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The epidemiology of favism

MARK A. BELSEY¹

Favism is a potential obstacle to the use of the fava bean in the development of a locally produced, inexpensive weaning food for the Middle East and North Africa. The purposes of this study were to define the epidemiology of favism, to evaluate the advisability of using the fava bean in a weaning food, and to suggest ways of avoiding or eliminating the toxic factor in the bean. Field observations, locally acquired data, and a literature review suggested that the use of the fava bean in a weaning food would be hazardous, but that the hazard might be overcome by using certain strains of the bean or, more particularly, by using old dried beans. The disease is usually directly related in time to the harvesting and availability of fresh beans, but it is also associated with fresh dried beans. On the basis of the age distribution of the disease, patterns of bean consumption, and local food taboos it appears that the toxic factor is concentrated in the skin of the bean, that it is heat-stable, that in dried beans it decreases with age, and that it crosses into the breast milk of lactating mothers. It also appears that disease expression may be a result of the interaction of several host factors, such as nutritional status and the consumption of other foods. These observations are consistent with the results of laboratory studies, which incriminate vicine, divicine, and DOPA in the etiology of favism.

In order to provide an adequate source of protein for infants and children, a combination of a cereal grain and broad beans (*Vicia fava*) has been suggested as a weaning food for use in the Middle East and North Africa, where both wheat and broad beans are grown extensively. Although the fava bean is low in methionine content it is rich in lysine (Aykroyd & Doughty, 1964), and can thus compensate for the low level of lysine in wheat (FAO, 1955).

However, there are potential risks in so using the fava bean. Some individuals who eat or are exposed to it are reported to develop an acute haemolytic anaemia, favism. The disease may be fatal, usually occurs in children (especially males), and is generally thought to be related to the genetic deficiency of erythrocyte glucose-6-phosphate dehydrogenase (1.1.1.49) (G6PD). Favism therefore must be viewed as a potential obstacle to this solution to the problem of malnutrition in the Middle East and North Africa. In some areas the disease itself is a major public health problem (Donoso et al., 1969).

The following review and field investigation of favism in the Middle East and North Africa is

intended to define the potential effect of favism on a nutrition programme based on the use of a weaning food containing *V. fava*. A second purpose is to describe and relate the epidemiology of favism to laboratory and clinical studies, thereby seeking clues to the approach to be taken in preventing the disease.

DESCRIPTION OF THE DISEASE

Clinical description

Favism is characterized most often by four signs and symptoms: weakness or fatigue, pallor, jaundice, and haemoglobinuria. The symptoms are distinct enough to be recognized as characterizing a specific disease entity among populations experiencing the disease. Five different forms of the disease, based on the degree of severity, have been described by Gasbarrini (1915).

The interval between exposure to the fava bean and the onset of symptoms may be only a few hours and is usually under 24 h in both clinical and experimental studies, but it may be as long as several days (Panizon & Vullo, 1961). In contrast, the interval between drug exposure and haemolysis in the G6PD-deficient individual is several days (Burka et al., 1966; Dern et al., 1954).

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Favism has been observed among individuals who had previously consumed fava beans without showing signs or symptoms of the disease; others have developed the disease on the first exposure (Kattamis et al., 1969; Angelov & Andrev, 1959). In Egypt most of the cases occur among infants on their first exposure to the bean, which is reflected in the high proportion of cases among children under 1 year old (Ghafsarpur, personal communications). These later reports do not support the hypothesis of Kantor & Arbesman (1959) that favism represents in part a hypersensitivity phenomenon among individuals who have previously ingested or been exposed to the bean.

Repeated attacks of favism are not uncommon; second attacks of favism were noted in 10 of 120 patients studied by Kattamis et al. (1969). No note of repeated attacks has ever been made in the same year in any of the reported studies or personal communications, although a history of annual overt attacks or compatible symptoms was elicited from villagers and physicians in Egypt, Iran, and Tunisia.

Family clustering of cases is noted, both among the sporadic cases (Vince-Ribarić, 1962; Gehrman et al., 1963) and in larger series. Kattamis et al. (1969) noted the frequent occurrence of mild compensated symptoms in mothers at the time their male children developed favism.

An acute haemolytic anaemia with symptoms identical to those in favism was ascribed by Lederer (1925) to an infectious process before the G6PD defect was known. Subsequent writers have speculated that many of the cases described as Lederer's anaemia actually were cases of favism in which a history of *V. fava* ingestion was not specifically asked for, was unknown, or was denied despite actual ingestion (Gelin, 1952; Wharton & Duesselman, 1947). Other cases of Lederer's anaemia may represent drug exposure or infection superimposed on G6PD deficiency (Burka et al., 1966).

Laboratory findings

Laboratory findings in favism reflect the underlying G6PD defect, the haemolytic anaemia, and its consequences. They may also reflect the severity of the G6PD deficiency, the dose and form of fava bean exposure, and the acuteness and severity of the anaemia.

Erythrocyte counts are markedly diminished among the hospitalized patients, most being between 1 and 2 million cells per mm³ (Kattamis et al., 1969; Joannides, 1952; Messerschmitt et al., 1967). Since

patients with symptoms severe enough to necessitate blood transfusion are hospitalized, the "true" distribution of either erythrocyte counts or haemoglobin levels among all patients with haemolysis following fava bean exposure is not known.

Urinary findings are frequent in hospitalized patients. Haemoglobin is found in large amounts in the urine for 1-3 days; more prolonged haemoglobinuria is not usually observed. Small amounts of oxyhaemoglobin and methaemoglobin are noted in the urine, which appears dark brown, red, or even black. Oliguria and even anuria may occur in severe cases, with concomitant azotaemia. Death may occur from renal failure.

The G6PD level of patients with favism is generally low even during the acute episode (Kattamis et al., 1969; Larizza et al., 1958; Russo & Balsamo, 1962). The G6PD deficiency has also been noted in the granulocytes of patients with favism (Ideo et al., 1965). Nearly all studies on patients with favism indicate that there is a low level of reduced glutathione (GSH) and instability of GSH on *in vitro* incubation with 1-acetyl-2-phenylhydrazine (Sansone & Segni, 1956).

