

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Favism and Glucose-6-Phosphate Dehydrogenase Deficiency

Lucio Luzzatto, M.D., and Paolo Arese, M.D.

From the Department of Hematology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (L.L.); and the Department of Oncology, Biochemistry Unit, University of Turin, Turin, Italy (P.A.). Address reprint requests to Dr. Luzzatto at the Dept. of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences, United Nations Rd., P.O. Box 65001, Dar es Salaam, Tanzania, or at lluzzatto@blood.ac.tz.

N Engl J Med 2018;378:60-71.  
DOI: 10.1056/NEJMr1708111

Copyright © 2018 Massachusetts Medical Society.

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.<sup>1,2</sup> This gives him a place in nutrition science but not in nutrigenomics: 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.<sup>3</sup> 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,<sup>4-6</sup> on all aspects of G6PD deficiency. In this review, we focus on favism.

The contemporary medical history of “ictero-hemoglobinuric favism”<sup>1,2</sup> 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 Martinetti<sup>7</sup> in 1905 and by Luisada<sup>8</sup> in 1941. Because this is old literature, favism is often perceived as a thing of the past. In fact, on a global basis,<sup>9</sup> 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 domesticated,<sup>10,11</sup> 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.<sup>12</sup> The beans can be eaten raw or cooked, fresh or dried. *V. faba* contains high concentrations of two  $\beta$ -glucosides (up to 2% in dry weight): vicine and convicine.<sup>13</sup> On ingestion of fava beans, vicine and convicine undergo hydrolysis by glucosidases present both in the beans and in the gastrointestinal tract,<sup>14</sup> 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 antifungal<sup>15</sup> and pesticide<sup>16</sup> 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 high<sup>17</sup> and where fava beans (also known as broad beans) are a popular food item ([https://readtiger.com/img/wkp/en/Broadbean\\_Yield.png](https://readtiger.com/img/wkp/en/Broadbean_Yield.png)), which reflects its

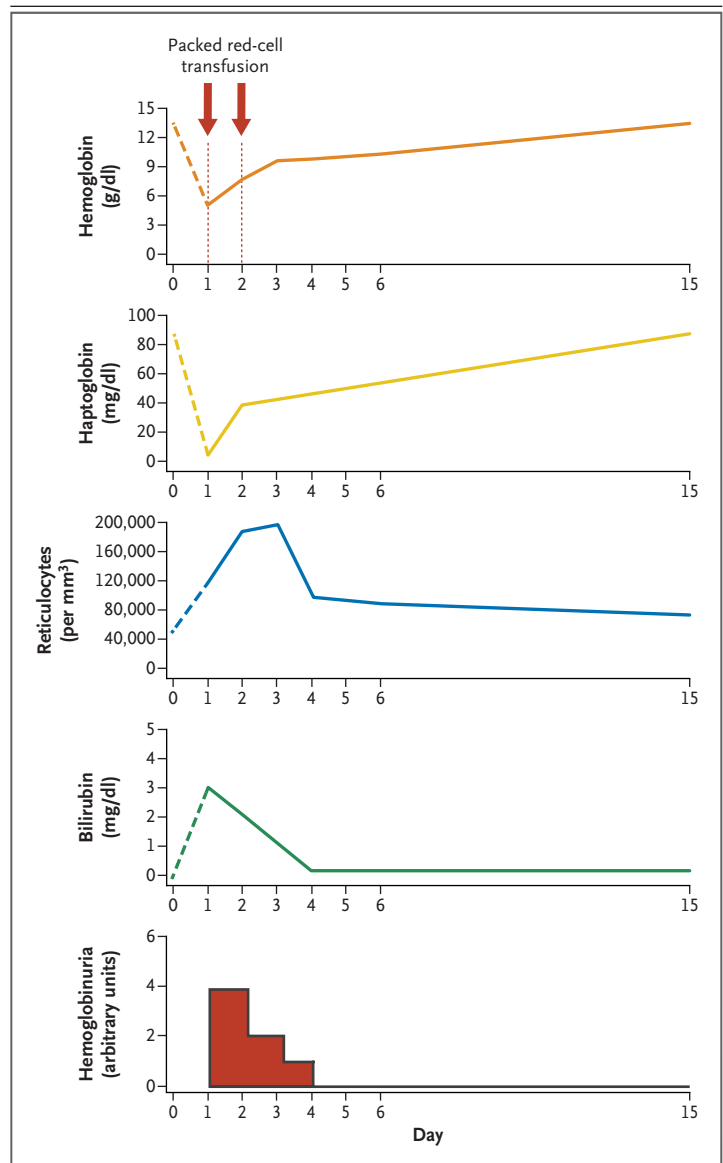
bifactorial nature. This is true, for instance, in southern Europe, in the Middle East, and in Southeast Asia but not, for example, in northern Germany, where fava beans are grown but G6PD deficiency is rare, or in West Africa, where G6PD deficiency has a high prevalence but fava beans are not grown.

