Pythagoras of Samos, a great mathematician rather than a physician, may have been first in stating emphatically, in the 5th century B.C., that fava beans could be dangerous and even lethal for humans.1,2 This gives him a place in nutrition science but not in nutrogenomics: it seems he did not realize that the danger depended on the genotype of the person eating the beans. This has become clear only since 1956, when glucose-6-phosphate dehydrogenase (G6PD) deficiency was discovered.3 It quickly became apparent that this inherited trait underlies at least three diseases, which had seemed until then unrelated: drug-induced hemolytic anemia, severe neonatal jaundice, and favism. There is a large literature, including many reviews,4-6 on all aspects of G6PD deficiency. In this review, we focus on favism.

The contemporary medical history of “ictero-hemoglobinuric favism”1,2 came into its own in the 19th century in Portugal, Italy, and Greece, and its features were well reflected in two landmark reviews, by Fermi and Martinetti7 in 1905 and by Luisada8 in 1941. Because this is old literature, favism is often perceived as a thing of the past. In fact, on a global basis,9 it is probably still the most common form of acute hemolytic anemia.

In favism, there are two main actors: the bean and the red cell. Favism defies the classic distinction between intraerythrocytic and extraerythrocytic causes of acute hemolytic anemia, since it develops only when a person with G6PD-deficient red cells is exposed to certain substances contained in fava beans. The fava bean plant (Vicia faba) was probably one of the first plants to be domesticated10,11 in Asia and in the Middle East, for human consumption, and it is one of the leguminous plants that benefit from symbiosis with rhizobia, the nitrogen-fixing bacteria that grow on its roots and make the use of fertilizers unnecessary. V. faba produces beans that (apart from being delicious) contain more than 25% protein in dry weight.12 The beans can be eaten raw or cooked, fresh or dried. V. faba contains high concentrations of two β-glucosides (up to 2% in dry weight): vicine and convicine.13 On ingestion of fava beans, vicine and convicine undergo hydrolysis by glucosidases present both in the beans and in the gastrointestinal tract,14 releasing the respective aglycones: divicine (2,6-diamino-4,5-dihydroxypyrimidine) and isouramil (6-amino-2,4,5-trihydroxypyrimidine). These highly reactive redox compounds have antifungal15 and pesticide16 activity, which probably helps prevent fava beans from rotting, but the compounds are also capable of triggering a favism attack.

Epidemiologic Features of Favism

Favism occurs commonly only where the frequency of G6PD deficiency is relatively high17 and where fava beans (also known as broad beans) are a popular food item (https://readtiger.com/img/wkp/en/Broadbean_Yield.png), which reflects its...
bifactorial nature. This is true, for instance, in southern Europe, in the Middle East, and in Southeast Asia but not, for example, in northern Germany, where fava beans are grown but G6PD deficiency is rare, or in West Africa, where G6PD deficiency has a high prevalence but fava beans are not grown.

There is no registry for favism, and its incidence is not known precisely. However, in the Sassari province of Sardinia, with a population of 0.5 million, 948 cases were reported over a 15-year period (1965–1979), for a yearly incidence, at that time, of 1.2 cases per 10,000 population. In a recent report from Gaza, with a population of 1.9 million, 223 children with favism were admitted to one hospital over a 6-year period, for a yearly incidence of 1 case per 50,000. Since we know that only the most severe cases were seen at the hospital (and possibly not all of them), this is a minimum estimate.

Favism has been reported in 35 countries, and reports of more than 3000 cases, mostly involving children, have been published during the past 40 years, with 12 publications each reporting series of 50 or more cases of favism (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In contrast, with respect to drug-induced acute hemolytic anemia in patients with G6PD deficiency, only one large series (involving 295 patients, of whom 200 were heterozygotes) has been published; all other reports have been limited to one or very few cases. It is reasonable to presume that thousands more cases of favism must have occurred, since there is no compelling reason to publish a report on a well-known condition. Therefore, favism is by far the most common form of G6PD deficiency–related acute hemolytic anemia. Since in Europe and the United States the incidence of autoimmune acute hemolytic anemia is estimated to be on the order of 1 case per 50,000 population, favism is also one of the most common types of acute hemolytic anemia, especially among children.