In the Mediterranean type of G6PD deficiency young erythrocytes appear to be almost as deficient of G6PD as old erythrocytes. During haemolytic crises among Caucasians with G6PD deficiency, the GSH instability of surviving erythrocytes is not decreased, nor is the GSH significantly increased (Zannos-Mariolela & Kattamis, 1961). This observation contrasts with that made among primaquine-sensitive¹ G6PD-deficient Negroes, in whom the continued administration of primaquine results in a younger population of erythrocytes with a higher G6PD level (Kellermeyer et al., 1961). Other studies among patients with favism indicated a fall in GSH during haemolytic crises, but a later rise of GSH (Panizon & Pujatti, 1958).

Genetics of G6PD deficiency

The G6PD deficiency is clearly inherited as a sex-linked trait. This has been demonstrated in mammals other than man (Trujillo et al., 1965). Marked variability occurs in the phenotypic expression of the female heterozygotes (Beutler, 1968). This variability has been explained by the observation that one X chromosome is euchromatic, whereas the other is heterochromatic and genetically inactive (Ohno et al., 1959). Since the pattern of X-linked inheritance

¹ Primaquine is 8-[(4-amino-1-methylbutyl)amino]-6-methoxyquinoline.

precludes the possibility that an inactive X chromosome was derived either from the paternal X or the maternal X exclusively, it would be necessary to assume the existence of mosaicism in which the paternal X was inactive in some cells and the maternal X in others (Beutler et al., 1962). In effect, the female heterozygote possesses two populations of erythrocytes. Techniques for detecting such heterogeneous populations of cells have been developed (Beutler et al., 1963) and heterozygous females have been shown to have a varying pattern of erythrocyte staining reflecting such heterogeneity; all the erythrocytes of homozygous subjects fail to stain (Caruso et al., 1967). The varying proportion of G6PD-deficient cells might then account for the very variable expression of disease among heterozygous females.

Several forms of G6PD exist in human populations. The pattern of deficiency has been thought to correspond to the distribution of malaria caused by *Plasmodium falciparum*. Although this hypothesis is still in dispute (Kidson & Gorman, 1962) many studies support it (Choremis et al., 1962; Siniscalco et al., 1961).

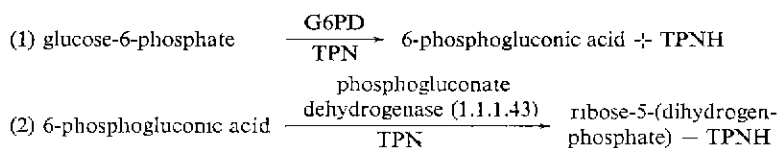
In Sardinia, the variations in gene frequency for G6PD deficiency are directly related to the variations in the prevalence of malaria (Siniscalco et al., 1961). The high frequency (21%) of G6PD deficiency among Kuwaitis, in the absence of falciparum malaria, has been attributed to the high degree of intermingling in the Persian Gulf area of groups

from areas where falciparum malaria is highly endemic, e.g., Iraq and Iran (Shaker et al., 1966).

G6PD and haemolysis

The mechanism of haemolysis in individuals exposed to *V. fava* or to certain drugs was elaborated by Sansone & Segni (1956), who showed that a lowered reduced glutathione (GSH) level was found in patients who had had favism or acute drug-induced haemolytic anaemia. Carson et al. (1956) showed that the erythrocytes of individuals with a primaquine-sensitive haemolytic anaemia had low levels of G6PD. These two characteristics of the deficient cells are related to one another and to the further decrease of GSH after incubation with 1-acetyl-2-phenylhydrazine (Zinham et al., 1958).

The administration of primaquine or *V. fava* to individuals deficient in G6PD results in a fall in the GSH levels of their erythrocytes before haemolysis develops (Szenberg et al., 1957). GSH makes up 95% of the reduced nonprotein mercapto compound in the erythrocyte and is thought to be important for the integrity of the cell (Fegler, 1952; Benesch & Benesch, 1954; Klebanoff, 1957). The role of the G6PD deficiency in the haemolytic disorder appears to be related to the important role of the enzymes in the pentose phosphate pathway, which is the only means by which glucose may be metabolized by mature erythrocytes. The following reactions generate reduced triphosphopyridine nucleotide (TPNH):



Without G6PD, TPNH will not be formed. The TPNH is necessary with glutathione reductase (1.6.4.2) in the reduction of oxidized glutathione (GSSG): in G6PD-deficient cells the level of GSSG is increased (Srivastava & Beutler, 1968). Substances capable of oxidizing TPNH or GSH might then be expected to cause haemolysis.

The defect in the erythrocytes *per se* may not be the only host-determinant of disease. Panizon & Vullo (1961) demonstrated that radioactive-chromium-tagged G6PD-deficient cells transfused into a normal individual lysed more slowly than the same cells transfused into a patient who had recovered from

favism after the ingestion of fava bean extract. Others have failed to demonstrate any haemolysis of such cells in normal recipients (Greenberg & Wong, 1961).

Among the factors that may explain the erratic pattern of the disease and the difference between it and drug-induced haemolysis are (1) the toxic factor in the fava bean may have to be activated in the host or in the presence or absence of other dietary factors; (2) the intake of the toxic factor may vary although bean consumption may be constant; and (3) the expression of disease may also be a function of another enzyme system, which may be either genetically directed or nutritionally affected.

INCIDENCE, DISTRIBUTION, AND MORTALITY

The reported incidence of favism in the Middle East varies considerably from one country to another and within each country, and depends on the distribution of the genetic defect, the presence of the fava bean in the local diet, and the availability and utilization of medical facilities. An incidence of 5 cases per 1 000 population has been estimated in Sardinia (Crosby, 1956). In 1965, the incidence in Guilan and Mazanderan, Iran, was 6.39 and 2.23 per 10 000 population, respectively (Lapeysonnie & Keyhan, 1966); in 1969 the incidence was 1.85 and 0.65, respectively (unpublished data). In the Rasht area of Guilan the 1965 incidence was 9.27 per 10 000. In view of the local awareness of the problem of favism, the availability of medical facilities, and the existence of a specific reporting system for the disease, the data from these Iranian *ostans* (provinces) appear reliable and probably approximate to the true situations. Although other data on incidence are lacking, favism is known to be widespread in the Mediterranean and Middle East regions.