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),<sup>18</sup> for a yearly incidence, at that time, of 1.2 cases per 10,000 population. In a recent report from Gaza,<sup>19</sup> 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<sup>20</sup>; 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<sup>21</sup> 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

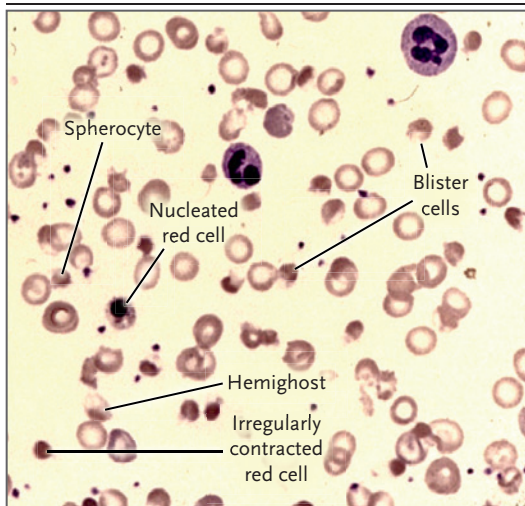
Since G6PD-deficient persons are as a rule asymptomatic, the acute hemolytic anemia of favism<sup>22</sup> appears to come out of the blue (hence the term



**Figure 1. Clinical Course in a 3-Year-Old Boy with a Severe Attack of Favism.**

The values on day 0 are assumed to have been normal. Thus, we estimate that the hemoglobin level fell by about 50% in 24 hours. Transfusions of packed red cells were given on an emergency basis on day 1 and day 2 (red arrows). The clinical course was marked by persistent hemoglobinuria, a brisk and immediate reticulocyte response, and fairly rapid resolution of hyperbilirubinemia, with a return to normal hemoglobin levels within 2 weeks. The boy had the glucose-6-phosphate dehydrogenase (G6PD) Mediterranean mutation.

“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



**Figure 2. Blood Specimen from a 3-Year-Old Boy with a Severe Attack of Favism.**

May–Grünwald–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.

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.

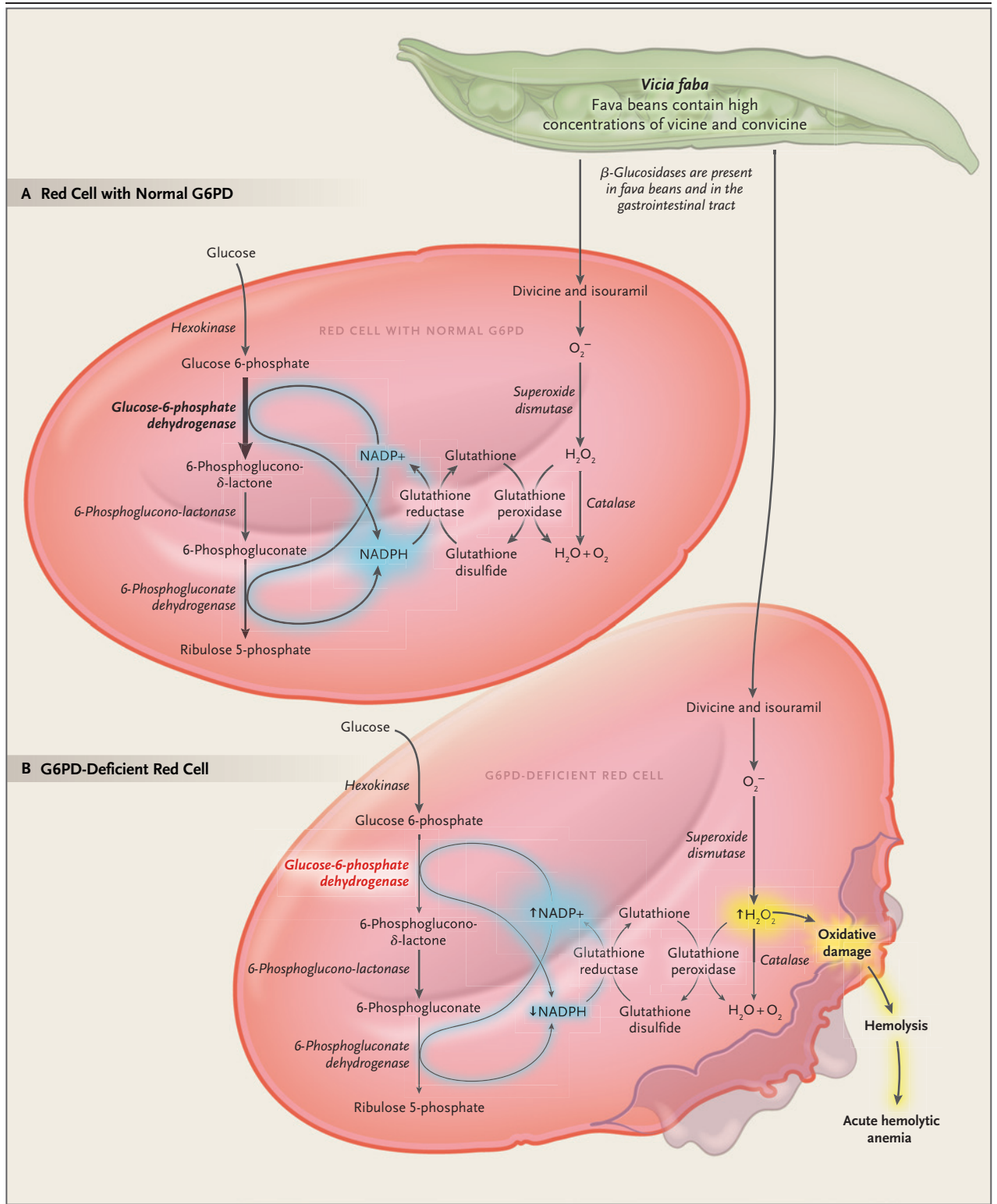
A blood count will show anemia that is moderate to very severe, with a spectacular blood smear, including “hemighosts”<sup>23</sup> and red cells with evidence of membrane cross-bonding<sup>24</sup> (Fig. 2). Supravital staining with methyl violet would show Heinz bodies (large aggregates of denatured 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<sup>25</sup>). In the large majority of

**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.,  $O_2^-$  and  $H_2O_2$ ).  $O_2^-$  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,<sup>31</sup> whereas her red-cell G6PD activity was normal.

