotions or wet dressings are generally used to cleanse and cool acutely inflamed lesions, especially where there is much exudation. The initial application, and the cooling effect of evaporation of the water, is thought to reduce the inflammatory response by inducing superficial vasoconstriction. Sodium chloride solution 0·9%, or Aluminium Acetate Lotion, B.N.F., are often used. Soaks of approximately 0·05% potassium permanganate are satisfactory if the lesion is on the limbs. Lotions containing more active ingredients (e.g. ichthammol, coal tar) are sometimes used on subacute lesions, but occasionally these irritate the skin further. The use of lotions or wet dressings over very large areas can reduce body temperature dangerously in the old or the very ill.

Shake lotions (e.g. Calamine Lotion, B.P.) are essentially a convenient way of applying a powder to the skin with additional cooling due to evaporation of the water. They are contra-indicated when there is much exudate because crusts form. They sometimes produce excessive drying of the skin, but this can be reduced if oils are included, as in Calamine Lotion, Oily, B.P.C.

Creams are emulsions either of oil-in-water (cosmetic vanishing creams) or water-in-oil. A cooling effect (cold creams) is obtained with both groups as the water evaporates. Water-in-oil creams (e.g. Oily Cream, B.P., Zinc Cream, B.P.) behave like oils in that they do not mix with serous discharges, but their chief advantage over ointment is that the water content makes them easier to spread, and they give a better cosmetic effect. They are specially useful for protecting the skin, e.g. when it is chapped or dried, or on babies' buttocks, and can be used on hairy parts. They can be used as vehicles, particularly for fat-soluble substances. A dry skin is short of water, not of oil, but oily substances are used to provide a barrier which reduces evaporation of water.

Oil-in-water creams (Aqueous Cream, B.P.) do mix with serous discharges and are especially useful as vehicles for water-soluble substances.

Barrier creams of many different kinds have been devised for use in industry to reduce occupational dermatitis. They are not usually very effective, because it is impossible to maintain a complete barrier during work that is also easily removed by ordinary washing afterwards. If it is not readily removable, complications due to blockage of sweat glands and follicles and skin irritation follow. Allergic reactions occur.

Barrier creams may make the cleansing of the skin more easy after dirty work, but it is essential that they should be shown to be less harmful than the dirt itself before being used for this.

They are more effective in protecting skin from discharges and secretions (colostomies, napkin rash) than when used under industrial working conditions. Silicone sprays may be effective in preventing and treating bed sores.

The compositon of proprietary barrier creams is complex, but silicones and soaps and talc seem to be important ingredients.

Masking creams for obscuring unpleasant blemishes from view are greatly valued by the victims. They may consist of the inert titanium oxide in an ointment base with colouring appropriate to the site and the patient. Best results are got by consulting a cosmetician.

Ointments are thicker than creams; they are of three kinds:

1. *non-emulsifying*. These do not mix with water: they adhere to the skin and prevent evaporation and heat loss: they can be considered a form of occlusive dressing: skin maceration occurs: although they are helpful in chronic conditions to soften crusts, and as vehicles, they are not used in acute conditions where free removal of exudate and cooling are needed: they are difficult to remove except with oil or detergents and are messy and inconvenient, especially on hairy skin: Paraffin Ointment, B.P. contains beeswax, paraffins and cetostearyl alcohol: Simple Ointment, B.P. is similar.

2. *emulsifying*. These allow evaporation as they mix with water and skin exudate: they are useful as vehicles for active drugs:

Emulsifying Ointment, B.P. is made from emulsifying wax (cetostearyl alcohol and sodium lauryl sulphate) and paraffins: Aqueous Cream, B.P. is an oil-in-water emulsion of Emulsifying Ointment.

3. *water soluble*. These are mixtures of macrogols and polyethylene glycols: the consistency can be varied readily: they are easily removable and are used in burn dressings, as lubricants and as vehicles that readily allow passage of active drugs into the skin (e.g. hydrocortisone).

Dusting powders (e.g. Zinc Starch and Talc Dusting-powder, B.P.C.) may cool by increasing the effective surface area of the skin and they reduce friction between skin surfaces by their lubricating action. Though usefully absorbent, they cause crusting if applied to exudative lesions.

Pastes (e.g. Zinc Compound Paste, B.P.) are ointments containing insoluble powders. They are very adhesive and give good protection. Their powder content enables them to absorb a moderate amount of discharge. They are also used as vehicles (e.g. Coal Tar Paste, B.P.C., which is Zinc Compound Paste with 3·5% coal tar).

Caustics are used to destroy unwanted tissue, including warts and corns. Great care is obviously necessary to avoid ulceration. They include trichloracetic acid (10 to 20%), silver nitrate sticks, salicylic acid (10 to 50%) and many others. Podophyllin (15%) is also used but may act as an antimitotic rather than as a caustic.

Keratolytics are mild caustics and are used for softening and removing the horny layer of the skin. They are all liable to damage normal skin and should therefore be strictly confined to the lesion. If used too strong or for too long they may cause ulcers. They are used particularly in the chronic scaling conditions, especially psoriasis. Salicyclic acid, 2%, is probably the first choice, as in Salicylic Acid Ointment, B.P. or Zinc and Salicyclic Acid Paste, B.P. Tretinoin (Retin-A) is an alternative.

Tars are mildly antiseptic, antipruritic and they modify keratinisation. They are comparatively safe in low concentrations (up to 5%). They are used in chronic conditions associated with parakeratosis, e.g. psoriasis. There are very many preparations, which usually contain other substances, e.g. Calamine and Coal Tar Ointment, B.P.C. or Coal Tar and Salicylic Acid Ointment, B.N.F.; it is sometimes useful to add an adrenal steroid. Ichthammol is a sulphurous tarry distillation product of fossilised fish (obtained in the Austrian Tyrol), it is used as a mild antiseptic, Ichthammol Ointment, B.P.C. Tars increase the sensitivity of the skin to sunlight.

Insect repellents. Dimethyl or dibutyl phthalate is applied to the skin where its effect lasts for some hours; the insects find contact with the skin unpleasant and are not repelled by odour, so that all exposed skin should be treated.

Insect bites and stings. Pain-producing substances in insect bites and stings include histamine, 5-hydroxytryptamine and various kinins as well as formic acid. These probably also account for much of the local inflammatory reaction; systemic reactions may be due to other potent toxins or to allergic reactions (which see). Although bee venom is acid and wasp venom alkaline or neutral it is doubtful if the traditional use of alkali such as ammonia or bicarbonate on bee strings, or vinegar or lemon juice on wasp stings has much more than a cooling and placebo effect. Antihistamines used locally may relieve the itch, partly by their local anæsthetic action. Severe septic bites may require systemic chemotherapy.

Calcium is a traditional remedy amongst bee-keepers for general urticarial reactions to stings. Given i.v., calcium has been shown to hasten the disappearance of the wheal caused by locally injected histamine, perhaps by an action on capillary permeability.

Antiseptics and Skin Disinfection

Doctors are rarely actively concerned to exercise personal choice from amongst the huge number of antiseptics and disinfectants. They generally just want to be told which preparation has been found most suitable for each particular task.

There are various techniques: the following will serve:

Surface disinfection of clean objects (glass, stainless steel): hypochlorites with or without a detergent, or 70% solutions of industrial methylated spirit or of isopropyl alcohol are suitable. Iodophors may be equally satisfactory. These are combinations of iodine with detergents: the iodine is slowly released.

Skin disinfection: for needling: general: 70% ethyl or isopropyl alcohol.

For surgery or for needling for blood culture or lumbar puncture: iodine or chlorhexidine in 70% ethyl or isopropyl alcohol. Chloroxylenol (Dettol), organic Hg, quaternary ammonium compounds (laurolinium, dequalinium etc) are less active and slow drying. Ether and cetrimide (a detergent) are cleansing agents, not antiseptics.

Hands: repeated washing with liquid soap or cream containing hexachlorophane (3%) or regular rinsing with aqueous chlorhexidine (0·5%).