The disease is frequently encountered in Algeria (Messerschmitt et al., 1967), Bulgaria (Angelov & Andrev, 1959), China (Chung, 1965), Cyprus (Joannides, 1952), Iran (Lapeysonnie & Keyhan, 1965), and Lebanon (Shahid, 1960). Sporadic cases have been reported from the Federal Republic of Germany (Gehrmann et al., 1966), France (Auquier et al., 1968), Poland (Rokicka-Milewska et al., 1968), Romania (Schneer et al., 1966), Yugoslavia (Vince-Ribarić, 1962), and the USA (Wharton & Diesselmann, 1947; Burka et al., 1966).

No large series of cases of favism have been reported from Egypt but the disease is common, accounting for approximately 1–2% of paediatric hospital admissions in Cairo and Alexandria (M. Gabr & M. Khalil, personal communication). On the basis of the number of hospital admissions of patients with favism to two of the paediatric services, the minimum incidence is 0.4 cases per 10 000 population per year. In Tunisia, in the past 8 years, fewer than one patient a year has been admitted to the children's hospital with a diagnosis of favism (A. B. Hamza, personal communication).

In the areas where the genetic defect is prevalent and the fava bean is a major food staple, only 10–20% of the population at risk ever appear to develop the disease. Kattamis et al. (1969) noted a history of favism in 10.3% of 223 G6PD-deficient males; Siniscalco et al. (1961) noted that 20% of 121 G6PD-deficient males had had episodes of favism.

The annual variation of cases in Mazanderan and Guilan is illustrated in Fig. 1. The decline in 1964 appears to have been real, since the reporting system was in operation in 1963; so does the rise in 1965. The variation has in part been attributed to the availability of the local *V. fava* crop, which was poor in 1964 and 1966 in Guilan. In Khuzestan, although few cases of favism are reported, a decline from 20 cases in 1968 to 8 in 1969 paralleled the poor crop in 1969.

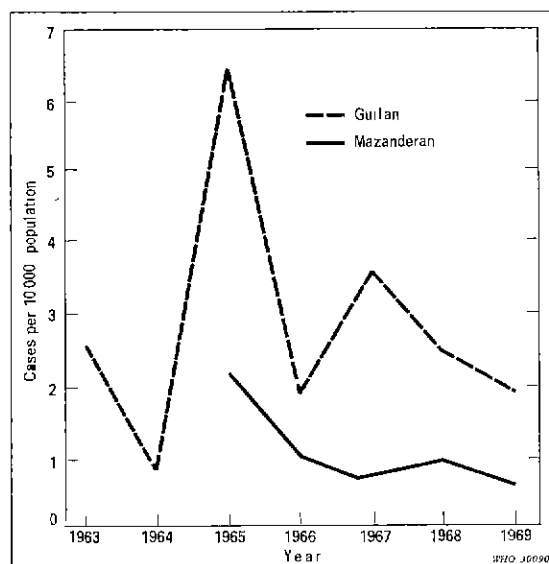


Fig. 1. Incidence of favism in Guilan and Mazanderan, Iran, 1963–69.

Seasonal distribution

Wherever favism is endemic, the disease generally has a characteristic seasonal distribution corresponding to the harvesting of fresh fava beans (Crosby, 1956; Chung, 1965; Lapeysonnie & Keyhan, 1966; Kattamis et al., 1969), although most large series include cases during other seasons. The peak incidence of cases in Iran also occurs in the harvest season: March and April in the south-eastern area, May in Mazanderan, and 3 weeks later in Guilan. In Greece 42% of cases occur in May (Kattamis et al., 1969); in Bulgaria, 90% in June (Angelov & Andrev, 1959); in Cyprus, 57% in April and May (about 25% were seen in January to March, when small quantities of fresh beans are available) (Joannides, 1952); and in Kwangtung, China, 95%

between 11 March and 10 April, 50% of them in the last 10 days of March (Chung, 1965). The direct relationship between cases and the availability of beans is seen in the shift of the occurrence of cases by time of onset in Guilan in 1965, 1968, and 1969 (Fig. 2). These changes correspond to the shift in time of the fava bean harvest; in 1969, owing to floods and a long winter, the beans were planted late and ripened even later than usual (W. Kaiser, personal communication).

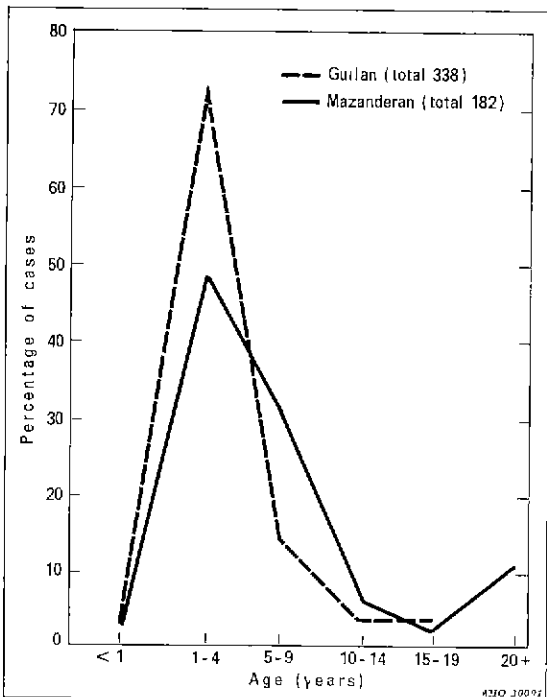


Fig. 2. Occurrence of favism in Guilan (1965, 1968, and 1969).