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.<sup>26</sup> 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,<sup>14</sup> but it has gradually been clarified. Divicine and isouramil, transferred through the intestinal epithelium into the blood, produce reactive oxygen species (ROS)<sup>13,27,28</sup> 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<sup>13,29,30</sup> (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



the hemolysis is extravascular,<sup>14</sup> as a result of the following sequence of events. Hydrogen peroxide and ROS oxidize protein thiol groups and lipids in red cells<sup>28,32,33</sup>; convert oxyhemoglobin into the powerful oxidants ferryl hemoglobin, methemoglobin, and hemechromes (partially denatured hemoglobin)<sup>14,28,32</sup>; and cause the release of iron from hemoglobin and ferritin.<sup>34</sup> 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 hemechromes 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<sup>35</sup>). The red cells thus opsonized are subject to erythrophagocytosis.<sup>14,36,37</sup>

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,<sup>38</sup> 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<sup>39</sup> or dapsone<sup>20</sup> 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.<sup>22</sup> 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.<sup>40</sup>

#### 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 either is 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.<sup>22</sup>

#### 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.”<sup>41</sup> 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](http://www.g6pddeficiency.org)). We now know that the concentrations of vicine and convicine are negligible in beans other than fava beans.<sup>42,43</sup> There is one case report of hemolysis in an 8-year-old boy<sup>44</sup> 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 convicine<sup>45</sup>) and one report of hemolysis in an 8-month-old baby after the ingestion of a pumpkin contaminated by fava beans.<sup>46</sup> 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.<sup>14</sup> (Cooking and roasting also cause degradation of the glucosides,<sup>47</sup> and the aglycones are very thermolabile.<sup>48</sup>) This is probably the main reason why in most cases an attack of favism is triggered by eating raw beans rather than cooked beans.<sup>14</sup> (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.<sup>49</sup> Third, different cultivars of fava beans vary in vicine and convicine content by more than one to two orders of magnitude.<sup>50</sup> 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 fa-

vism, 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.<sup>51</sup> 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.<sup>6</sup> (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,<sup>52</sup> 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.<sup>53,54</sup> 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).<sup>55</sup>

#### HETEROGENEITY OF G6PD DEFICIENCY

Since *G6PD* was cloned,<sup>56</sup> nearly 200 mutations within its coding region have been identified.<sup>57</sup> 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.<sup>58</sup> 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.<sup>59</sup> 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<sup>60</sup>; 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.<sup>6</sup> For instance, it was thought for a long time that with G6PD A<sup>-</sup>, 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.<sup>20,61</sup> 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<sup>-</sup>, and the rate of recovery from the attack was more prompt with G6PD A<sup>-</sup>.<sup>19</sup>

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<sup>79</sup> and 12 in Tunisia<sup>67</sup>). 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,<sup>80,81</sup> confers a relative resistance against *Plasmodium falciparum* malaria.<sup>82,83</sup> 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.<sup>84</sup> The evidence that G6PD deficiency is a genetic polymorphism with a heterozygote advantage balanced by malaria selection is now overwhelming,<sup>85-88</sup> but space does not allow us to review that evidence here. (It has been suggested that such protection may extend to *P. vivax* malaria.<sup>89</sup>)

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.<sup>3</sup> 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.<sup>90</sup> 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.<sup>91</sup> This dose can be regarded as safe for a person with G6PD deficiency.

**Table 1. Molecular Heterogeneity of G6PD Deficiency in Patients with Acute Favism.\***

G6PD Variant	Amino Acid Replacement	Class†	Geographic Areas‡	Source§
Aures	I48T	III	North Africa, Arabian Peninsula	Nafa et al. <sup>62</sup>
A-	M68V¶	III	Africa, Middle East, United States, Brazil, Caribbean islands	Galiano et al. <sup>63</sup>
Cairo	N135T	II–III	Egypt, Palestine	Reading et al. <sup>19</sup>
Mahidol	G163S	II	Thailand, other countries in Southeast Asia	Laosombat et al. <sup>64</sup>
Mediterranean	S188F	II	Mediterranean, Middle East, India, Malaysia	Vulliamy et al. <sup>65</sup>
Coimbra	R198C	II	Portugal, India	Goncalves et al. <sup>66</sup>
Viangchan	V291 M	II	China, Southeast Asia	Laosombat et al. <sup>64</sup>
Nefza	L323P	III	Tunisia	Benmansour et al. <sup>67</sup>
Chatham	A335T	II	Tunisia, India, Iran, Malaysia, Indonesia	Benmansour et al. <sup>67</sup>
Cassano	Q449H	II	Italy, Croatia, Greece	Calabrò et al. <sup>68</sup>
Union	R454C	II	Worldwide	Rovira et al. <sup>69</sup>
Canton	R459L	II	China, Southeast Asia	Laosombat et al. <sup>70</sup>
Cosenza	R459P	II	Italy, Iran	Noori-Dalooi et al. <sup>71</sup>
Kaiping	R463H	II	China, Indonesia	Laosombat et al. <sup>64</sup>

\* 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<sup>17,72</sup>; 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.<sup>73,74</sup> The classification is probably due for revision.<sup>6</sup>

‡ 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.