Laboratory tests and the skin: antiseptics should be allowed to evaporate before the skin is punctured or contamination of a blood specimen can occur: hæmolysis (alcohol, detergents): iodine leads to falsely raised protein bound iodine (PBI).

Extensive application of iodine to the skin can allow enough absorption to raise the PBI for about a week.

Hexachlorophane is a bactericidal chlorinated phenol widely used for prophylaxis of infection in soaps, emulsions and dusting powder. Babies have even been washed or dipped in solutions of various strengths. Absorption can occur through the skin and it is toxic to the CNS. Therefore recommended strengths and techniques should be adhered to. Deaths have occurred from overdose.

Skin Infections

Superficial infections, e.g. impetigo, can best be treated by local application of bactericidal antimicrobials, but deep infections, e.g. boils, need systemic administration (but only if severe or multiple).

Early use of sulphonamides and then of penicillin on the skin soon showed that allergic reactions to the treatment could be more unpleasant than the disease, and the patient could also be left in a situation where later systemic use for a more serious infection was precluded because of the danger of serious allergic reactions.

To avoid sensitisation, drugs should be applied for as short a time as is reasonable and, to minimise further trouble if sensitisation does occur, the drug should, where practicable, be one that will not be needed for systemic administration in the future.

Commonly used ointments include: chlortetracycline: gentamicin: neomycin + bacitracin: clioquinol cream.

Nystatin cream will control candidiasis. Zinc undecanoate, benzoic acid, tolnaftate and pecilocin are typical fungicides.

Antimicrobial creams are generally applied 8-hrly after cleaning the area.

Antimicrobials are combined with an adrenal steroid in treating infected eczema. The steroid alone will allow the infection to spread by suppressing local inflammatory reaction. The steroid does not prevent an allergic reaction to the antimicrobial.

The following drugs readily induce allergy when used on the skin, penicillin, sulphonamides, streptomycin, chloramphenicol; neomycin reactions are increasing.

Tetracyclines do not commonly cause skin allergy, but staphylococci, which are common skin pathogens, are often resistant to them and as they are also widely used for systemic infections some people think that they are best avoided on the skin.

Counter-irritants

Counter-irritants are used to stimulate nerve endings in intact skin to relieve pain in viscera or muscle supplied by the same nerve root. All produce inflammation of the skin. They are often effective, and, though how they act is unknown, there is no lack of theories. The psychological effect is certainly important and other possibilities are:

1. That vasodilatation at the site of the pain, produced either reflexly or by antidromic stimulation, may promote relief.

2. That the arrival of numerous pain impulses from the skin may alter the effect of impulses from other parts supplied by the same nerve root. The best counter-irritants are physical agents, especially heat. Many drugs have, however, been used for this purpose and suitable liniments (e.g. Turpentine Liniment, B.P.), ointments (e.g. Methyl Salicylate Ointment, B.P.C.) and poultices (e.g. Kaolin Poultice, B.P.) and menthol are available.

Antipruritics

Impulses responsible for the sensation of itching pass along the same nerve fibres as those of pain, but the sensation experienced differs qualitatively as well as quantitatively from pain. Liberation of histamine in the skin causes itching and may be responsible for the itching of urticarial allergic reactions. Many drugs, especially the morphine group, are known to be histamine liberators; bile salts also release histamine and this may explain some, but certainly not all, of the itching of obstructive jaundice.

Treatment of the underlying cause is obviously required (e.g. parasites, renal failure and reticuloses), but there remain those patients in whom the cause either cannot be removed or is not known. Scratching or rubbing seems to give relief by converting the intolerable persistent itch into a more bearable pain, and may even cure the itch at the cost of removing the epidermis. A vicious circle can be set up in which itching provokes scratching and scratching leads to skin leasions which itch, as in neurodermatitis. Covering the lesion or enclosing it in plaster so as to prevent any further scratching or rubbing may help.

In severe pruritus sedation is sometimes helpful during the day and hypnotics are usually required at night.

Antihistamines orally are used in pruritus, but except in urticarial conditions they probably act by their sedative effect; they should not be applied topically due to risk of allergy. Any cooling application has some antipruritic effect, but a number of substances, such as phenol (0·2 to 1%), menthol (0·2 to 1%) or camphor (0·2 to 5%), are often added because they have a reputation as specific antipruritics. *Local anæsthetics* do not offer any long term solution and since they are liable to sensitise the skin they are best avoided; but lignocaine is least troublesome in this respect.

Chlorpromazine or a related drug, e.g. methdilazine (Dilosyn) or trimeprazine (Vallergan) sometimes helps, probably by altering the patient's attitude to the itching.

Crotamiton, an acaricide, is reputed to have a specific but unexplained antipruritic action, although it may exacerbate an already inflamed skin; convenient proprietary preparations (Eurax, Teevex) are available. Local *hydrocortisone* or fluorinated steroid preparations are probably the most effective antipruritics. Grenz rays are also very effective and may be used together with drugs.

The itching of *obstructive jaundice* may be relieved by androgens (e.g. fluoxymesterone orally, up to 5 mg daily; or methyltestosterone, 25 mg sublingually daily for men or norethandrolone, 20 to 30 mg orally daily for women), but jaundice may increase. If obstruction is only partial, cholestyramine can be useful.

Hydrocortisone, Fluorinated Steroids, etc.

"Very few patients are referred to dermatological out-patient departments who have not had one of these preparations applied to their skin."*

Adrenal steroids topically are effective in a variety of skin diseases, particularly where there is an allergic factor; they may act by reducing the response of the skin to injury. They also reduce epidermal activity, which is useful in psoriasis. Since the cause of the lesion is not affected it is not surprising that relapse often follows when they are withdrawn.

The difficulties and dangers of systemic adrenal steroid therapy are sufficient to restrict such use to serious conditions (such as pemphigus and generalised exfoliative dermatitis) not responsive to other forms of therapy.

Local applications of fluorinated steroids (which are highly potent) can be absorbed from large areas (especially if occlusive dressings are used) in amounts sufficient to cause systemic effects, including adrenocortical suppression. They are teratogenic in animals and the risk for man is uncertain.

Cortisone and prednisone are ineffective as they must be metabolised to the active forms hydrocortisone and prednisolone, which should therefore be used instead. The most potent steroids for use on the skin are the fluorinated compounds, e.g. triamcinolone, fluocinolone (Synalar) and betamethasone (Betnovate).

Excessive use causes skin atrophy and striæ.

Hydrocortisone 0·25–1% is suitable for use in most eczemas. The potent fluorinated steroids are best reserved for resistant cases and diseases, e.g. psoriasis.

Unfortunately, adrenal steroids impair the natural defences of the skin; existing infection may get worse, or superinfection may occur. For this

* MILNE, J. A. Medical Progress 1970–71. Ed. J. Richardson. Butterworths, London.

reason some think that they should always be used together with a local antimicrobial. Others think that this is only necessary where the lesion is already, or seems particularly likely to become, infected.

Examples of adrenal steroid plus antiseptic ointment or cream include Quinoderm H.C., Barquinol H.C., Vioform Hydrocortisone, Tri-Adcortyl and many others. The steroid does not prevent contact dermatitis from the various ingredients.

Occlusive dressings consist of impermeable plastic sheets fixed to the skin at the edges by adhesive tape. By preventing evaporation they allow hydration of the horny layer of the skin so that soluble drugs penetrate more readily. They are particularly used with adrenal steroids in highly keratinised lesions, e.g. psoriasis. They are generally kept in place for up to two days or only at night; substantial absorption with systemic effects can occur. Complications include infections (bacterial, monilial) and heat stroke.

Intralesional injections are occasionally used to provide high local concentrations without systemic effects in chronic dermatoses.

Sun-burn and Photosensitivity

Sun-burn is produced by ultra-violet light of shorter wave length than that which produces tanning. However, increased pigment in the skin does protect against sun-burn. Ideally, preparations should block only the harmful rays and so allow tanning, but prevent burn. It is doubtful if this can be achieved, but there are many proprietary preparations which act by screening out a proportion or all the ultra-violet rays.