**Clinical and Pathophysiological Features of Favism**

Since G6PD-deficient persons are as a rule asymptomatic, the acute hemolytic anemia of favism appears to come out of the blue (hence the term “favism attack”) (Fig. 1). It can be a very severe, life-threatening form of acute hemolytic anemia. In most cases, the patient is a boy between the ages of 2 and 10 years who is brought to the emergency department because he appears to be...
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Figure 2. Blood Specimen from a 3-Year-Old Boy with a Severe Attack of Favism.

May–Grünewald–Giemsa staining of a peripheral-blood smear obtained on day 1 shows marked anisocytosis and poikilocytosis, which are unspecific; spherocytes and dense red cells, indicating cells on the way to hemolysis; neutrophil leukocytosis, suggesting inflammation; and nucleated red cells, indicating stimulated erythropoiesis. The presence of blister cells and hemighosts is characteristic of oxidative hemolysis.

Figure 3 (facing page). Role of G6PD in Protection against Oxidative Damage.

In red cells with normal G6PD activity (Panel A), G6PD and 6-phosphogluconate dehydrogenase — two of the first enzymes of the pentose phosphate pathway — provide an ample supply of NADPH (in blue), which in turn regenerates glutathione when it is oxidized by reactive oxygen species (e.g., \( \text{O}_2^\cdot \) and \( \text{H}_2\text{O}_2 \)). \( \text{O}_2^\cdot \) is one of the most reactive oxygen species generated by divicine and isouramil. In red cells with reduced G6PD activity (Panel B), NADPH production is limited and is insufficient to regenerate glutathione, although it is urgently required to manage the excess of reactive oxygen species generated by divicine and isouramil. The oxidative damage to red cells (in yellow) causes both intravascular and extravascular hemolysis. The central role of glutathione in withstanding the oxidative attack by the fava bean glucosides is supported by genetic evidence: a woman who first presented with severe favism was found to have an inherited, severe deficiency of glutathione reductase, whereas her red-cell G6PD activity was normal.

quite ill, with pallor, jaundice, abdominal pain, and often fever. The parents, if asked, almost always report that their son has dark urine and has eaten fava beans. On examination, the signs and symptoms are confirmed, and the spleen may be enlarged.

A blood count will show anemia that is moderate to severe, with a spectacular blood smear, including “hemighosts”\(^23\) and red cells with evidence of membrane cross-bonding\(^24\) (Fig. 2). Supravital staining with methyl violet would show Heinz bodies (large aggregates of denatured hemoglobin). This test takes time and must be performed by a competent hematologic technologist, but it does not require expensive equipment or reagents; the test is unlikely to be performed nowadays. The urine is often dark and positive for hemoglobin, and the serum unconjugated bilirubin level is always elevated (but to even higher levels in cases with the coexistence of the UGT1A allele that is characteristic of Gilbert’s syndrome\(^25\)). In the large majority of cases, there is no methemoglobinemia, which is not surprising, since the main pathway of methemoglobin reduction depends on NADH, not NADPH, and probably also because red cells containing methemoglobin are among the first to be destroyed (see below). However, in a small minority of cases, there is increased methemoglobinemia, causing skin discoloration and an apparent decrease in oxygen saturation.\(^26\) It is not clear why this happens, but we must presume that in these cases the NADH diaphorase activity is insufficient.

Red-cell destruction in favism is a complex process,\(^14\) but it has gradually been clarified. Divicine and isouramil, transferred through the intestinal epithelium into the blood, produce reactive oxygen species (ROS)\(^13,27,28\) such as superoxide anion, as well as hydrogen peroxide, which rapidly oxidize NADPH and glutathione. In red cells with normal G6PD activity, hydrogen peroxide is detoxified by catalase and by glutathione peroxidase\(^23,29,30\) (Fig. 3A). Both these enzymatic reactions depend on NADPH. Since NADPH is in short supply in G6PD-deficient red cells, they are unable to reverse glutathione depletion and they therefore sustain severe oxidative damage (Fig. 3B). The most severely damaged red cells undergo intravascular hemolysis, but much of
A Red Cell with Normal G6PD