A unique seasonal pattern of disease occurs in Egypt. There are two seasonal peaks, and cases are not frequent in the spring until several weeks after the fresh beans are ripe (W. Gabr, personal communications). Analysis of 30 cases showed that 14 occurred from May to July and 10 from November to January. Although not documented, a similar pattern was noted in Alexandria (N. Hashem, personal communication). The onset of cases in May and June corresponds to the time of harvesting the dry bean, most cases being related to the consumption of stewed dried fava beans (*medamass*). It is

possible that the second seasonal increase in cases in November corresponds to the time of marketing of fava beans from Manuf that have been stored in a way peculiar to Egypt.

In the areas where cases are related to the locally harvested crop, most occur within 3-4 weeks. The distribution of cases in time resembles that of an infectious disease, i.e., the sudden introduction of an agent into a susceptible population leads to a rapid appearance of cases, followed by a less rapid decline.

Age distribution

Favism is generally a paediatric disease; however, even within the paediatric age range there is a variation in the age distribution, which probably reflects the varying risk of exposure to *V. fava* in different cultures and host factors that may enhance or inhibit expression of the disease. In Greece, 65% of the cases occurred in the 2-5-year age group, 7.2% in the 10-15-year group, and 5.5% in infants (Kattamis et al., 1969). Similar patterns have been noted in Bulgaria (Angelov & Andrev, 1959), Lebanon (Shahid, 1960), Cyprus (Joannides, 1952) and parts of Iran (Lapeyssonie & Keyhan, 1966). There is a consistently larger percentage of cases in the 1-4-year age group in Guilan than in Mazandaran (Fig. 2).

Several of the previously noted sources in Egypt report (unpublished data) a greater proportion of cases in children aged 0-1 and 1-4 years. In one hospital where 85 cases are seen each year, 50% of the patients were under 1 and 95% under 5 years of age. The occurrence of disease at these ages probably reflects the consumption pattern of *V. fava* in Egypt.

Kattamis et al. (1969) reported one case in a 45-day-old infant; Chung (1965) noted that the youngest of his 1464 patients was 6 months old, and Emanuel & Schoenfeld (1961) reported a case in a 4-month-old nursing infant. One of the oldest patients who developed favism for the first time was a 67-year-old woman (Faiola et al., 1969).

Occurrence of cases by sex

Favism is a disease to which male children are predisposed, the ratio of male to female cases ranged from 21:1 in Cyprus (Joannides, 1952) to 2.7:1 in Mazandaran (Lapeyssonie & Keyhan, 1966) (Table 1). These facts are explicable on the hypothesis that G6PD deficiency is a sex-linked trait with marked variability for phenotypic expression in the heterozygous female. The ratio of male to female cases would then be expected to be slightly lower than the calculated ratio of males with G6PD defi-

Table 1. Relationship between the ratio male gene : female homozygote and the ratio male cases : female cases in selected areas

Area	δ gene/ ♀ homozygote (1)	δ cases/♀ cases (2)	Ratio $\frac{1}{2}$
Egypt (average)	33.4	14	2.4
Cyprus	32	21.3	1.5
Athens (average)	120	6.2	19.4
Fars	12.5	3.9	3.2
Persian Gulf	14.36	7.0	2.1
Guilan	2.39	3.38	.71
Mazanderan	2.39	2.70	.89

ciency genes to female homozygotes for this gene because there would be some disease expression in female heterozygotes. For example, the calculated ratio¹ in Shiraz, Iran, would be 12.5 : 1; the actual ratio of cases is approximately 4 : 1. These findings can be explained by any (or a combination) of the following hypotheses: (1) there are two female heterozygotes per female homozygote developing disease, (2) relative to female homozygotes only one third of all males with G6PD deficiency are at risk of developing disease, or (3) the risk of exposure to the bean is markedly less in the males than in the homozygous females.

¹ Calculated on the basis of $2q(1-q) + q^2$ where q is the male gene frequency; q^2 represents the female homozygote.

The consistent pattern of a greater than expected number of female cases, based on a ratio of male gene frequency to female homozygote deficiency (column 3 of Table 1) greater than 1.0, is not observed in the Caspian region of Iran. Either disease expression is more likely in males in this region or there is a markedly different exposure pattern by sex.

The distribution of cases by age and sex suggests a changing pattern of either exposure or disease expression among females (Table 2). The ratio of male to female cases is lower in those aged under 10 years than in those aged 10 years or over. The difference could reflect cultural patterns in respect of cooking, tasting, and other eating habits or biological changes affecting expression of the disease.

The severity of disease, as judged by the severity of the anaemia, does not appear to be sex-dependent.

Urban-rural distribution

Most reports of large series of patients with favism do not include a breakdown of the data according to the occurrence of cases in urban and rural areas. In Bulgaria cases are more frequent in rural areas (Angelov & Andrev, 1959), though specific rates are not reported; nor are they included in the extensive reports from China, Cyprus, Greece, Iran, or Italy. The cases reported from Egypt are nearly all from the urban areas of Cairo and Alexandria; no data exist on the rural distribution.

Mortality

The mortality from favism varies from area to area: in Sardinia it has been reported to be as high as

Table 2. Distribution of cases of favism by sex and age in selected areas¹

Area	Year	Age <10 years			Age ≥10 years		
		No. of cases		Ratio $\frac{\delta}{\eta}$	No. of cases		Ratio $\frac{\delta}{\eta}$
		δ	η		δ	η	
Rasht (2 hospitals in Guilan)	1958-62	530	95	5.6	22	14	1.6
Guilan	1965	490	154	3.2	61	37	1.6
	1968	243	68	3.6	19	7	2.7
Mazanderan	1965	234	75	3.1	38	14	2.7
	1968	105	40	2.6	22	15	1.5

¹ Source: Lapeyssonnie & Keyhan (1966), except for the 1968 data for Guilan and Mazanderan, which were provided by the Ministry of Health of Iran.