Drug photosensitivity means that an adverse effect occurs as a result of drug plus light. Drugs taken *systemically* that induce photosensitivity include: sulphonamides (including sulphonylurea hypoglycæmics and thiazide diuretics), tetracyclines, griseofulvin, phenothiazines, nalidixic acid, oral contraceptives, chlordiazepoxide.

Substances that, applied *locally*, can produce photosensitivity include: various deodorant substances, halogenated salicylanilides, hexachlorophane, para-aminobenzoic acid and its esters (used as sunscreens), coal tar derivatives, juices of various plants, etc.

There are two forms of **photosensitivity:**

1. **phototoxicity:** this is, like drug toxicity, a normal effect of too high a dose of the appropriate wave length. Drugs may lower or raise the threshold for a phototoxic reaction. Effects occur only whilst the drug is being taken.

Protection is needed against the 290–320 nanometer ultraviolet waveband. It can be achieved by topical application of substances which absorb or scatter these rays. Effective substances include para-aminobenzoic acid, its esters, cinnamic acid, petroleum jelly and benzophenones (mexenone or Uvistat). Simple creams are often enough to limit sunburn to a simple erythema.

If screening blocks the above wavelengths, but permits passage of longer waves and visible light, then tanning will occur. Much of the demand for sunscreens is from people who want to be brown, even though they can give no sensible reason for it; in any case cosmetic acceptability plays a large part in choice. Mexenone is too effective for these people; it prevents tanning.

Many formulations are available, some are more easily removed by sweating and bathing than others and so need frequent reapplication.

Treatment of mild sunburn is usually with a lotion such as Calamine Lotion, Oily, B.P.C. Severe cases are helped by Hydrocortisone Lotion, B.P.C. (or a cream).

2. **photoallergy:** is, like drug allergy, an abnormal effect, that occurs only in some people, and may be severe with a small dose. In relation to drugs it is the result of a photochemical reaction by which the drug combines with tissue protein to form an antigen. Reactions may persist years after the drug is withdrawn.

Photoallergy is caused by longer wavelengths and so preparations that are adequate against phototoxicity do not suffice. Titanium dioxide, zinc oxide and calamine are effective, though cosmetically unattractive. But patients with photoallergy are not concerned with the social one-upmanship of tannin g; they simply want protection.

Systemic protection, as opposed to application of drug to exposed areas, should only be considered in the most severe cases of photosensitivity where a patient may be confined indoors. Chloroquine may be effective in polymorphic light eruptions for short periods, but it is contraindicated in porphyria. Claims for vit A are not substantiated. It is a cumulative poison.

Psoralens (obtained from leguminous plants) e.g. methoxsalen, are photosensitisers that activate melanocytes; they can be used to repigment areas of disfiguring depigmentation. Severe reactions may occur and they are only used by specialists. They are far too toxic to be used merely to obtain a suntan.

Eruptions Due to Drugs

Drugs taken systemically or applied locally often cause rashes. These take many different forms and the same drug will produce different rashes in different people.

Contact dermatitis is commonly eczematous and is often caused by antimicrobials, local anæsthetics and antihistamines. It can also be due to the vehicle in which the active drug is applied.

Reactions to systemically administered drugs are commonly erythematous, like those of measles, scarlatina or erythema multiforme. They give no useful clue to the cause, though hypnotics and purgatives are common culprits.

However, despite great variability, some hints at drug-specific or characteristic rashes, etc. can be discerned, as follows:—

Fixed eruptions are those that recur at the same site, often circumoral, with each administration of a drug. The commonest cause is phenolphthalein, but they also occur with sulphonamides, barbiturates, phenacetin, phenazone and dapsone.

Acne occurs with bromides, iodides, hyoscine, propantheline, ethionamide, isoniazid, PAS, phenobarbitone and troxidone, adrenal steroids and androgens.

Lichen planus may be induced by prolonged administration of heavy metals, antimicrobials, antimalarials, phenylbutazone and thiazides.

Photoallergy and phototoxicity: see above.

Exfoliative dermatitis or erythrodermia may be caused by heavy metals, phenothiazines, phenytoin, phenylbutazone, antimalarials, sulphonamides, chlorpropamide PAS, penicillin and other antibiotics.

Toxic epidermal necrolysis (skin is shed leaving raw areas like burns) is rare and occurs with phenylbutazone, phenolphthalein, sulphonamides and dapsone.

Stevens-Johnson syndrome (skin bullae, arthritis, lymphadenopathy, etc.) may be caused by sulphonamides and barbiturates.

Urticaria and angio-œdema occurs with antibiotics, especially penicillin, and also with heterologous sera and salicylates, especially aspirin.

Pigmentation occurs with progestagens (face) and with phenothiazines, quinidine, chloroquine and arsenic.

Lupus erythematosus occurs with hydrallazine, sulphonamides, procainamide and practolol.

Alopecia occurs with antineoplastic drugs and heparin.

Depigmentation of the hair occurs with chloroquine and mephenesin.

In general, *diagnosis* by provocative test dosing is safe with fixed eruptions, but not with others.

Skin testing is only reliable with contact dermatitis.

Sex Hormones and the Skin

Androgens stimulate the sebaceous glands. Thus they tend to produce seborrhœa and acne. Œstrogens have the opposite effect, but only at doses which have all the other typical effects and so their use for acne in men is seldom justified or acceptable except for a short initial period in severe cases.

Œstrogen-containing creams are advertised as cosmetics to enable women to look younger than they really are, by preventing and removing facial wrinkles. In women before the menopause there is no evidence that œstrogen-containing creams have a greater effect on the skin than the vehicle alone, unless sufficient is absorbed for systemic effects to occur. Post-menopausal atrophic changes do sometimes seem to be improved by their topical use, but seldom to the extent claimed by the manufacturers and desired by emotionally immature women obsessed with lost physical youth.

SUMMARY OF THE TREATMENT OF SOME SKIN DISEASES

The traditional advice, if it's wet, dry it; if it's dry, wet it, contains enough truth to be worth repeating. One or two applications a day are all that is usually necessary unless common sense dictates otherwise.

The table below is not intended to give the complete treatment of even the commoner skin conditions but merely to indicate a reasonable approach.

Secondary infections of ordinarily uninfected lesions may require local or general antimicrobials in addition. Analgesics, sedatives or tranquillisers may be needed in painful or uncomfortable conditions, or where the disease is intensified by emotion or anxiety.

X-ray therapy is helpful in many chronic skin conditions, but special experience is required and so it is not included in the table.

Psoriasis

In psoriasis, keratin production is increased in amount and is also qualitatively abnormal.

Keratin may be removed by scrubbing followed by a dithranol in Zinc and Salicylic Acid Paste, B.P. (Lassar's Paste) beginning with 0·1% and increasing to 1%; it stains skin and fabrics. Tretinoin (Retin-A) (vit A derivative) may be effective.

Resorcinol and sulphur are obsolescent.

If the lesions are wet, then weaker wet dressings of keratolytics are used.

Adrenal steroids reduce epidermal activity and local application, especially under occlusive dressings, can be very effective. Intralesional injections are useful in particularly resistant plaques. Systemic steroid administration should be avoided if at all possible, for high doses are needed to suppress the disease, which is liable to recur when treatment is withdrawn as it must be if complications of long-term steroid therapy are to be avoided.

Folic acid antagonists also suppress epidermal activity temporarily, but they are too toxic for use in any but the most extreme and hospitalised patient; in these they can be life-saving.

Condition	*Treatment*	*Remarks*
Abscess: boils and carbuncles (staphylococcal)	Pus evacuated surgically. Dakin's solution or 1% cetrimide for cleansing. Magnesium Sulphate Paste, B.P.C., is a strongly hypertonic dressing to loosen slough.	Local antimicrobials relatively ineffective, but 2% Na fusidate useful Systemic cloxacillin may be needed in severe cases and may abort an early lesion.