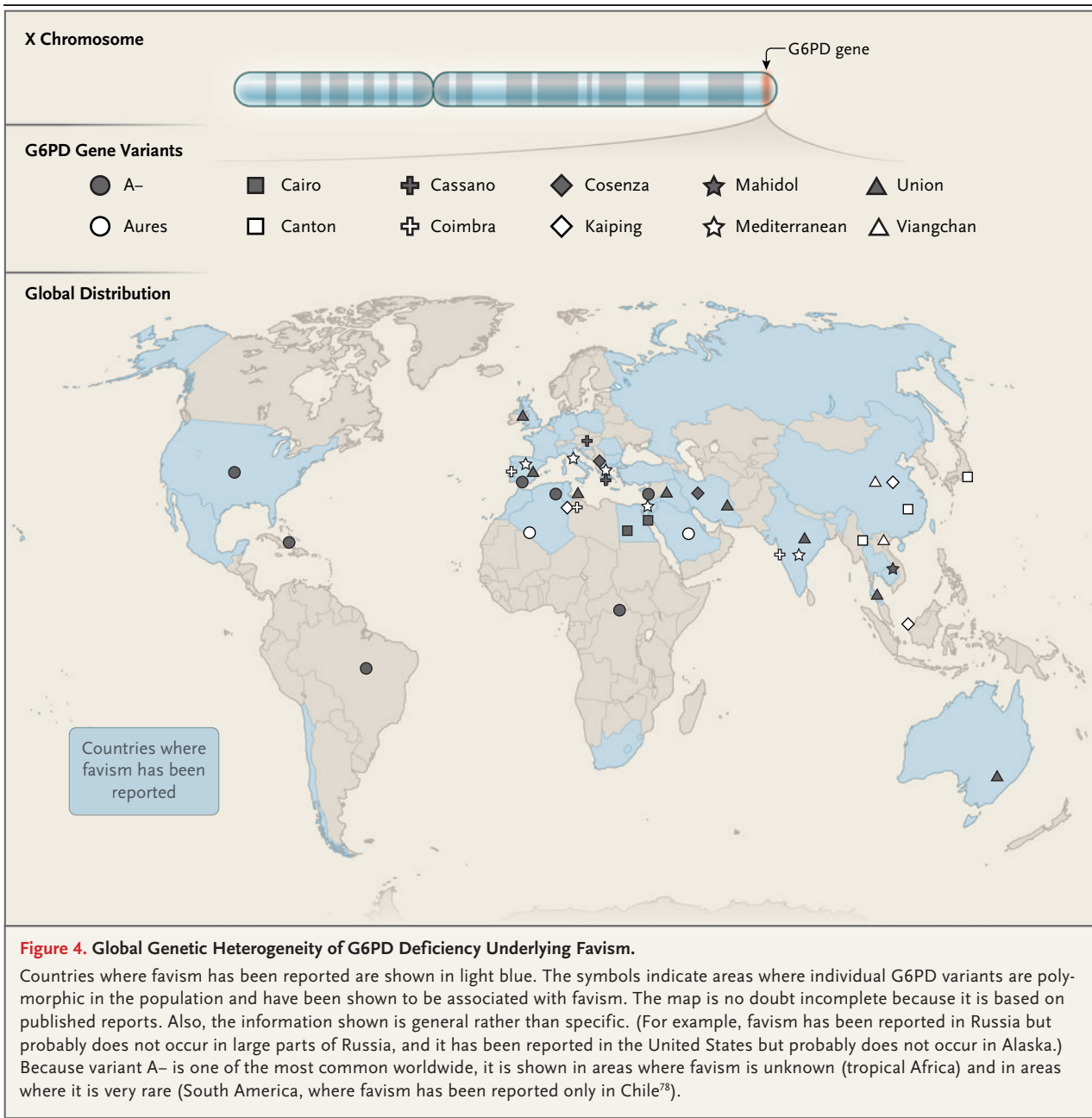
¶ “A-” is the time-honored term for the G6PD deficiency that is common in Africa and in people of African descent. In fact, there are three different A- alleles,<sup>75</sup> and their relative frequencies vary from one area in Africa to another.<sup>76,77</sup> All three alleles have two mutations, 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,<sup>1,9</sup> it is probably just about at the border between class II and class III.

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.<sup>39,92</sup> 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](http://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.<sup>93,94</sup> In fact, very inexpensive screening tests for G6PD deficiency have been available for more than half a century.<sup>95,96</sup> 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





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,<sup>97</sup> just as primaquine does.<sup>98</sup> 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.<sup>99</sup> Clearly, these measures can be successful and were esti-

mated to be cost-effective in Iran, for example.<sup>100</sup> 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.<sup>50,101,102</sup> 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,<sup>12</sup> 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 with 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 fava beans are popular.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all those with whom we have collaborated on G6PD and favism research, particularly Adeyinka Afolayan, the late Olaniyi Babalola, Olugbemiro Sodeinde, and Essien Usanga in Ibadan, Nigeria; the late Giorgio Battistuzzi, the late Graziella Persico, and the late Michele D'Urso, as well as Stefania Filosa, Cristina Mareni, Giuseppe Martini, and Daniela Toniolo in Naples, Italy; Nick Foulkes, Philip Mason, and Tom Vulliamy in London; Rosario Notaro in New York and in Florence, Italy; the late Lidia Mannuzzu; Anna Sisini, Anna Naitana, Franco Turriani, and Luigi Simula in Sassari, Italy; Gianfranco Gaetani and Antonio De Flora in Genoa, Italy; Amalia Bosia and Gianpiero Pescarmona in Turin, Italy; Margaret Baker in New York; Thomas Fischer in Aachen, Germany; and Hans Lutz in Zurich, Switzerland; we also thank Marina Dachà and Marina Carcea for advice on nutritional aspects of fava beans; Gianfranco, Tullio, and Rosa Meloni for providing valuable details of their clinical cases of favism; Caterina Nannelli for compiling supplementary information on clinical series, and Bruno Mbandando and Flavio Azza-relli for valuable help with the preparation of an earlier version of Figure 1.