2 per 10 000 population (Crosby, 1956); in Tunisia there are few cases and practically no deaths (B. Hamza, personal communications). In Kwangtung the case mortality was 2.3% (Chung, 1965) and in Bulgaria it was 2.1% (Angelov & Andrev, 1959). Among Joannides' (1952) patients, 3 of 67 died. In the Caspian region in 1965 the case mortality was 1.2% in Guilan and 1.8% in Mazanderan (Lapeysonie & Keyhan, 1966). In 1968 in Guilan only 1 death was recorded among 338 patients. Mortality is a function of age; in Guilan in 1965, the case mortality rate was 4.7% for children less than 2 years old and 1.11% for those aged 2-4 years; among children aged 5-16 there were no deaths (Lapeysonie & Keyhan, 1966).

THE FAVA BEAN: PRODUCTION, CONSUMPTION, AND TOXIC FACTORS

Production

The broad bean is planted throughout the Middle East between October and December; only one crop a year is produced. The plant usually flowers 40-50 days after planting; few, if any, cases of favism are noted during the months of flowering. In a given region, fresh beans are harvested over a period of approximately 4-5 weeks, a period that corresponds to the usual interval of the epidemic curve of favism cases in each local area. The shifts in the epidemic curves of cases in Guilan correspond to the variations in the time of planting and harvesting (Fig. 3).

In Egypt approximately 5% of the dried bean crop is stored in such a way that the beans retain to all outward appearances the characteristics of fresh dried beans, from which they are indistinguishable in taste. It is possible that the introduction of these beans into the local markets in October and November accounts for the second peak in cases of favism in Cairo and Alexandria.

Disease of *V. fava*, such as chocolate spot disease, caused by the fungus *Botrytis fava*, or rust, cannot be responsible for the production of the toxic factor in *V. fava*, since the years in which these diseases have been common have been those with a marked decrease in the number of cases of favism in both the Caspian and the Khuzestan regions of Iran (Kaiser et al., 1967, 1968).

Consumption

Form associated with acute haemolysis. The predominant type of exposure associated with favism is the ingestion of fresh beans at the time of harvest,

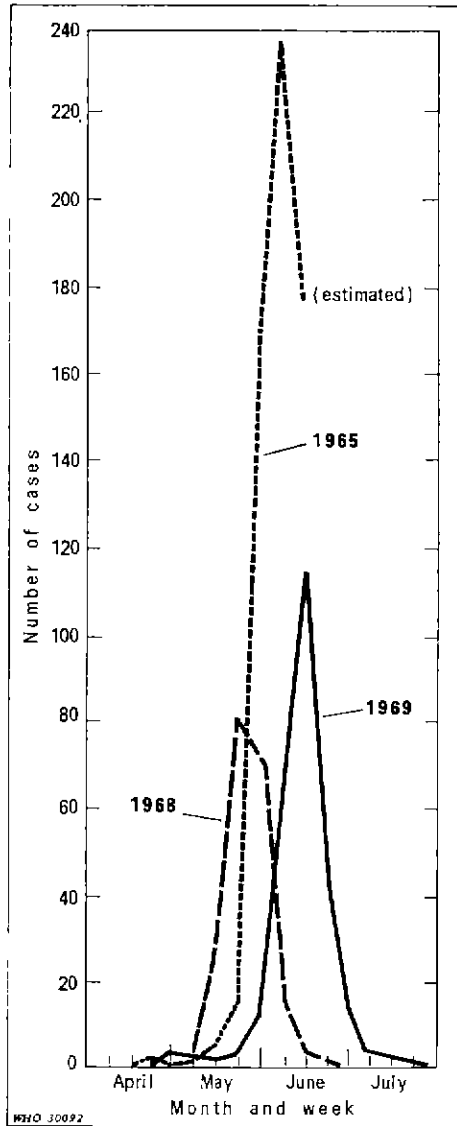


Fig. 3 Age distribution of cases of favism in Guilan and Mazanderan, 1968 (data from the Department of Health, Mazanderan and Guilan).

although dry beans may also be implicated (Gasbarini, 1915; Kattamis et al., 1969; Chung, 1965). In addition, cases of favism have been well documented in suckling infants whose unaffected mothers had eaten fava beans (Chung, 1965; Angelov & Andrev, 1959; Kattamis et al., 1969; Emanuel & Schoenfeld, 1961); such cases have been noted in the Caspian

Table 3. Form of *V. fava* contact associated with favism¹

Area and year	Breast-fed Infants	Passage through <i>V. fava</i> field	Contact with pollen or flower	Eaten raw	Eaten cooked	Eaten, form unknown	Total
Guilan, 1967	90 (14.5)	93 (15.0)	90 (14.5)	166 (26.8)	171 (27.6)	9 (1.5)	619
Mazanderan							
1965	2 (0.8)	47 (18.1)	15 (5.8)	181 (69.9)	14 (5.4)	0	259
1968	1 (0.5)	37 (16.9)	6 (2.7)	154 (70.3)	21 (9.6)	0	219
1969	1 (0.7)	28 (20.1)	0	96 (69.1)	14 (10.1)	0	139
Fars, 1968-69	3 (4.9)	1 (1.6)	0	8 (13.1)	49 (80.2)	0	61

¹ The table gives the number of cases and, in parentheses, the proportion of total number of cases associated with each form of contact. Source: Departments of Health Guilan, Mazanderan, and Fars (unpublished data).

² The mothers had eaten fava beans.

region of Iran (Table 3). Luisada (1941) cites one case that was possibly associated with the ingestion of milk from a goat that was fed on fava beans. Thus, whatever the toxic factor, it is capable of crossing from the mother into breast milk.

Although many authors indicate that cases are associated with inhalation of the pollen of the *V. fava* flower, most of them refer to the early papers of Gasbarrini (1915) (Luisada, 1941; Wharton & Dueselman, 1947). Recent reports on large series of patients fail to confirm the occurrence of pollen-produced cases of favism (Kattamis et al., 1969; Chung, 1965). In Guilan and Mazanderan associated cases have been claimed (Table 3), yet no reported cases have occurred in January or February, when the flowers are in bloom. The few cases reported in Cyprus and in Shiraz, Iran, during December and January may have this cause, or may be cases of haemolytic anaemia related to drugs or infection.