Condition	*Treatment*	*Remarks*
Acne Vulgaris	Soap and water. Ointments containing sulphur and mild keratolytics in resistant cases. Systemic tetracycline in *lowest* effective dose (may act by directly inhibiting sebum lipase). Co-trimoxazole also effective. Topical adrenal steroid may be needed. Detergents worth trying. Œstrogens reduce sebaceous gland activity. Used in severe cases for short initial period to get it under control.	There is increased sebaceous gland activity. Local treatment is to remove the keratin and sebum plugs blocking the sebaceous glands, and generally to reduce the greasiness of the skin. Products of lipolysis are irritant. Severe cases need treatment to prevent permanent scarring of the skin and the mind of the teenage victims.
Alopecia: baldness	None.	No convincing evidence exists that any treatment restores scalp hair.
Chilblains	*Prevention:* short-wave diathermy may help. *Cure:* vasodilators and counter-irritants of dubious value. Vitamins are useless.	Use warm clothing.
Dermatitis Herpetiformis	Dapsone 25 to 250 mg daily. Sulphapyridine 0·25 to 1·5 g daily. Adrenal steroid systemically in resistant cases.	Antipruritics locally as required. Not other sulphonamides; beneficial effect *not* due to antimicrobial action. Methæmoglobinæmia may complicate dapsone therapy.
Drug Eruptions (see above)	Cooling applications and antipruritics.	Adrenal steroid may be needed. Antihistamine systemically for urticaria.
Eczema Acute: **Allergic states: Dermatitis** Subacute:	Lotions (calamine), wet dressings or soaks. Zinc oxide creams or pastes sometimes with mild keratolytics added, e.g. Zinc Oxide and Salicylic Acid Paste, B.P. (Lassar's Paste).	Remove the cause where possible. Often exacerbated by soap and water. Antihistamines orally probably useless. Antipruritics (not antihistamines or local anæsthetics) may be added to lotions, creams or pastes. Adrenal steroid locally may have dramatic effect, with or without coal tar (keratolytic). Stronger keratolytics may be needed.
Chronic:	Zinc Oxide and Coal Tar Paste, B.P.C. Psychiatry can help some.	
Erysipelas and other streptococcal infections	Systemic penicillin.	

Condition	*Treatment*	*Remarks*
Exfoliative Dermatitis	Chelating agent if due to a heavy metal. Cooling creams and powders locally. Adrenal steroid systemically when severe.	
Herpes Simplex	Mild antiseptics for cleansing. Powder for cover.	Symptomatic treatment and prevention of secondary infection. See idoxuridine.
Herpes Zoster	Analgesics. Local antibiotics if the vesicles are large or ruptured.	Prevention of secondary infection reduces scarring.
Hyperhidrosis	Atropine or propantheline. 5% sodium hexametaphosphate either as a solution or in talc. Astringents may reduce sweat production.	Better in theory than practice. The characteristic smell is produced by bacterial action so cosmetic deodorants contain antibacterials rather than substances which reduce sweat production.
Impetigo and Sycosis Barbæ (mainly staphylococcal)	Antimicrobial ointments 2 to 3 times a day. Chlorhydroxyquinolines (e.g. Vioform) especially useful in chronic cases. Systemic antibiotic in severe cases.	Astringent and antiseptic, lotions obsolete except in resistant cases. Pediculosis may be precipitating factor.
Intertrigo	Cleansing lotions. Powders and pastes.	To cleanse, lubricate and reduce friction.
Lichen Planus	Antipruritics	Often very resistant to treatment. Adrenal steroid locally but systemically in severe cases.
Lichen Simplex (neurodermatitis)	Antipruritics. Sedatives.	Covering the lesion so as to prevent scratching sometimes breaks the vicious cycle. Grenz rays and adrenal steroid locally of great value.
Lupus Erythematosus (*a*) Discoid	Fluorinated steroid topically or intralesionally. Chloroquine sulphate or hydroxychloroquine sulphate, but eye toxicity serious hazard.	Amodiaquine may succeed where chloroquine fails. Toxicity is sometimes serious (eye, liver, blood). Mepacrine is safer but turns skin yellow. Resistant cases may need local adrenal steroid in addition.
(*b*) Systemic	Adrenal steroid.	Perhaps chloroquine as well.
Marginal Blepharitis (various organisms)	Ointment containing adrenal steroid and an antimicrobial.	Undue persistence can be due to allergy to treatment.

Condition	*Treatment*	*Remarks*
Monilia	Nystatin ointments or pessaries. Amphotericin B lotions or gargles. Gentian violet paint in the mouth.	
Nappy Rash	*Prevention:* rid nappies of soaps, detergents and ammonia by rinsing. Change frequently and use barrier cream to keep skin dry. *Cure:* mild: Zn cream or calamine lotion, plus above measures. Severe: adrenal steroid locally, plus antimicrobial.	Absorption occurs from raw areas.
Paronychia (monilial and bacterial)	Nystatin ointment under the nail fold, or other appropriate antimicrobial: surgery.	Keep fingers dry.
Pediculosis	Gamma benzene hexachloride (Lorexane). Malathion (an anticholinesterase insecticide) topically. Ritual of application is important. DDT (dicophane) is effective but is accumulating in man and is now less favoured.	
Pemphigus: pemphigoid	Adrenal steroids systemically: cytotoxics sometimes.	Oral hygiene and general nutrition very important.
Pityriasis Rosea	Antipruritics.	Ultra-violet light of value.
Ringworm, Tinea (various fungi)	Acute lesions need lotions and soaks. Chronic lesions on dry skin: Benzoic Acid Compound Ointment, B.P.C. (Whitfield's ointment), Zinc Undecenoate Ointment, B.P. Sub-acute lesions need only half strengths of these ointments. In flexures (e.g. tinea cruris) Magenta Paint, B.P.C. (Castellani's paint) is more satisfactory.	Most preparations are both fungicidal and keratolytic. so the cells containing the fungus are removed. In tinea capitis epilation has been replaced by griseofulvin. Clipping the hair short and thorough local treatment of the whole scalp prevent self reinfection. Ringworm of nails is very resistant to everything except griseofulvin.

Condition	*Treatment*	*Remarks*
Ringworm, Tinea (various fungi) (*cont.*)	Fungicidal powders, e.g. undecenoate, are helpful together with ointments and foot hygiene in tinea pedis. Griseofulvin valuable, but disappointing for feet.	Diamthazole ointment (Asterol), tolnaftate (Tinaderm) and pecilocin (Variotin) are useful.
Rosacea	1 to 2%sulphur in emulsion base. Perhaps tetracycline.	Flushing makes it worse. Œstrogens for menopausal flushing.
Scabies	Benzyl Benzoate Application, B.P., to whole body below the neck. Correct ritual is essential. Alternatives: gamma benzene hexachloride (Lorexane): monosulphiram (Tetmosol): crotamiton (Eurax).	
Scleroderma		No proved therapy.
Seborrhœic Dermatitis, Acute: Chronic: **Dandruff**	Lotions, wet dressings. Daily use of soapless shampoos, e.g. cetrimide 1%. Selsun shampoo contains selenium sulphide. Mild cases need only daily applications of Lotion or Salicyclic Acid Lotion, B.P.C. If more severe, hydrocortisone or fluorinated steroid scalp applications are needed.	Antimicrobials if badly infected. Sulphur in various forms helps the seborrhœic state but the reason is not known. Selsun irritates the eyes and is poisonous if swallowed. Local adrenal steroid often helps seborrhœa.
Urticaria, Angioneurotic Œdema	As for allergic reactions.	
Vitiligo	No safe and reliable treatment.	Methoxsalen or other psoralen, topically or systemically, plus daily exposure to U.V.L. is toxic, troublesome and often fails.
Warts*	Surgical removal. Liquid nitrogen. Solid CO_2. Podophyllin daily. Salicylic acid 20% in collodion daily. Many other caustic preparations. Salicylic and lactic acid lotion (Salactol) topically under occlusion after removing surface layer with coarse emery.	Warts often disappear spontaneously. For plantar warts formalin 3% footsoaks 20 mins nightly for 6–8 weeks cures 80% cases.
X-ray Dermatitis	Adrenal steroid locally.	