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 favism.

## REFERENCES

- Meletis J, Konstantopoulos L. Favism — from the “avoid fava beans” of Pythagoras to the present. *Haema* 2004;7:17-21.
- Simoons FJ. *Plants of life plants of death*. Madison: University of Wisconsin Press, 1998.
- Alving AS, Carson PE, Flanagan CL, Ickes CE. Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science* 1956; 124:484-5.
- Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med* 1991; 324:169-74.
- Mason PJ, Bautista JM, Gilsanz F. G6PD deficiency: the genotype-phenotype association. *Blood Rev* 2007;21:267-83.
- Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. *Hematol Oncol Clin North Am* 2016;30:373-93.
- Fermi C, Martinetti P. Studio sul favismo. *Ann Ig Sper* 1905;15:76-112.
- Luisada A. A singular disease affecting chiefly red blood cells. *Medicine (Baltimore)* 1941;20:229-50.
- Belsey MA. The epidemiology of favism. *Bull World Health Organ* 1973;48: 1-13.
- Zohary D, Hopf M. Domestication of pulses in the Old World: legumes were companions of wheat and barley when agriculture began in the Near East. *Science* 1973;182:887-94.
- Kislev ME, Bar-Yosef O. The legumes: the earliest domesticated plants in the Near East? *Curr Anthropol* 1988;29:175-9.
- Multari S, Stewart D, Russell WR. Potential of fava bean as a future protein supply to partially replace meat intake in the human diet. *Comp Rev Food Sci Food Saf* 2015;14:511-22.
- Chevion M, Navok T, Glaser G, Mager J. The chemistry of favism-inducing compounds: the properties of isouramil and divicine and their reaction with glutathione. *Eur J Biochem* 1982;127:405-9.
- Arese P, De Flora A. Pathophysiology of hemolysis in glucose-6-phosphate dehydrogenase deficiency. *Semin Hematol* 1990;27:1-40.
- Pavlik M, Vanova M, Laudova V, Harmatha J. Fungitoxicity of natural heterocyclic glucoside vicine obtained from *Vicia faba* L. against selected filamentous fungi. *Rostlinna Vyroba* 2002;48:543-7.
- Desroches P, El Shazly E, Mandon N, Duc G, Huignard J. Development of *Callisobruchus chinensis* (L.) and *C. maculatus* (F.) (*Coleoptera: bruchidae*) in seeds of *Vicia faba* L. differing in their tannin, vicine and convicine contents. *J Stored Prod Res* 1995;31:83-9.
- WHO Working Group. Glucose-6-phosphate dehydrogenase deficiency. *Bull World Health Organ* 1989;67:601-11.
- Meloni T, Forteleoni G, Dore A, Cuttillo S. Favism and hemolytic anemia in glucose-6-phosphate dehydrogenase-deficient subjects in North Sardinia. *Acta Haematol* 1983;70:83-90.
- Reading NS, Sirdah MM, Shubair ME, et al. Favism, the commonest form of severe hemolytic anemia in Palestinian children, varies in severity with three different variants of G6PD deficiency within the same community. *Blood Cells Mol Dis* 2016;60:58-64.
- Pamba A, Richardson ND, Carter N, et al. Clinical spectrum and severity of hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient children receiving dapsone. *Blood* 2012;120:4123-33.
- Kalfa TA. Warm antibody autoimmune hemolytic anemia. *Hematology Am Soc Hematol Educ Program* 2016.2016(1): 690-7.
- Luzzatto L, Poggi VE. Glucose-6-phosphate dehydrogenase deficiency. In: Orkin SH, Fisher DE, Ginsburg D, Look AT, Lux SE, Nathan DG, eds. *Nathan and Oski's hematology and oncology of infancy and childhood*. Philadelphia: Elsevier-Saunders, 2015:609-29.
- Chan TK, Chan WC, Weed RJ. Erythrocyte hemighosts: a hallmark of severe oxidative injury in vivo. *Br J Haematol* 1982;50:575-82.
- Fischer TM, Meloni T, Pescarmona GP, Arese P. Membrane cross bonding in red cells in favic crisis: a missing link in the mechanism of extravascular haemolysis. *Br J Haematol* 1985;59:159-69.
- Iolascon A, Faienza MF, Giordani L, et al. Bilirubin levels in the acute hemolytic crisis of G6PD deficiency are related to Gilbert's syndrome. *Eur J Haematol* 1999; 62:307-10.
- Odièvre MH, Danékova N, Mesples B, et al. Unsuspected glucose-6-phosphate dehydrogenase deficiency presenting as symptomatic methemoglobinemia with