- Glucose
- Hexokinase
- Glucose-6-phosphate dehydrogenase
- 6-Phosphogluconate
- NADP+
- Glutathione reductase
- NADPH
- Glutathione peroxidase
- Catalase
- H2O2
- O2
- Superoxide dismutase

B G6PD-Deficient Red Cell

- Glucose
- Hexokinase
- Glucose-6-phosphate dehydrogenase
- 6-Phosphogluconate
- NADP+
- Glutathione reductase
- NADPH
- Glutathione peroxidase
- Catalase
- H2O2
- O2
- Superoxide dismutase

Vicia faba
Fava beans contain high concentrations of vicine and convicine

β-Glucosidases are present in fava beans and in the gastrointestinal tract

Hemolysis
Acute hemolytic anemia

Oxidative damage

Divicine and isouramil

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the hemolysis is extravascular, as a result of the following sequence of events. Hydrogen peroxide and ROS oxidize protein thiol groups and lipids in red cells; convert oxyhemoglobin into the powerful oxidants ferryl hemoglobin, methemoglobin, and hemichromes (partially denatured hemoglobin) and cause the release of iron from hemoglobin and ferritin. At the same time, sulfhydryl groups in cytoplasmic and membrane proteins are also oxidized; this is followed by aggregation of membrane proteins, formation of cross-bonded rigid hemighosts, and binding of hemichromes to the membrane cytoskeleton (with formation of Heinz bodies). Without the protective action of glutathione and NADPH, this chain of oxidative events leads to deposition on clustered band 3 of autologous IgG and factor C3c produced by the complement alternative pathway (tick-over mechanism). The red cells thus opsonized are subject to erythrocytic phagocytosis.

That both intravascular and extravascular hemolysis occur in favism was implied by the time-honored term “ictero-hemoglobinuric favism.” We can attribute the splenic enlargement and the jaundice to extravascular hemolysis and the hemoglobinuria to intravascular hemolysis, which in turn causes plasma hemoglobin to bind nitric oxide. Nitric oxide is a major determinant of vasomotor tone and depletion of nitric oxide can result in a variety of symptoms, including abdominal pain. The clinical course of acute hemolytic anemia that is triggered by primaquine or dapsone is very similar to that of favism, and there is every reason to believe that the pathophysiology of favism as outlined here is also a good model for drug-induced acute hemolytic anemia in persons with G6PD deficiency.

A well-known clinical manifestation of G6PD deficiency is neonatal jaundice, which is covered in detail elsewhere. It may be severe, but its pathophysiology is quite different from that of favism, since there is little evidence of hemolysis. However, full-blown favism itself can occur in breast-fed newborns whose mothers have eaten fava beans.

**Management of Favism**

Once a diagnosis of favism has been made, management is usually not difficult. In mild cases, prompt hydration and symptomatic treatment will suffice. However, more severe cases warrant hospitalization. In a child or an adult, severe favism, like any other acute hemolytic anemia, is a medical emergency requiring immediate action, the mainstay being blood transfusion. Although there are no formally established guidelines, immediate blood transfusion should be given whenever the hemoglobin level is either 7 g per deciliter or less or is less than 9 g per deciliter with persistent hemoglobinuria, indicating that brisk hemolysis is ongoing. In all cases, the need for blood transfusion should be reassessed at short intervals. Fortunately, unlike other forms of acute hemolytic anemia, the acute hemolytic anemia of favism subsides on its own (unless the patient eats more fava beans). If there is acute renal failure, hemodialysis may be necessary, but in patients with no previous kidney disease, recovery from acute renal failure also occurs on its own. The management of favism and other clinical manifestations of G6PD deficiency is covered in more detail elsewhere.

**Misconceptions, Facts, and Terminology**

Despite (or because of) the long history of favism, there are still several associated myths and anecdotes. One myth is that an attack can be triggered by inhalation of the pollen from blossoming plants. In the entire literature on favism, there is only one report of an undocumented case of “pollen favism.” Of course, a person may be allergic to pollen from the fava plant, but an allergic reaction will not lead to acute hemolytic anemia. If the parents of a boy with acute favism state that he has not eaten fava beans but has just walked through a field of beans, there are two possible explanations: either the boy has eaten the beans surreptitiously or the parents are embarrassed to report that he has eaten them. The culprit chemicals are now known, and they are not volatile substances. Thus, there is neither a rationale for nor experimental evidence of “inhalation favism”; the notion should be abrogated.