* Non-surgical remedies may act by disrupting the wart so that virus is absorbed, antibodies develop and the wart is rejected immunologically.

Drugs and venous ulcer healing. Drugs are not primary treatment for ulcers. But zinc sulphate orally can hasten healing, though its place in routine treatment is still uncertain (*14*).

Drugs applied locally are only adjuvants to remove sloughs, e.g. Aserbine (malic, benzoic, salicylic acids). Allantoin dubiously hastens healing.

Adrenocortical steroids may make ulcers worse.

Infections and œdema are treated as usual.

Removal of hair

"Unfortunately, our formalised cosmetic standards do not conform with the normal biological range, and this discrepancy brings misery to many individuals" (*15*).

Epilation is removal of the intact hair, one at a time or embedded in wax and pulled out in quantity. This is temporary, and electrolytic destruction of the follicle is the only permanent technique.

Depilation is removal of the hair above the skin surface. Shaving is effective. Women are ashamed to shave their faces, but not their legs. Chemical depilatories are preferred. They act by reducing the disuphide bond between cystine molecules in polypeptide chains. The result is that osmotic pressure within the hair fibre causes swelling and jellification so that it can be wiped off (*15*). Many chemicals are effective. Substituted mercaptans in alkali are much used.

Guide to Further Reading

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Chapter 31

POISONING: CHELATING AGENTS: POISONS

POISONING

THE treatment of poisoning due to particular therapeutic agents is largely dealt with under the drug concerned. In this chapter the principles of treatment and miscellaneous antidotes and poisons are described.

A Note on Deliberate Self-poisoning (39)

Until recently, most of those who poisoned themselves were seriously trying to commit suicide. A curious by-product of the modern "drug explosion" is that this is no longer so and "self-poisoning" flourishes, "since few who practise it have their minds set on dying," and live to give another display. "To take tablets knowing that this will remain undiscovered for many hours is a very different matter from promptly entering the living room and brandishing the offending bottle before the assembled family's startled gaze" (5).

More than one in every thousand of the adult population of Edinburgh have been admitted to hospital each year after an act of self-poisoning (5). Drugs are used by 90% of cases (barbiturates 55%, aspirin 12% and other drugs, generally sedatives, tranquillisers or antidepressants for the rest). Coal gas is used by 9%. Thirty five years ago corrosive poisons, e.g. lysol, and coal gas accounted for nearly all cases of self-poisoning (domestic gas is now manufactured less from coal and contains less or no carbon monoxide. Natural gas is largely methane.)

Some Aspects of Acute Poisoning*

For centuries it was supposed not only that there could be, but that there actually was, an antidote to all poisons. This was Theriaca Andromachi, a formulation of 72 (a magical number) ingredients amongst which particular importance was attached to the flesh of the viper. The antidote was

* MATTHEW, H. (1971). Acute poisoning: some myths and misconceptions *Brit. med. J.*, **1**, 519. "Much of the available information on the features and management of poisoned patients is still presented with an air of authority by persons who seldom deal with live patients or by others who are not clinically involved to any depth. Pharmacologists . . . have . . . been accepted as authorities in clinical toxicology, and the literature remains rich in their folklore . . . " "The time has come for . . . pharmacologists to cease writing about the clinical effects and treatment of acute poisoning in humans." There is considerable justice in this complaint, and the notes offered here are written with it in mind.

devised by Andromachus, physician to the Roman Emperor, Nero* (54–68 A.D.).

In practice most emergency treatment of acute poisoning is symptomatic, success depending on a combination of speed and common sense as well as on the poison, the amount taken and the time which has since elapsed. In clinical practice a selective antagonist (antidote) is available for less than 2% of episodes. Where there is a selective antidote, its use can be vital, e.g. naloxone against morphine-like drugs, atropine against cholinergic drugs, pralidoxime against anticholinesterases.

In Britain there are now regional poisons centres (listed in B.N.F.) which can provide information and advice on the telephone throughout the day and night. Doctors who use the service are later asked for a short report to provide information for future reference, but only 60% of those asked trouble to reply.†

There has been much controversy over *the relative values and indications for emesis and gastric aspiration and lavage.*

Evidence from experiments on man and dogs and clinical experience suggests the following as reasonable:

If the patient is conscious vomiting may be induced by Syrup of Ipecacuanha‡ (which works in about 20 mins), or by putting the patient's own fingers down his throat. Mechanically induced vomiting is less effective than Syrup of Ipecac.§ The amount of drug recovered will obviously vary with time since episode and with vigour of vomiting; but more than 30% of recovery cannot be counted on. The advantage of emesis is that it can be done on first seeing the patient whereas gastric aspiration and lavage should be done in hospital.

On arrival at hospital a decision whether to do gastric aspiration or lavage must be made. It will depend on a general assessment of the case, including what is known of the amount taken.

If the patient is unconscious gastric aspiration and lavage should be performed if the drug was taken within 4 hrs, (but up to 12 hrs or longer with aspirin or salicylate which remain longer in the stomach). The technique of lavage (with repeated small volumes) is important but will not be considered here. The chief danger is aspiration into the lungs. This is avoidable by inserting a cuffed endotracheal tube.

After corrosive poisons there is a hazard of gastric perforation and the decision to use a tube or not will be influenced by the amount taken, its concentration and by time since the episode.

* A remarkable man whose subjects believed him to be a god. He even believed it himself, with results that were as inevitable as they were disastrous. His conduct soon caused him to have an urgent need for a universal antidote, "But the domestic infelicities of the Caesars are no part of our present story. The reader greedy for criminal particulars must go to the classical source, Suetonius." (H. G. Wells. The Outline of History: 1920: many editions).

† Editorial (1965). *Lancet*, **1**, 592.

‡ 15-20 ml, followed by a small volume to drink (water).

§ N.B. *Not* Liq. Extr. Ipecac. (B.P.), emetic dose 0·5–2 ml, though this can be diluted to substitute for Syrup.

Where it is thought necessary to pass a stomach tube, this may have to take second place to emergency resuscitation measures, artificial respiration or suppression of convulsions. Nothing is gained by aspirating the stomach of a corpse, except practice.

It is essential that the immediate aim be clear for, without this, treatment will not combine maximum efficacy with minimum risk, e.g. in narcotic poisoning the aim is to keep the patient oxygenated, to sustain his circulation and electrolyte balance until the poison has been eliminated, and to prevent the development of pneumonia. It is *not* to wake the patient up at once, for this, though satisfying to the physician, may be impossible to achieve without poisoning the patient with convulsant drugs.

The principles of treatment may be stated thus:—

1. **Identification of the poison(s).** Since there are few selective antagonists this is not always as useful as could be hoped.

2. **Removal of the poison.**

a. **External:** wash with water, sodium bicarbonate, vinegar, alcohol, as appropriate.

b. **From the gut:** (i) by emesis, in conscious patients only, especially if solids (e.g. berries) which might block a tube have been eaten. Aspiration must be considered, especially if the patient will not vomit.

(ii) gastric aspiration and lavage (see above). Fluid obtained should be kept for chemical analysis.

3. **Prevention of further absorption of the poison**

a. **From an injection site:** tourniquet;

b. **From the gut:**

(i) Specific antidotes which combine chemically with the poison. This is important in the case of acids and alkalies but is probably ineffective with most other substances except iron (desferrioxamine). Generation of gas in the alimentary tract is undesirable and can be dangerous; an elementary knowledge of chemistry should suffice to avoid this.

(ii) Non-specific antidotes, mostly demulcents, e.g. raw eggs, milk, kaolin, flour and water, activated charcoal (useful in salicylate, barbiturate, glutethimides, kerosene poisoning etc), castor oil (reduces glutethimide absorption).