- severe hemolysis after fava bean ingestion in a 6-year-old boy. *Int J Hematol* 2011;93:664-6.
27. Albano E, Tomasi A, Mannuzzo L, Arese P. Detection of a free radical intermediate from divicine of *Vicia faba*. *Biochem Pharmacol* 1984;33:1701-4.
28. Winterbourn CC, Benatti U, De Flora A. Contributions of superoxide, hydrogen peroxide, and transition metal ions to auto-oxidation of the favism-inducing pyrimidine aglycone, divicine, and its reactions with haemoglobin. *Biochem Pharmacol* 1986;35:2009-15.
29. Gaetani GF, Galiano S, Canepa L, Ferraris A-M, Kirkman HN. Catalase and glutathione peroxidase are equally active in detoxification of hydrogen peroxide in human erythrocytes. *Blood* 1989;73:334-9.
30. McMillan DC, Bolchoz LJ, Jollow DJ. Favism: effect of divicine on rat erythrocyte sulphydryl status, hexose monophosphate shunt activity, morphology, and membrane skeletal proteins. *Toxicol Sci* 2001;62:353-9.
31. Kamerbeek NM, van Zwieten R, de Boer M, et al. Molecular basis of glutathione reductase deficiency in human blood cells. *Blood* 2007;109:3560-6.
32. Gaetani GF, Mareni C, Salvidio E, Galiano S, Meloni T, Arese P. Favism: erythrocyte metabolism during haemolysis and reticulocytosis. *Br J Haematol* 1979;43:39-48.
33. Skorokhod A, Schwarzer E, Gremo G, Arese P. HNE produced by the malaria parasite *Plasmodium falciparum* generates HNE-protein adducts and decreases erythrocyte deformability. *Redox Rep* 2007;12:73-5.
34. Ferrali M, Signorini C, Ciccoli L, Comperti M. Iron release and membrane damage in erythrocytes exposed to oxidizing agents, phenylhydrazine, divicine and isouramil. *Biochem J* 1992;285:295-301.
35. Lachmann PJ, Hughes-Jones NC. Initiation of complement activation. *Springer Semin Immunopathol* 1984;7(2-3):143-62.
36. Turrini F, Naitana A, Mannuzzo L, Pescarmona G, Arese P. Increased red cell calcium, decreased calcium adenosine triphosphatase, and altered membrane proteins during fava bean hemolysis in glucose-6-phosphate dehydrogenase-deficient (Mediterranean variant) individuals. *Blood* 1985;66:302-5.
37. Arese P, Turrini F, Schwarzer E. Band 3/complement-mediated recognition and removal of normally senescent and pathological human erythrocytes. *Cell Physiol Biochem* 2005;16:133-46.
38. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA* 2005;293:1653-62.
39. Tarlov AR, Brewer GJ, Carson PE, Alving AS. Primaquine sensitivity. Glucose-6-phosphate dehydrogenase deficiency: an inborn error of metabolism of medical and biological significance. *Arch Intern Med* 1962;109:209-34.
40. Kaplan M, Hammerman C. Severe neonatal hyperbilirubinemia: a potential complication of glucose-6-phosphate dehydrogenase deficiency. *Clin Perinatol* 1998;25:575-590, viii.
41. Brodribb HS. Favism from pollen. *BMJ* 1966;2:642.
42. Pitz WJ, SosulskiFW, Hogge LR. Occurrence of vicine and convicine in seeds of some *Vicia* species and other pulses. *Can Inst Food Sci Technol* 1980;13:35-9.
43. Griffiths DW, Ramsay G. The distribution of vicine and convicine in *Vicia faba* and some related species and their distribution within mature seeds. *J Sci Food Agric* 1992;59:463-9.
44. Bicakci Z. A hemolysis trigger in glucose-6-phosphate dehydrogenase enzyme deficiency: *Vicia sativa* (Vetch). *Saudi Med J* 2009;30:292-4.
45. Farran MT, Darwish AH, Uwayjan MG, Sleiman FT, Ashkarian VM. Vicine and convicine in common vetch (*Vicia sativa*) seeds enhance beta-cyanoalanine toxicity in male broiler chicks. *Int J Toxicol* 2002;21:201-9.
46. Zuccotti GV, Redaelli F, Gualdi V, et al. Hemolytic crisis in a G6PD-deficient infant after ingestion of pumpkin. *Ital J Pediatr* 2014;40:71.