Fresh beans accounted for 68% of the cases studied by Kattamis (1969), but the report did not differentiate the forms in which the fresh beans were consumed. In the Caspian region fresh beans account for nearly all the cases; raw beans account for 26-70% of them and cooked beans for 5-27% (Table 2). In Egypt nearly all cases are associated with dried stewed beans, almost the only form in which they are consumed.

The form in which the bean is ingested does not affect the time interval between ingestion and the onset of symptoms (Kattamis et al., 1969), suggesting that, whatever the toxic factor, it is present in the fresh and in the dried beans in a similar form.

No data exist relating the risk of favism to the form in which the bean is consumed. Table 4 shows the attack rates of favism associated with the different forms of exposure. Since the table is based on the total population and an assumed equal risk of

Table 4. Attack rate of favism associated with different forms of contact (per 10 000 population)

Area and year	Breast-fed infants	Passage through <i>V. fava</i> field	Contact with pollen or flower	Eaten raw	Eaten cooked	Eaten, form unknown	Total
Guilan 1967	0.66	0.68	0.66	1.22	1.25	0.07	4.54
Mazanderan							
1965	0.01	0.26	0.08	0.98	0.08	0	1.41
1968	0.005	0.20	0.03	0.64	0.11	0	0.99
1969	0.005	0.15	0	0.52	0.08	0	0.79

exposure for the different forms, it is a gross simplification. However, such a simplification is appropriate when the patterns of bean consumption and disease in Guilan and Mazanderan are compared (Tables 3 and 4). The higher attack rate in Guilan is due to exposure of breast-fed infants, partially to pollen (which is already questioned), and to the consumption of cooked beans, which on the basis of the seasonal pattern of disease and the consumption pattern would be fresh cooked beans (Table 4). The consumption of cooked fava beans is similar in Mazanderan and in Guilan, and the prevalence of the G6PD deficiency is the same, yet the disease is more frequent in Guilan. The explanation may lie in different folk attitudes and the manner in which the bean is prepared and consumed in the two areas, particularly since the attack rates based on raw bean ingestion are similar (assuming equal risk of exposure).

Consumption patterns. The daily consumption of the fava bean in rural areas of Egypt, Iran, and Tunisia is shown in Tables 5 and 6. Consumption is greatest in the urban areas of Egypt, where up to 46 g per day may be eaten by pregnant and lactating women (Abdou & Amer, 1965) and where there is little seasonal variation; the mean daily consumption is 28 g (Abdou, personal communication). The pattern of consumption in rural Egypt appears to resemble that in Iran (Iranian Statistical Center, 1965?) and Tunisia (personal communications).

In Iran the pattern varies markedly from one region to another and is in part dependent on the pattern of bean production. The data in Table 5 understate consumption in some areas since only

Table 6. Consumption of fava beans (g per person per day) in Tunisia

Area	Fresh beans	Dried beans
rural areas ^a		
north	18	6
central & south	10	3
average	14	4.5
large cities	16.7	7.7
villages	14.2	4.9
dispersed settlements	13.1	3.6
average	14.7	5.4

^a Villages and dispersed settlements.

about one-third of the villages sampled in the survey (Iranian Statistical Center, 1965?) represented areas of heavy bean production and consumption; in many villages the bean was neither produced nor consumed.

In Tunisia, where favism is rare, the *per caput* consumption of fava beans, particularly fresh beans, appears to exceed even that of Iran, where favism is common. The pattern varies in Tunisia; increasing consumption is associated with increasing urbanization and proximity to the growing areas. The implications are that in Tunisia (1) there is a lower frequency of G6PD deficiency (probable), (2) the bean is less toxic (possible), or (3) the preparation of the bean minimizes any toxic factor present.

Different varieties of fava bean are consumed in Egypt, Iran, and Tunisia, but in the medical literature the variety associated with cases of favism has never been specified. One problem in differentiating the species of *V. fava* is that, among the pulses, *V. fava* is the only one that cross-pollinates between species (W. Kaiser, personal communication). Pure strains may be difficult to find in areas where more than one strain is grown.

In Egypt three different strains are consumed, and they are often eaten together in the dried form in the urban areas. In Iran there are three main strains; in addition, the Algerian strain has recently been introduced into several areas, particularly parts of Khuzestan, in order to increase the yield and attempt to decrease susceptibility to various *V. fava* diseases. In Tunisia there are two main strains; a third is produced but is fed only to animals.

The form in which the bean is eaten varies

Table 5. Seasonal consumption of fava and other beans (g per person per day) in Egypt and Iran

Country and type of bean	Winter	Spring	Summer	Autumn
Egypt				
pulses ¹	7	19	2	12
Iran (rural areas)				
fresh beans	0.4	4.5	1.9	0
split dried beans	0.5	0	0.3	0.4
dried beans & chick peas ²	7.18	2.65	4.85	7.50

¹ Data from 560 households (2,800 persons). Whether the pulses were dried or fresh was not specified.

² Separate data not available.

throughout the Middle East and North Africa. In the clinical descriptions and large series of cases, reference is made only to whether the beans associated with disease were raw or cooked and, if the latter, whether they were fresh or dried.

The raw bean is consumed with or without the skin and rarely, if ever, with the pod. In most areas the skin of the raw fava bean is tough and inedible, yet in Guilan the raw bean is frequently eaten with the skin, particularly by younger children. Fresh beans, whether raw or cooked, are not considered an appropriate food for children in Egypt. In rural areas of Iran and Tunisia, raw beans are frequently consumed, particularly by children.

The fresh fava bean is generally cooked in water, in or out of the pod; in the latter case, the skin may or may not be removed. Only in Guilan and occasionally in Mazanderan is the cooked bean eaten with the skin. In Tunisia, large fresh beans are always eaten without the skin. Fresh cooked beans are not commonly eaten in Egypt, but are widely eaten in Iran and Tunisia when in season. In Iran the fresh beans may be consumed without the skin though this is more common with the dried beans.