(iii) Saline purgatives may be useful if the patient is conscious; to leave one in the stomach of an unconscious patient invites vomiting.

4. **Specific pharmacological antidotes (antagonists)**

E.g. nalorphine, atropine, antihistamines, pralidoxime or chelating agents.

5. **Non-specific pharmacological antidotes (antagonists)**

E.g. anticonvulsants in convulsant, and analeptics in narcotic, poisoning. Analeptics have no place where assisted respiration is available.

6. **Alteration of excretion or metabolism of the poison**

The techniques of forced diuresis and dialysis can make a contribution to recovery when used *skilfully* in the *right* patients. The decisions to use them are generally made on clinical grounds, though sometimes blood levels are useful in predicting the need, e.g. barbiturates, salicylates. It is easy to kill the patient by unskilled handling.

Diuresis and forced diuresis. Obviously, good urine volume will promote the elimination of drugs that are excreted by the kidney. In some cases the increase obtainable by giving maximum safe amounts of fluid and a diuretic is enough to be of practical importance in treating overdose. Sometimes, too, controlling urinary pH has practical importance (see index). The technique and its rationale are described under barbiturate pharmacokinetics (ch 10).

Forced diuresis, with or without pH change, can be expected to be particularly helpful with the following:—

Forced diuresis

Bromide, lithuim, barbiturates (including the "shorter-acting" drugs)*.

Forced alkaline diuresis

Phenobarbitone, salicylates, nitrofurantoin, phenylbutazone, probenecid.

Forced acid diuresis

Amphetamine, pethidine, levorphanol, quinine, chloroquine.

Hæmodialysis and peritoneal dialysis are specialised techniques that are more effective than diuresis.

Criteria for dialysability. The drug should:—

1. pass readily through the dialysing membrane.

2. readily equilibrate with plasma: tight binding to plasma proteins or tissues is disadvantageous.

3. be dialysable in clinically useful amount in relation to the body's powers to metabolise or excrete.

Hæmodialysis is 5–10 times as efficient as peritoneal dialysis. But peritoneal dialysis is easy to do in any hospital whereas hæmodialysis can only be done in special centres.

Good results have been reported with hæmodialysis of barbiturates (removed 10 to 60 times as fast as by spontaneous processes), salicylates (3 times as fast), bromide (80 to 100 times as fast), ethanol and methanol (10 to 50 times as fast) and isoniazid (twice as fast).

Dialysis is probably also worthwhile in patients with renal insufficiency in whom streptomycin, vancomycin or neomycin have accumulated to toxic levels during therapeutic use.

* Simon, N. M. *et al.* (1971). *Rational drug therapy*. **3**, No. 5.

With plasma protein-bound drugs, dialysis becomes more effective if serum albumin is incorporated in the dialysing fluid, to reduce the free and exchangeable drug in the fluid so that the concentration gradient of *free* drug from plasma to dialysing fluid is maximal. But this may only be practicable with the smaller volumes of dialysing fluid used in peritoneal dialysis.

Drugs that can be dialysed usefully include: the commonly used barbiturates, phenytoin, primidone, ethchlorvynol, paraldehyde, chloral, heroin, amphetamines, alcohols, salicylates, paracetamol, many antibiotics, isoniazid, quinine, quinidine, many metals, bromide, iodide, ergotamine, carbon tetrachloride, etc.

Ion-exchange resins. Blood may be passed over resins to remove poisons.

Exchange blood transfusion is sometimes practicable in children.

Metabolism. The rate of metabolism of methanol can be slowed by giving ethanol to compete in the metabolic paths. The rate of **excretion** of lithium and bromide can be hastened by giving NaCl.

7. **General supportive treatment** is of prime importance.

This cliché can be taken to mean measures directed towards maintaining circulation, respiration and electrolyte balance, and to preventing pneumonia in **unconscious patients,** whose care may be summarised:—

a. Treatment of the cause of unconsciousness, if possible.

b. Preservation of respiration and oxygenation, by artificial respiration or drugs if necessary.

c. Prevention of hypostatic pneumonia by altering the posture of the patient about every three hrs and prevention of inhalation of foreign material by posture (head lower than chest) and suction of airways as needed. Chemoprophylaxis (which see) of pneumonia by, say, penicillin, is often used if the patient has been unconcious more than 12 hrs, although the merits of this are dubious. It may be better to wait for an infection and then to treat it vigorously than to use antimicrobials and increase the risk of a drug-resistant pneumonia.

d. Prevention of starvation, dehydration and electrolyte abnormalities, but nothing given orally.

e. Prevention of bladder distension.

f. Prevention of hypothermia.

g. Prevention of bed sores.

Serum enzymes in poisoning. Increased amount of some serum enzymes (creatine kinase etc), that occur with tissue damage due to disease also occur in severe poisoning. This can indicate direct drug toxicity to an organ, or non-specific damage to many tissues (e.g. muscles) by fibrin deposition in the microcirculation, hypothermia, hypoxia and hypotension (*17*).

MISCELLANEOUS ANTIDOTES AND POISONINGS

Chelating Agents

A chelating agent is any compound that will render an ion (generally a metal) biologically inactive by incorporating it into an inner ring structure in the molecule (Greek, *chele* = claw). It does this by means of chemical groups called ligands. Where the stable complex is non-toxic and is excreted in the urine, this offers a way of inactivating and eliminating toxic metals.

The principal uses of chelating agents are as follows:—

Dimercaprol (B.A.L.) for *arsenic*, *mercury*, *gold*, chromate, antimony.

Sodium calciumedetate for *lead*, calcium, copper, manganese and radioactive plutonium, uranium, thorium, yttrium.

Penicillamine (dimethylcysteine) for *copper*, *lead*, mercury: also in cystinuria.

Desferrioxamine for *iron*, (which see).

Dimercaprol (B.A.L., British Anti-Lewisite) competes with body enzymes for toxic metal ions. It was synthesised during a systematic study of possible antagonists to arsenical vesicant war gases such a Lewisite. Arsenic and other metal ions are toxic in relatively low concentration, probably because they combine to form a ring structure with the —SH groups of essential enzymes, thus inactivating them. Dimercaprol protects by combining its —SH groups with the metal ions to form relatively harmless ring compounds which are excreted, mainly in the urine. Dimercaprol is therapeutically effective because the ring compound formed with many heavy-metal ions is more stable than is the ring structure that the ions form with enzymes. It is obviously desirable that there should be an excess of dimercaprol available until all the metal has been excreted and, as it is both oxidised in the body and excreted in the urine, repeated administration is necessary.

Use. Dimercaprol is useful and may be life-saving in poisoning with the metals listed above. It is ineffective primary therapy in lead poisoning because it does not combine with the metal sufficiently firmly, but it may be useful given *with* sodium calcium edetate. It may be used similarly in hepato-lenticular degeneration.

Dimercaprol, as 5% solution, is given by deep and painful i.m. injection. The dose in chronic poisoning is 3 mg/Kg, 4-hrly for 2 days, 6-hrly on the third day and then 12-hrly for 7 days. In severe acute poisoning the course can be started with 5 mg/Kg 4-hrly during the first 24 hours. It may be applied to damaged skin in lewisite or chromate poisoning.

Toxic effects are common, particularly with the larger doses. They include nausea and vomiting, lachrymation and salivation, paresthesiæ, muscular aches and pains, urticarial rashes, tachycardia and a raised blood pressure. Gross over-dosage may cause overbreathing, muscular tremors, convulsions and coma. The mechanism of the toxic effects is not known, but it has been suggested that the removal of metallic groups from essential enzymes may be responsible. Ephedrine or an antihistamine may reduce adverse reactions if given 30 min before an injection.

Tetraethyl lead (in petrol) is non-ionic and so is not bound by chelating agents.