Another myth is that other beans can cause an attack of favism. This has led to clinical recommendations that patients avoid eating green peas, lupine beans, soybeans, many other types...
of beans, and derivatives thereof (see, for instance, www.g6pddeficiency.org). We now know that the concentrations of vicine and convicine are negligible in beans other than fava beans.42,43 There is one case report of hemolysis in an 8-year-old boy44 after the ingestion of vetch (which is not surprising because vetch, or Vicia sativa, normally used as an animal feed, has high concentrations of vicine and convicine45 and one report of hemolysis in an 8-month-old baby after the ingestion of a pumpkin contaminated by fava beans.46 Persons with G6PD deficiency should be told not to eat fava beans. This is the correct advice, and it is more likely to encourage compliance than a recommendation to avoid all legumes.

A 72-year-old man admitted for severe favism stated that he had always eaten fava beans, with no ill effects. We are not yet able to explain fully the somewhat erratic character of this condition; we do know, however, that there are many sources of variation in the levels of divicine and isouramil that will attack red cells. First, the glucosidases in the beans, when they are eaten raw, are mainly responsible for the release of divicine and isouramil, but when the beans are cooked, the glucosidases are largely inactivated.14 (Cooking and roasting also cause degradation of the glucosides,47 and the aglycones are very thermolabile.48) This is probably the main reason why in most cases an attack of favism is triggered by eating raw beans rather than cooked beans.34 (Vicine and convicine are not very good substrates for the glucosidases in the human gut.) Second, the time of harvesting the beans affects the glucoside content; younger beans have higher levels than older beans.49 Third, different cultivars of fava beans vary in vicine and convicine content by more than one to two orders of magnitude.50 Overall, acute hemolytic anemia in patients with G6PD deficiency is strongly dose-dependent. In the case of the 72-year-old man, modest helpings of fava beans may have previously caused subclinical favism, but this time, perhaps, the man had a large helping. The ratio of fava beans consumed to body weight may account in large part for the fact that favism attacks are much more common and more severe in children than in adults.

The term “favic” is unfortunately still used to describe persons who have had an attack of favism, as well as those with G6PD deficiency who have never had favism. Of course, persons who are G6PD-deficient but do not eat fava beans will never become favic.

### Genetic Features of G6PD Deficiency and Favism

The G6PD gene maps to the subtelomeric region of the long arm of the X chromosome, and it is subject to the phenomenon of X-chromosome inactivation.51 This has important implications for both population genetics and clinical genetics. First, since males have only one X chromosome, the frequency of G6PD-deficient hemizygous males in a particular population is identical to the gene frequency; in the same population, if it is in Hardy–Weinberg equilibrium, the frequency of heterozygous females will be almost double the gene frequency, whereas homozygous G6PD-deficient females will be much more rare.6 (Considerable confusion in the literature has arisen from mixed-sex population data.) Second, and contrary to statements in many publications (including some textbooks), G6PD deficiency is not recessive. Indeed, any series of patients with favism includes females, most of whom are heterozygous: a trait expressed in heterozygotes is, by definition, not recessive. This is not surprising because in a heterozygous female, X inactivation produces a dual red-cell population: some red cells have normal levels of G6PD, whereas others are G6PD-deficient. The latter, on exposure to redox agents, are just as susceptible to hemolysis as G6PD-deficient red cells in a hemizygous male. Third, X inactivation is a stochastic phenomenon, and the ratio of G6PD-deficient red cells to red cells with normal G6PD activity is thus highly variable,52 so much so that at the two ends of the resulting normal (gaussian) distribution, there is overlap with normal-G6PD and G6PD-deficient homozygotes, respectively. Not surprisingly, the severity of acute hemolytic anemia in heterozygous women is greater in those who have a larger proportion of G6PD-deficient red cells; thus, not only is G6PD deficiency not recessive, but its expression in heterozygotes also depends on the X-chromosome inactivation ratio. An estimate of this ratio in any individual heterozygote can be obtained from the G6PD activity of the total red-cell population.
or from cytochemical counts (which are rather laborious) of the two red-cell types. A flow-cytometric technique has been developed for accurate quantification of the two populations (red cells with normal G6PD levels and G6PD-deficient red cells).