The dried beans are eaten in many forms. Stewed dried beans form a main staple in the Egyptian diet and are often fed to infants; the skins are not removed when the beans are eaten. Most cases of favism in Egypt have been associated with this form of bean. The dried beans may also be soaked in water overnight, the skins removed, and the beans incorporated into stew-like dishes.

Boiled dried beans are frequently purchased from street vendors or in eating places in both Iran and Tunisia. In Iran the dried beans are cooked in their skins, but the latter are peeled off when the beans are eaten. Older children and adults are the principal consumers of these beans, the consumption of which is greatest during winter.

In the Caspian region during winter, dried beans are soaked overnight; the skins are then removed and the beans cooked for a few hours. In Rasht and the surrounding areas the soaked dried beans may be eaten uncooked (without the skin).

In much of Iran, wheat flour with added fava bean flour is used. Individual bakers, particularly in the Caspian region, may also use fava bean flour.

Folk attitudes. In areas where the disease or its symptom complex is recognized by villagers the association with the fava bean has usually been made. In some areas villagers feel the disease is associated with eating the raw bean together with the

skin; in other areas the eating of the raw bean alone is associated with the disease. A series of prohibitions has evolved against the consumption of the fava bean by certain persons or under certain circumstances. In Iran there is an attitude that women should not eat the fava bean for at least 30-45 days after the delivery of a child. Many of the prohibitions cover other foods, but these patterns are not as constant as that relating to the fava bean.

Villagers in most of the areas where the bean is eaten consider that it should not be given to young children and infants, especially when it is raw. In the Caspian region, and especially in areas of Guilan, this view is not particularly strong. In the Mazanderan area consumption of the skin, whether cooked or raw, is often thought to be dangerous for children; there is no such recognition of any inherent danger in the Rasht area of Guilan. Outside the Caspian region, the consumption of the raw fava bean is frowned upon and it is thought that only young children, particularly those who are helping in the fields, eat the raw bean. In Egypt there is a strong feeling against the consumption of the fresh fava bean by children.

Folk remedies for the prevention or treatment of the disease have evolved in three widely separated areas, in Guilan and Fars in Iran and in Tunisia. The consumption of large amounts of sweets in the form of grape juice, honey, dates, or sugar water is advocated in these regions both to prevent and to cure the disease. The cure rate for this type of therapy has been reputed to be about 50% in both Guilan and Fars. This therapy is thought to be fairly effective in Tunisia, where few such patients ever come to medical attention. In Rasht, where all classes consume the fava bean, the lower-class peasants look upon the disease as being imposed on them because they are too poor to afford the sweets and meats of the upper-class diet.

Weaning practices and consumption by infants. In Egypt a large proportion of infants are exposed to the fava bean before the age of 2 years (Abdou et al., 1965); in Iran and Tunisia only a small proportion of such infants are so exposed. Weaning usually takes place at about 6 months of age, although frequently, particularly in the rural areas, mothers will continue breast feeding at least through the first year and often into the second year of a child's life. In urban areas of Egypt, 14% of the infants between 6 and 12 months old and 47% of those aged 12-14 months eat the fava bean (Abdou et al., 1965). There are no precise data on the food-consumption patterns of

infants and children in Iran. In Tunisia, an infant is unlikely to get fava beans unless it is with the family's food; at 6-9 months of age only 11%, and at 9-12 months 24%, of the infants eat the family food.

The development of a weaning food containing *V. fava* would appear to be a potential health hazard to infants with the G6PD deficiency. If it were to be incorporated in such a food, the bean would presumably have to be dried. The relative risk of dried (as compared to fresh) beans is not known, but on the basis of experience in Egypt the risk is real. In most areas it is evident that young children have a greater probability of disease expression, but it is not known whether this is determined biologically (i.e., whether it is directly related to age) or circumstantially (i.e., by ingestion in an unknown manner, consumption of the skin, etc.). It is possible that exposure at an earlier age might result in even more cases. Since mortality is greater at a younger age, the introduction of the fava bean into the infant's diet would have a major effect on infant health.

The only way of diminishing the risk of favism is to identify the toxic factors in the bean and then determine whether they can be removed by strain selection or by modifying the way in which the bean is prepared for use in a weaning food.

Toxic factors. The substances that have received the greatest attention as the possible toxic factor in favism are vicine [2,6-diamino-5-(β -D-glucopyranosyloxy)-4-pyrimidinol] and divicine (2,6-diamino-4,5-pyrimidinediol) (Razin et al., 1968; Lin & Ling, 1962) and 3-(3,4-dihydroxyphenyl)alanine (DOPA) and its glycoside (Kosower & Kosower, 1967). Vicine, divicine, and isouramil (6-aminoisobarbituric acid), another constituent of the fava bean, have been shown to oxidize reduced glutathione (GSH) in G6PD-deficient erythrocytes but not in normal cells (Lin & Ling, 1962; Lin, 1963; Razin et al., 1968; Mager et al., 1965). Vicine has also been isolated from beet juice and peas (Donoso et al., 1969), but these have not been associated with acute haemolytic anaemia.

On aging, vicine becomes brown, presumably by oxidation, with a loss of activity (Mager et al., 1965). When incubated with normal erythrocytes *in vitro*, vicine inhibited 38% of the activity of G6PD (Lin & Ling, 1962).

The fava-bean pyrimidines can oxidize GSH in pure solution, in contrast to 1-acetyl-2-phenylhydrazine (APH) and primaquine, which require the presence of erythrocytes or haemoglobin. The pattern of metabolic disturbance resulting from the

incubation of G6PD-deficient erythrocytes with the pyrimidine aglycon of vicine and divicine is identical to that produced by the incubation of such cells with APH (Mager et al., 1965). The pyrimidines are found as their glycosides in *V. fava*. The aglycons may arise from the hydrolytic action of β -glycosidases, either in the bean or in the digestive tract (Mager et al., 1965). The action of isouramil in reducing the GSH of both normal and G6PD-deficient erythrocytes is potentiated by either DOPA or ascorbate and is inhibited by glucose (Razin et al., 1968). Kosower & Kosower (1967) demonstrated that incubation of DOPA with G6PD-deficient erythrocytes resulted in a sharp loss of GSH and that oxidation of GSH in normal cells took place only in the absence of glucose.