Sodium calciumedetate (Calcium Disodium Edathamil: the calcium chelate of the disodium salt of ethylenediamine-tetra-acetic, EDTA) is a calcium chelate which has revolutionised the treatment of lead poisoning. The chelating agent combines more avidly with lead than with calcium and the lead chelate is formed by exchange and is excreted in the urine, leaving behind a harmless amount of calcium. Dimercaprol combines with lead less firmly but is usefully given with sodium calciumedetate in acute lead poisoning.

The symptoms and signs of *lead poisoning* respond dramatically to this treatment.

Sodium calciumedetate is given i.v., 1·0 g, 12-hrly (over 1 hr), usually in 5-day courses, repeated as necessary after a 7-day interval. Alternatively it can be given i.m., with 0·5% procaine (to reduce pain). A second course should be given in lead poisoning if urinary coproporphyrin excretion exceeds 250 mcg/24 hrs, or if severe signs persist.

Ill-effects are fairly common, and include hypotension, lachrymation, nasal stuffiness, sneezing, muscle pains and chills. Renal damage can occur.

Disodium edetate forms sodium calciumedetate in the body, inducing hypocalcæmia so that tetany may occur. This action can be used in *hypercalcæmia* and in *digitalis poisoning*.

D-Penicillamine (dimethylcysteine) is a metabolite of penicillin that contains —SH groups, so that it is similar to dimercaprol in action. It can be given orally or injected.

Its principal use is in **hepatolenticular degeneration** (Wilson's disease) in which there is an inherited defect that prevents normal copper disposal so that the metal accumulates in the body. Although dimercaprol can be useful in this disease, penicillamine is more effective and can be taken orally, which is important because therapy must be life-long.

Penicillamine can halt the progress of the disease, but improvement is limited by the amount of irreversible brain damage that has occurred. Therefore early diagnosis of hepatolenticular degeneration is important.

Potassium sulphide, 20 mg orally, after meals, is often given as well, to reduce absorption of copper from the intestine by forming insoluble copper sulphide.

Penicillamine combines with cystine and prevents formation of stones in **cystinuria;** it also combines with pyridoxine and can cause pyridoxine deficiency. An effect on collagen may explain its benefit in advanced **rheumatoid arthritis.**

Lead poisoning. Sodium calciumedetate i.m. or i.v. plus dimercaprol in acute cases are the drugs of choice. But penicillamine is an alternative. After the acute phase is over, oral penicillamine can be used until the blood lead concentration falls.

Cyanide poisoning. Effects of cyanide appear so rapidly that usually the patient is either dead before treatment can be started or else has taken so little that recovery is inevitable if he is left alone. However, speedy treatment may save an occasional life. Cyanide causes cellular anoxia by chelating the metallic part of the intracellular respiratory enzyme, cytochrome oxidase. The combination is reversible.

Therapy consists of measures to chelate cyanide in the blood by means of the ferric iron of methæmoglobin to form cyanmethæmoglobin. If enough methæmoglobin is formed (20 to 30% of the total hæmoglobin), it will compete successfully for the cyanide already combined with cytochrome oxidase. Methæmoglobin is made by giving inhalations of amyl nitrite and by injecting sodium nitrite i.v., followed by sodium thiosulphate to convert the cyanide to inactive thiocyanate.

Gastric lavage with an oxidising solution to convert cyanide to inactive cyanate should be done after the formation of methæmoglobin, e.g. sodium thiosulphate (5%): potassium permanganate (0·2%): hydrogen peroxide (3%).

A chelate of cobalt (hydroxocobalamin) has been shown to be effective in experimental animals poisoned by cyanide (it is converted to the stable cyanocobalamin) and it may well be clinically useful. It has the advantage that it does not reduce the oxygen-carrying capacity of the blood as does methæmoglobin. Cobalt edetate and acetate have also been used (*30*).

There is evidence that oxygen, especially if at high pressure (hyperbaric) overcomes the cellular anoxia in cyanide poisoning; the mechanism is uncertain, but oxygen should be used in therapy.

In **carbon monoxide** poisoning oxygen also hastens the conversion of carboxyhæmoglobin. Hyperbaric oxygen is additionally useful because enough can dissolve in *plasma* to oxygenate tissues.

Dinitro-compounds. Dinitrophenol, abandoned as an explosive, had a short career in therapy of obesity, but it was so toxic that it shortened life more than obesity does. It was tried because it increased cellular respiration (by uncoupling oxidative phosphorylation), increasing the metabolic rate so that the surplus fat would be used up.

Related compounds, dinitro-orthocresol (DNOC) and dinitrobutylphenol (DNBP), are used as selective weed killers and insecticides and cases of poisoning occur accidentally and when safety precautions are ignored. They can be absorbed through the skin and the hands, face or hair are usually stained yellow. Symptoms and signs are mainly those associated with a very high metabolic rate. Copious sweating and thirst are early warning signs and may proceed to dehydration with vomiting, weakness, restlessness, tachycardia and deep rapid breathing. Eventually convulsions and coma may occur. Treatment is urgent and consists of cooling the patient and attention to fluid and electrolyte balance. It is essential to differentiate this type of poisoning from that due to cholinesterase inhibitors because if atropine is given to a patient poisoned with a dinitro-compound he may stop sweating and die of hyperpyrexia.

Organophosphorus pesticides are anticholinesterases (which see); they also cause delayed neurotoxicity. Organic carbamates are similar.

Organochlorine pesticides (DDT, etc) may cause convulsions in acute overdose. Treat as for status epilepticus.

Fluoracetamide and relatives are rat poisons. They cause muscular twitching and convulsions with death from cardiorespiratory collapse. Selective antidotes have been found in the laboratory but have not been proved in man (*28*).

Paraquat and diquat are widely used herbicides. A mouthful is enough to kill. When swallowed there may be mouth and gut irritation and vomiting. After several days signs of lung, gut, liver and renal damage develop and the victim dies unpleasantly. Activated charcoal swallowed, and forced diuresis or dialysis may help.

Kerosene (paraffin or diesel oil), **petrol** (gasoline) chiefly cause CNS depression and pulmonary damage from inhalation. It is vital to avoid aspiration into the lungs during attempts to remove the poison or in spontaneous vomiting: gastric aspiration should only be performed if a cuffed endotracheal tube is in place. It may be necessary to anæsthetise the subject to do this.

Harassing Agents
(short-term incapacitants: anti-riot agents)

"Harassing agents may be defined as chemical agents that are capable, when used in field conditions, of rapidly causing a temporary disablement that lasts for little longer than the period of exposure" (*15*). They are sensory irritants that cause pain in the most sensitive tissues with which they come into contact, i.e. the eyes and respiratory tract. This results in reflex lachrymation, sneezing (some chemicals have therefore been classed as *sternutators*) and cough. If the agent is a gas, or an aerosol of particles less then 0·5μm in diameter, it will penetrate to the small bronchi and cause chest pain.

A description of the effect of one substance will suffice:—

"According to the concentration of CS to which a person is exposed, the effects vary from a slight pricking or peppery sensation in the eyes and nasal passages up to the maximum symptoms of streaming from the eyes and nose, spasm of the eyelids, profuse lachrymation and salivation, retching and sometimes vomiting, burning of the mouth and throat, cough and gripping pain in the chest" (*13*). The onset of symptoms occurs immediately on exposure (an important factor from the point of view of the user) and they disappear dramatically; "At one moment the exposed person is in their grip. Then he either stumbles away, or the smoke plume veers or the discharge from the grenade stops, and immediately the symptoms begin to roll away. Within a minute or two, the pain in the chest has gone and his eyes, although still streaming, are open. Five or so minutes later the excessive salivation and pouring tears stop and a quarter of an hour after exposure, the subject is essentially back to normal" (*13*).

The pharmacological requirements for a safe and effective harassing agent (it is hardly appropriate to refer to "benefit" versus risk) must be stringent. As well as potency and rapid onset and offset of effect, in open areas under any atmospheric condition, it must also be safe in confined spaces where concentration may be very high and may affect an innocent bedridden invalid should a projectile enter the window.