HETEROGENEITY OF G6PD DEFICIENCY

Since G6PD was cloned, nearly 200 mutations within its coding region have been identified. Almost all these mutations entail more or less marked G6PD deficiency, but with all of them, some residual G6PD activity is present in red cells; a total absence of G6PD activity would be lethal. In persons with normal G6PD activity, the activity is high in reticulocytes, but once they mature into erythrocytes and lose protein synthesis, the enzymatic activity decays exponentially as red cells age in the circulation. In most persons with G6PD deficiency, reticulocytes start out with lower activity than normal, and the subsequent exponential decay is much faster, so that the oldest cells have nearly no activity; hence, they are the first to hemolyze under oxidative challenge.

The clinical manifestations of G6PD deficiency are similar with all variants, but the severity does correlate in some measure with the residual fraction of G6PD activity. However, there is extensive overlap. For instance, it was thought for a long time that with G6PD A−, the variant most common in Africa and in people of African descent (including African Americans), acute hemolytic anemia would be mild and favism would not occur, but both these contentions turned out to be incorrect. This does not mean that having one particular mutation rather than another is irrelevant. In a recent study in the Gaza population, favism attacks were, on average, significantly more severe with G6PD Mediterranean and G6PD Cairo than with G6PD A−, and the rate of recovery from the attack was more prompt with G6PD A−.

At least 14 different G6PD mutations have been reported in patients with favism (Table 1) in different parts of the world (Fig. 4) and even within the same country (e.g., 5 mutations in Spain and 12 in Tunisia). We can assume that any G6PD-deficient person is at risk, regardless of the underlying mutation.

G6PD DEFICIENCY AND MALARIA CONTROL

Early studies suggested that G6PD deficiency, along with other erythrocytic traits such as hemoglobin S and the thalassemias, confers a relative resistance against Plasmodium falciparum malaria. Indeed, parasites do not fare as well in G6PD-deficient red cells as they do in red cells with normal G6PD; however, if there are no red cells with normal G6PD, then the parasites can still thrive in G6PD-deficient red cells. The evidence that G6PD deficiency is a genetic polymorphism with a heterozygote advantage balanced by malaria selection is now overwhelming, but space does not allow us to review that evidence here. (It has been suggested that such protection may extend to P. vivax malaria.)

At the same time, another important relationship exists between G6PD deficiency and malaria, in that some antimalarial agents cause acute hemolytic anemia, similar to favism, in G6PD-deficient persons. Indeed, it was “primaquine sensitivity” that some 60 years ago led to the discovery of G6PD deficiency. Since that time, many other antimalarial drugs have become available, but for two specific indications there is still no alternative to primaquine: the elimination of gametocytes in P. falciparum infection and the elimination of hypnozoites (parasites dormant in the liver) in P. vivax infection. The former is important because, after an attack of P. falciparum malaria is successfully cured, gametocytes circulate for 1 to 2 weeks, and the patient therefore remains infectious through mosquito bites; the elimination of hypnozoites in P. vivax infection is important because hypnozoites are a major source of relapse and chronic illness in patients with P. vivax infection. Fortunately, very little primaquine is required for the elimination of gametocytes in P. falciparum infection, and the single dose recommended for an adult has been reduced from 75 mg to 25 mg. This dose can be regarded as safe for a person with G6PD deficiency.
For the elimination of hypnozoites in *P. vivax* infection, the situation is quite different. The recommended dose for an adult is at least 30 mg per day for 14 days, and this regimen will cause hemolytic anemia in a person with G6PD deficiency. Therefore, it is necessary to test for G6PD deficiency before administering such a course of primaquine, an imperative adopted by the World Health Organization in 2014 (www.who.int/malaria/mpac/mpac-march2015-erg-g6pd.pdf). This problem has been a stimulus for the development of point-of-care testing methods for G6PD deficiency. In fact, very inexpensive screening tests for G6PD deficiency have been available for more than half a century. Although simple, they did require a minimum of laboratory facilities, and the introduction of even more user-friendly procedures is therefore welcome, provided that their price is contained. At the moment, the only alternative to primaquine

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* Included in this table are only G6PD variants for which one or more cases of favism have been published. The list probably ought to be much longer, since cases of favism with other variants may not have been published.