If these *in vitro* models are relevant *in vivo*, it becomes obvious that a combination of potential toxic factors may be necessary for disease expression, i.e., both vicine and DOPA may produce the haemolysis of erythrocytes. Other possible requirements for such expression may be an associated metabolic state, i.e. the presence or absence of hypoglycaemia, and the status of other enzyme systems, such as the β -glycosidases and glutathione reductase (1.6.4.2), and the presence of other substances, such as ascorbic acid, in the diet.

It has been demonstrated that the browning of *V. fava* is related to the β -D-glucoside of DOPA, which is located almost exclusively in the skin coat, being absent from the cotyledon and present in only small amounts in the inner green tissue of the pod and the hilum (Nagasawa et al., 1961).

Broad beans when fresh have a green to buff skin and a buff to green interior. The seed slowly darkens because of oxidation and after a year is dark red-brown. Storage in the absence of oxygen (and light) retards this effect.

DISCUSSION

Throughout the Middle East favism constitutes a major health problem. The extent of the problem depends on the prevalence of the G6PD deficiency and on how and by whom the fava bean is consumed. Only within the Caspian region of Iran has the problem been accepted as a public health responsibility and its full magnitude appreciated. The problem could be aggravated, and many health resources strained in the treatment and management of patients, if the fava bean were introduced into the diet of weaning infants without removal or neutralization of the toxic factor.

The association of favism with fresh raw and

cooked fava beans is well documented throughout the Middle East. The onset of cases invariably starts with the harvesting of fresh beans and their appearance in the market. Individual case reports of favism after the ingestion of dry beans are found in Iran and other countries; such an association is common in Egypt. Since the consumption of dried beans is constant in the four seasons in Egypt, the decline of cases in the month of July and their disappearance in August may be a result of a decrease of the toxic factor in the bean. This appears to coincide with the normal darkening of the bean, i.e., the breakdown of DOPA or vicine or both.

The association of cases and of their frequency in areas where the bean is consumed with the skin, whether raw or cooked, appears to indicate that at least one toxic component of the bean is located in the skin. All the toxic components would have to be heat-stable, as disease is frequently associated with fresh or cooked dried beans. Furthermore, the toxic factors are capable of passing into breast milk.

The occurrence of favism may be erratic within a population, a family, and even an individual. Individuals are frequently exposed to the fava bean many times before they develop the disease, or they may develop it from initial but not from subsequent exposure. Part or much of this erratic pattern may be attributable to the form in which the bean is eaten and the season when it is consumed; in Egypt, for example, disease is unlikely to develop as a result of either initial or subsequent exposure during August and September. In Iran, persons who develop favism

following initial exposure to the bean with the skin may not develop it when they subsequently consume the bean without the skin.

Several factors in the status of the individual may affect disease expression. It is possible that the host's blood glucose level may affect the occurrence or degree of haemolysis. The individual's pre-existing haemoglobin level may be a determinant of the degree of disease expression. The presence of protein-calorie malnutrition might affect other enzyme systems and thus interfere with a child's reserve ability to reduce oxidized glutathione.

Although antibodies to *V. fava* have been demonstrated clinically and experimentally (Kantor & Hock, 1966), hypersensitivity to a factor in the fava bean does not appear to be related to the development of the disease, since most of the cases in Egypt and a large proportion of those in the Caspian region are associated with the first exposure of the infant to the bean.

The risk of contracting favism decreases with age. Individuals who have experienced an episode of favism will frequently abstain from further consumption of the fava bean. Individuals who suffer mild attacks are known to have them repeatedly over many years, indicating that desensitization has not occurred. The form in which the bean is consumed is likely to change with age. In most areas, even though some children may consume raw or cooked fava beans with the skin on, it is the general practice for adults and older children to peel the skin off with their teeth before eating the beans.

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RÉSUMÉ

L'ÉPIDÉMIOLOGIE DU FAVISME

Le favisme représente un obstacle potentiel à l'incorporation des fèves (*Vicia fava*) dans un aliment de sevrage susceptible d'être produit sur place et à bon compte au Moyen-Orient et en Afrique du Nord. Dans le présent article, l'auteur décrit les aspects épidémiologiques de l'affection, évalue l'opportunité d'utiliser les fèves comme composant d'un aliment de sevrage et suggère des moyens propres à neutraliser ou à éliminer les facteurs toxiques contenus dans ces légumineuses.

Les observations faites sur le terrain et l'examen des

publications consacrées au problème du favisme montrent que l'emploi des fèves dans un aliment de sevrage comporte des risques pour la santé, mais que le danger pourrait être fortement diminué par la sélection de certaines variétés de plantes et aussi, notamment, par l'utilisation de graines séchées depuis un temps suffisamment long. Les cas de favisme sont généralement associés dans le temps à la récolte et à la mise sur le marché des fèves fraîches, mais ils surviennent aussi à la suite de la consommation de fèves récemment séchées. De l'étude de la

répartition de la maladie selon l'âge, des modalités de la consommation des fèves et des tabous alimentaires locaux, il ressort que les facteurs toxiques, thermostables, sont concentrés dans la cuticule de la graine et qu'ils sont de moins en moins abondants avec le temps dans les fèves séchées. On les retrouve dans le lait des mères allaitantes. Le favisme peut se manifester à la suite de l'interaction

de différents facteurs individuels comme la carence en glucose-6-phosphate déshydrogénase (G6PD), l'état de nutrition et la consommation d'autres types d'aliments.

Ces observations concordent avec les résultats des recherches de laboratoire qui mettent en lumière le rôle de la vicine, de la divicine et de la dihydroxyphénylalanine dans l'étiologie du favisme.

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