A favoured substance at present is CS (orthochlorobenzylidene malanonitrile).

This is a solid that is disseminated as a particulate aerosol by including it in a pyrotechnic mixture. The spectacle of its dissemination has been rendered familiar by television. It is not a gas, it is an aerosol or smoke.

The particles aggregate and settle to the ground in minutes so that the risk of prolonged exposure out of doors is not great.

Exposed subjects absorb small amounts only, and the plasma $t_{\frac{1}{2}}$ is about 5 sec.

Investigation of the effects of CS are difficult in "field use", but some have been done and at present there is no evidence that even the most persistent rioter will suffer any permanent effect. The hazard to the infirm or sick seems to be low, but plainly it would be prudent to assume that asthmatics or bronchitics could suffer an exacerbation from high concentrations, though bronchospasm does not occur in normals. Whether or no CS can cause unconsciousness is uncertain and is difficult to investigate for, "In the highly charged circumstances of a riot, unconsciousness can occur for a variety of reasons," and deliberate use of CS in training operations has induced panic and fainting at first contact.

Vomiting seems to be due to swallowing contaminated saliva. Transient looseness of the bowels may follow exposure.

Hazard from CS is probably confined to situations where the missiles are projected into enclosed spaces.

Various formulations of CS can be prescribed, e.g. *Cartridge*, $1\frac{1}{2}$ *inch*, *Anti-riot*, *Irritant*, and *Grenade*, *Hand*, *Anti-riot*, *Irritant*.

There are other harassing agents (CN, and DM or adamsite) which are more persistent and toxic. CR is a recent introduction, but "authority" is reticent about its properties.

This brief account has been included because even the most well-conducted and tractable student may find himself exposed to CS smoke in our troubled world; and some may even feel it their duty to incur exposure. A description of such substances is a sad way to end a book on clinical pharmacology, a science that exists for the purpose of increasing happiness by relief of suffering.

Drugs used for Torture

Regrettably, drugs have been and are being used for torture, sometimes disguised as "interrogation" or "aversion therapy". Facts are, not surprisingly, hard to obtain, but it seems that suxamethonium, hallucinogens, thiopentone, neuroleptics, amphetamines, etc. have been

employed to hurt, frighten, confuse or debilitate in such ways as callous ingenuity can devise.

It might be urged that it is justifiable to use drugs to protect society by discovering serious crimes such as murder.

But there always must be uncertainty of the truth of evidence, obtained with drugs, that cannot be independently confirmed; also their use offers inducement to inhuman behaviour. In addition, the definition of criminal activity is so easily perverted to include activities in defence of human liberty, and opinions on what is desirable social change vary so widely, that this use of drugs, and any doctors or others who engage in it, must surely be outlawed.

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APPENDIX

WEIGHTS AND MEASURES

N.B. Tablet size is given in brackets after drug name throughout the book.

In this book all doses are given in the metric system. All new drugs are now prescribed metrically and there can be no doubt that it is both inevitable and desirable that this will be the sole system of dosage.

Equivalents: 1 litre (l) = 1·76 pints.
1 kilogram (Kg) = 2·2 pounds (lbs).

Abbreviations: 1 gram (g).
1 milligram (mg) (1×10^{-3}g).
1 microgram (mcg or μg) (1×10^{-6}g) but it is safer to write the word in full to avoid confusion with mg.
1 nanogram (ng) (1×10^{-9}g).
1 millilitre (ml). (1×10^{-3}l).
1 micrometre (μm) (1×10^{-6}metres).

Domestic measures. A standard 5 ml spoon is available. Otherwise the following approximations will serve:

1 tablespoonful = 14 ml.
1 dessertspoonful = 7 ml.
1 teaspoonful = 5 ml.

PRESCRIBING

Prescriptions of pure drugs or preparations from the British National Formulary (B.N.F.) are satisfactory for almost all purposes. The composition of many of the preparations in the B.N.F. is laid down in either the British Pharmacopœia (B.P.) or British Pharmaceutical Codex (B.P.C.). Hence there is nowadays seldom any need to write a traditional prescription comprising base, adjuvant, corrective, flavouring and vehicle and the skill is virtually lost.

It is both unnecessary and unwise to try to continue the use of traditional forms of prescription writing in Latin, for facility in their use can only be attained by frequent practice. To try to use these old-fashioned terms when they do not come naturally to the mind is to court the embarrassment of issuing an incomprehensible, or worse, an inaccurate, prescription.

It is both easier and safer to state the requirements in English. However, complete consistency is seldom to be achieved in any matter, and there is little doubt that certain convenient Latin abbreviations will survive for lack of English substitutes. These are chiefly used in hospital prescribing where instructions are given to nurses and not to patients for whom such abbreviations would be meaningless. They are listed at the end of this appendix. The elementary requirements of a prescription are that it should state *what* is to be given *to whom* and *by whom* prescribed, and give instructions on *how much* should be taken *how often*, by what route and sometimes for *how long*, thus:—

1. **Date.**
2. **Address of Doctor.**
3. **Name and Address of Patient.**
4. ℞. This is a traditional esoteric symbol for the word "Recipe"—"take thou!", which is addressed to the pharmacist. It is pointless; but since many doctors gain a harmless pleasure from writing ℞ with a flourish before the name of a proprietary preparation of whose exact nature they are ignorant, it is likely to survive as a sentimental link with the past.
5. **The Name and Dose of the Drug or Drugs.**
6. **Directions to the Pharmacist,** if any, thus—"mix", "make a solution". Write the total quantity to be dispensed if this is not stated in 5 above.
7. **Instruction for the Patient,** to be written on container by the pharmacist. Here brevity, clarity and accuracy are especially important. It is dangerous to rely on the patient remembering verbal instructions.
8. **Signature of Doctor.**

It is no longer considered necessary to conceal from every patient the nature of his treatment and it is now normal to write the name of the preparation on the label.

Example of a Prescription for a patient with an annoying unproductive cough.

1, 2, 3, as above.
4. ℞.
5. Codeine Linctus, B.P.C., 5 ml.
6. Send 60 ml.
7. Label: Codeine Linctus (or N.P.). Take 5 ml twice a day and on retiring N.P.
8. Signature of doctor.

Legal aspects of prescribing are given in the British National Formulary (B.N.F.) which is supplied free to doctors practising in the National Health Service and to medical students.

ABBREVIATIONS (see also *weights and measures*)

a.c., ante cibum	before food
b.d., bis in die	twice a day (b.i.d. is sometimes used)
B.N.F.	British National Formulary
B.P.	British Pharmacopœia
B.P.C.	British Pharmaceutical Codex
i.m., intramuscular	by intramuscular injection
I.U.	International Unit
i.v., intravenous	by intravenous injection
N.P., nomen proprium	proper name
o.d., omni die	every day
o.m., omni mane	every morning
o.n., omni nocte	every night
p.c., post cibum	after food
p.o., per os	by mouth

p.r.n., pro re nata	as required. It is best to add the maximum frequency of repetition, e.g. Aspirin Compound Tablets, 1 or 2 p.r.n., 4-hourly
q.d.s., quater in die sumendus	four times a day (q.i.d. is sometimes used)
q.s., quantum sufficiat	a sufficiency, enough
rep., repetatur	let it be repeated, as in rep. mist(ura), repeat the mixture
s.c., subcutaneous	by subcutaneous injection
s.o.s., si opus sit	if necessary. It is useful to confine s.o.s. to prescriptions to be repeated once only and to use p.r.n. where many repetitions are intended
stat., statim	immediately
t.d.s., ter in die sumendus	three times a day (t.i.d. is sometimes used)

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INDEX

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'Patients may recover in spite of drugs or because of them.
J. H. Gaddum, 1959

Intended primarily for medical students in their clinical years and for those newly qualified, this survey of the principal drugs with details of their use and pharmacology has achieved outstanding popularity. The new edition is thoroughly revised and emphasizes topics of current interest and clinical importance.

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