† Each G6PD variant, when originally described, was assigned to a class defined on the basis of residual enzymatic activity and clinical manifestations: class II variants had G6PD activity that was less than 10% of normal activity, and class III variants had G6PD activity that was 10 to 60% of normal activity. This classification was often taken to mean that class III variants, although involving G6PD deficiency, were mild, but we now know that this is not correct, since acute favism can develop in persons with either a class II or a class III variant. Cases involving class I variants are rare. They are characterized by a more severe condition, chronic nonspherocytic hemolytic anemia (i.e., no trigger for hemolysis is needed). However, with class I variants, eating fava beans will precipitate acute hemolytic anemia on top of chronic hemolytic anemia. The classification is probably due for revision.

‡ The geographic areas listed in the table are not comprehensive and are a crude approximation. The first area listed for a variant is the place where the variant was originally discovered. Many variants (e.g., G6PD Mediterranean, G6PD Chatham, and G6PD Coimbra) are much more widespread than was originally thought.

§ Additional sources are provided in the Supplementary Appendix.

¶ “A−” is the time-honored term for the G6PD deficiency that is common in Africa and in people of African descent. In fact, there are three different A− alleles, and their relative frequencies vary from one area in Africa to another. All three alleles have two mutations, one of which (the one that causes the amino acid replacement N126D) is not included in the table because it does not by itself cause G6PD deficiency. The amino acid replacement shown here is that of the most common A− variant, with which acute favism has been documented in different parts of the world.

‖ The Cairo variant, when originally described, was not assigned to any class. On the basis of subsequent data, it is probably just about at the border between class II and class III.
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for eliminating P. vivax hypnozoites is tafenoquine, a long-acting agent (not yet a licensed drug). A single dose of tafenoquine may be sufficient. However, it is an 8-aminoquinoline and causes hemolysis in G6PD-deficient persons, including heterozygotes, just as primaquine does. But whereas primaquine can be promptly discontinued if it has an adverse effect, tafenoquine stays on board, making it even more important to perform G6PD testing beforehand.

FAVA BEANS WITHOUT FAVISM

Favism would be completely prevented if all persons with G6PD deficiency, especially children, knew their status and refrained from eating fava beans. In Sardinia, over a 20-year period, the incidence of favism dropped by 75% after newborn screening and health education were introduced and consistently carried out. Clearly, these measures can be successful and were esti-

Figure 4. Global Genetic Heterogeneity of G6PD Deficiency Underlying Favism.

Countries where favism has been reported are shown in light blue. The symbols indicate areas where individual G6PD variants are polymorphic in the population and have been shown to be associated with favism. The map is no doubt incomplete because it is based on published reports. Also, the information shown is general rather than specific. (For example, favism has been reported in Russia but probably does not occur in large parts of Russia, and it has been reported in the United States but probably does not occur in Alaska.) Because variant A− is one of the most common worldwide, it is shown in areas where favism is unknown (tropical Africa) and in areas where it is very rare (South America, where favism has been reported only in Chile).
mated to be cost-effective in Iran, for example. An alternative (and not mutually exclusive) approach to prevention could be mounted on the basis that the content of vicine and convicine in different cultivars of fava beans is highly variable, with some cultivars being almost free of these glucosides, as documented in several reports. In a recent study, seven G6PD-deficient men were given a large meal of low-vicine fava beans, and favism did not develop in any of the men (unpublished data). In spite of contemporary interest in fava beans as a valuable source of protein-rich human nutrients, the notion of low-vicine fava beans does not yet seem to have affected the practice of agriculture. One will have to test in the field how the low-vicine cultivars compare to those currently in use, in terms of bean yield and palatability. At a time when most countries declare that preventive medicine is a priority, the seeds from the low-vicine cultivars that fare best ought to be distributed as soon as possible in all areas where favism in fava beans is popular.

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This article is dedicated to the memory of Ernie Beutler, who for half a century was a leader in the study of G6PD deficiency, and to the memory of Gennaro Sansone, the pediatric hematologist who first discovered G6PD deficiency in fava beans.

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