47. Cardador-Martinez A, Maya-Ocana K, Ortiz-Moreno A. Effect of roasting and boiling on the content of vicine, convicine and L-3,4-dihydroxyphenylalanine in *Vicia faba* L. *J Food Qual* 2012;35:419-28.
48. Pulkkinen M, Zhou X, Lampi AM, Pironen V. Determination and stability of divicine and isouramil produced by enzymatic hydrolysis of vicine and convicine of fava bean. *Food Chem* 2016;212:10-9.
49. Griffiths DW, Ramsay G. The distribution of pyrimidinone glucosides in developing seedlings of *Vicia faba* and *Vicia narbonensis*. *J Sci Food Agric* 1996;72:469-75.
50. Khamassi K, Jeddi FB, Hobbs D, et al. A baseline study of vicine-convicine levels in fava bean (*Vicia faba* L) germplasm. *Plant Genet Resour* 2013;11:250-7.
51. Beutler E, Yeh M, Fairbanks VF. The normal human female as a mosaic of X-chromosome activity: studies using the gene for C-6-PD-deficiency as a marker. *Proc Natl Acad Sci U S A* 1962;48:9-16.
52. Rinaldi A, Filippi G, Siniscalco M. Variability of red cell phenotypes between and within individuals in an unbiased sample of 77 heterozygotes for G6PD deficiency in Sardinia. *Am J Hum Genet* 1976;28:496-505.
53. Gall JC, Brewer GJ, Dern RJ. Studies of glucose 6-phosphate dehydrogenase activity of individual erythrocytes: the methemoglobin-elution test for the detection of females heterozygous for G6PD deficiency. *Am J Hum Genet* 1965;17:359-68.
54. Vogels IMC, Van Noorden CJF, Wolf BHM, et al. Cytochemical determination of heterozygous glucose-6-phosphate dehydrogenase deficiency in erythrocytes. *Br J Haematol* 1986;63:402-5.
55. Shah SS, Diakite SA, Traore K, et al. A novel cytofluorometric assay for the detection and quantification of glucose-6-phosphate dehydrogenase deficiency. *Sci Rep* 2012;2:299.
56. Martini G, Toniolo D, Vulliamy T, et al. Structural analysis of the X-linked gene encoding human glucose 6-phosphate dehydrogenase. *EMBO J* 1986;5:1849-55.
57. Minucci A, Moradkhani K, Hwang MJ, Zuppi C, Giardina B, Capoluongo E. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the "old" and update of the new mutations. *Blood Cells Mol Dis* 2012;48:154-65.
58. Longo L, Vanegas OC, Patel M, et al. Maternally transmitted severe glucose 6-phosphate dehydrogenase deficiency is an embryonic lethal. *EMBO J* 2002;21:4229-39.
59. Piomelli S, Corash LM, Davenport DD, Miraglia J, Amorosi EL. In vivo lability of glucose-6-phosphate dehydrogenase in GdA- and GdMediterranean deficiency. *J Clin Invest* 1968;47:940-8.
60. Morelli A, Benatti U, Gaetani GF, De Flora A. Biochemical mechanisms of glucose-6-phosphate dehydrogenase deficiency. *Proc Natl Acad Sci U S A* 1978;75:1979-83.
61. Calabrò V, Cascone A, Malaspina P, Battistuzzi G. Glucose-6-phosphate dehydrogenase (G6PD) deficiency in southern Italy: a case of G6PD A(-) associated with favism. *Haematologica* 1989;74:71-3.
62. Nafa K, Reghis A, Osmani N, et al. G6PD Aures: a new mutation (48 Ile→Thr) causing mild G6PD deficiency is associated with favism. *Hum Mol Genet* 1993;2:81-2.
63. Galiano S, Gaetani GF, Barabino A, et al. Favism in the African type of glucose-6-phosphate dehydrogenase deficiency (A-). *BMJ* 1990;300:236.
64. Laosombat V, Sattayasevana B, Chotsampancharoen T, Wongchanchailert M. Glucose-6-phosphate dehydrogenase variants associated with favism in Thai children. *Int J Hematol* 2006;83:139-43.
65. Vulliamy TJ, D'Urso M, Battistuzzi G, et al. Diverse point mutations in the human glucose-6-phosphate dehydrogenase gene cause enzyme deficiency and mild or severe hemolytic anemia. *Proc Natl Acad Sci U S A* 1988;85:5171-5.
66. Goncalves P, Ribeiro ML, Tamagnini G, Kaeda J, Youssef N, Vulliamy TJ. Favism:

- glucose 6 phosphate dehydrogenase deficiency, G6PD A-: a common occurrence among Portuguese children. *Br J Haematol* 1994;87:Suppl 1:146.
67. Benmoursir I, Moradkhani K, Mounni I, et al. Two new class III G6PD variants [G6PD Tunis (c.920A>C: p.307Gln>Pro) and G6PD Nefza (c.968T>C: p.323 Leu>Pro)] and overview of the spectrum of mutations in Tunisia. *Blood Cells Mol Dis* 2013;50:110-4.
68. Calabrò V, Mason PJ, Filosa S, et al. Genetic heterogeneity of glucose-6-phosphate dehydrogenase deficiency revealed by single-strand conformation and sequence analysis. *Am J Hum Genet* 1993; 52:527-36.
69. Rovira A, Vulliamy TJ, Pujades A, Luzzatto L, Corrons JL. The glucose-6-phosphate dehydrogenase (G6PD) deficient variant G6PD Union (454 Arg>Cys) has a worldwide distribution possibly due to recurrent mutation. *Hum Mol Genet* 1994; 3:833-5.
70. Laosombat V, Sattayasevana B, Janejindamai W, et al. Molecular heterogeneity of glucose-6-phosphate dehydrogenase (G6PD) variants in the south of Thailand and identification of a novel variant (G6PD Songklanagarind). *Blood Cells Mol Dis* 2005;34:191-6.
71. Noori-Daloi MR, Najafi L, Mohammad Ganji S, Hajebrahimi Z, Sanati MH. Molecular identification of mutations in G6PD gene in patients with favism in Iran. *J Physiol Biochem* 2004;60:273-7.
72. Yoshida A, Beutler E, Motulsky AG. Human glucose-6-phosphate dehydrogenase variants. *Bull World Health Organ* 1971;45:243-53.
73. Jablonska-Skwiecincka E, Lewandowska I, Plochocka D, et al. Several mutations including two novel mutations of the glucose-6-phosphate dehydrogenase gene in Polish G6PD deficient subjects with chronic nonspherocytic hemolytic anemia, acute hemolytic anemia, and favism. *Hum Mutat* 1999;14:477-84.
74. van Wijk R, Huizinga EG, Prins I, et al. Distinct phenotypic expression of two de novo missense mutations affecting the dimer interface of glucose-6-phosphate dehydrogenase. *Blood Cells Mol Dis* 2004; 32:112-7.
75. Beutler E, Kuhl W, Vives-Corróns JL, Prchal JT. Molecular heterogeneity of glucose-6-phosphate dehydrogenase A-. *Blood* 1989;74:2550-5.
76. Maiga B, Dolo A, Campino S, et al. Glucose-6-phosphate dehydrogenase polymorphisms and susceptibility to mild malaria in Dogon and Fulani, Mali. *Malar J* 2014;13:270.
77. Sirugo G. Reassessing an old claim: natural selection of hemizygotes and heterozygotes for G6PD deficiency in Africa by resistance to severe malaria. *Am J Hematol* 2013;88:436.
78. Monteiro WM, Franca GP, Melo GC, et al. Clinical complications of G6PD deficiency in Latin American and Caribbean populations: systematic review and implications for malaria elimination programmes. *Malar J* 2014;13:70.
79. Rovira A, Vulliamy T, Pujades MA, Luzzatto L, Corrons JL. Molecular genetics of glucose-6-phosphate dehydrogenase (G6PD) deficiency in Spain: identification of two new point mutations in the G6PD gene. *Br J Haematol* 1995;91:66-71.
80. Luzzatto L. Genetics of red cells and susceptibility to malaria. *Blood* 1979;54: 961-76.
81. Bunn HF. The triumph of good over evil: protection by the sickle gene against malaria. *Blood* 2013;121:20-5.
82. Motulsky AG. Metabolic polymorphisms and the role of infectious diseases in human evolution. *Hum Biol* 1960;32: 28-62.
83. Allison AC. Glucose-6-phosphate dehydrogenase deficiency in red blood cells of East Africans. *Nature* 1960;186:531-2.
84. Luzzatto L, Usanga FA, Reddy S. Glucose-6-phosphate dehydrogenase deficient red cells: resistance to infection by malarial parasites. *Science* 1969;164:839-42.
85. Luzzatto L. G6PD deficiency and malaria selection. *Heredity (Edinb)* 2012; 108:456.
86. Malaria Genomic Epidemiology Network. Reappraisal of known malaria resistance loci in a large multicenter study. *Nat Genet* 2014;46:1197-204.
87. Uyoga S, Carolyne M, Ndila CM, et al. Glucose-6-phosphate dehydrogenase deficiency and the risk of malaria and other diseases in children on the coast of Kenya: a case-control and a cohort study. *Lancet Haematol* 2015;2(10):e437-e444.
88. Luzzatto L. G6PD deficiency: a polymorphism balanced by heterozygote advantage against malaria. *Lancet Haematol* 2015;2(10):e400-e401.
89. Louicharoen C, Patin E, Paul R, et al. Positively selected G6PD-Mahidol mutation reduces Plasmodium vivax density in Southeast Asians. *Science* 2009;326:1546-9.
90. John GK, Douglas NM, von Seidlein L, et al. Primaquine radical cure of Plasmodium vivax: a critical review of the literature. *Malar J* 2012;11:280.
91. White NJ, Qiao LG, Qi G, Luzzatto L. Rationale for recommending a lower dose of primaquine as a Plasmodium falciparum gametocytocide in populations where G6PD deficiency is common. *Malar J* 2012;11:418.
92. Baird K. Origins and implications of neglect of G6PD deficiency and primaquine toxicity in Plasmodium vivax malaria. *Pathog Glob Health* 2015;109:93-106.
93. von Fricken ME, Weppelmann TA, Eaton WT, et al. Prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in the Ouest and Sud-Est departments of Haiti. *Acta Trop* 2014;135:62-6.
94. Bhutani VK, Kaplan M, Glader B, Cotten M, Kleinert J, Pamula V. Point-of-care quantitative measure of glucose-6-phosphate dehydrogenase enzyme deficiency. *Pediatrics* 2015;136(5):e1268-e1275.
95. Motulsky AG, Campbell-Kraut JM. Population genetics of glucose 6-phosphate dehydrogenase deficiency of the red cell. In: Blumberg BS, ed. Proceedings of conference on genetic polymorphisms and geographic variations in disease. New York: Grune & Stratton, 1961:159-80.
96. Brewer GJ, Tarlov AR, Alving AS. The methemoglobin reduction test for primaquine-type sensitivity of erythrocytes: a simplified procedure for detecting a specific hypersusceptibility to drug hemolysis. *JAMA* 1962;180:386-8.
97. Rueangweerayut R, Bancone G, Harrell EJ, et al. Hemolytic potential of tafenoquine in female volunteers heterozygous for glucose-6-phosphate dehydrogenase (G6PD) deficiency (G6PD Mahidol variant) versus G6PD-normal volunteers. *Am J Trop Med Hyg* 2017;97:702-11.
98. Chu CS, Bancone G, Moore KA, et al. Hemolysis in G6PD heterozygous females treated with primaquine for Plasmodium vivax malaria: a nested cohort in a trial of radical curative regimens. *PLoS Med* 2017;14(2):e1002224.
99. Meloni T, Forteleoni G, Meloni GF. Marked decline of favism after neonatal glucose-6-phosphate dehydrogenase screening and health education: the northern Sardinian experience. *Acta Haematol* 1992;87:29-31.
100. Darbandi B, Noghaei M, Mehrabian F, Jafroodi M. Medical expenses of patients with favism admitted to 17th Shahrvivar Hospital compared to G6PD enzyme screening cost, in north of Iran. *Iran J Ped Hematol Oncol* 2014;4:53-6.
101. Gutierrez N, Avila CM, Duc G, et al. CAPs markers to assist selection for low vicine and convicine contents in faba bean (*Vicia faba* L.). *Theor Appl Genet* 2006; 114:59-66.
102. Hendawey MH, Younes AMA. Biochemical evaluation of some faba bean cultivars under rainfed conditions at El-Sheikh Zuwayid. *Ann Agric Sci* 2013;58: 183-93.

Copyright © 2018 Massachusetts Medical Society.