

On the relation between malaria and G-6-PD deficiency

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SUMMARY On the basis of the hypothesis that in the regions where favism is present a high correlation exists between endemic malaria and the frequency of G-6-PD deficiency, Huheey and Martin (1975) in a recent paper suggest that the haemolytic event in a malarial environment is a favourable selective factor. Therefore, the fitness of the G-6-PD-deficient individual who shows haemolysis is higher than that of those who do not show haemolysis. Modiano (1976) also suggested that haemolysis may not be a negative component of the selective forces which act on the G-6-PD-deficient variants.

In this paper, some facts which make these hypotheses unlikely are considered. Other, more promising, lines for the analysis of the complex relation between malaria and G-6-PD deficiency are suggested.

In Sardinia and in the area of the Po Delta, even though favism is present, there is a very low correlation between the frequency of G-6-PD deficiency and past malarial morbidity. Therefore, the situation is similar to that observed in other parts of the world, in which malaria is highly endemic, but where favism is absent.

The following facts seem to be in contrast with the possibility that haemolysis could 'by itself' be a favourable event: (1) In the hemizygous male, haemolysis due to favism is generally severe and there is a high mortality rate; (2) In the heterozygous female, the erythrocytes with G-6-PD deficiency seem to show a low parasite rate compared to normal cells, and it is just these erythrocytes that are destroyed during the haemolytic crisis; (3) In malarial environments, enzymopenic variants associated with continuous haemolysis have not been selected. A positive selection of such variants would be expected if haemolysis was 'by itself' a positive factor.

Several observations suggest that the G-6-PD system interacts with various factors, both genetical (thalassaemia, erythrocyte acid phosphatase, adenosine deaminase) and environmental (Vicia Faba, altitude, viral and protozoal diseases). In a malarial environment, therefore, the fitness of the different G-6-PD genotypes depends on numerous variables. This could explain the low correlation generally observed between the degree of malarial endemicity and the frequency of G-6-PD deficiency.

Further analysis of the above interactions could elucidate the mechanisms which have brought about the selection of certain types of enzymopenic variants in malarial regions.

It is well known that the presence of G-6-PD deficiency is associated with malarial endemicity. The relation between the 2 variables, however, is far from clear and the malarial hypothesis has been challenged by various authors, mainly on the basis of the poor correlation between the frequency of G-6-PD deficiency and the intensity of malarial endemia.

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In the Mediterranean populations, it is also well known that people with G-6-PD deficiency may present a severe haemolytic disease (favism) following the ingestion of fresh seeds of Vicia Faba. The haemolysis has generally been considered a negative component in the balance of the selective forces acting upon G-6-PD variants associated with enzyme deficiency. Recently, however, some authors have suggested that the

haemolytic event itself may represent an advantage in a malarial environment.

In a paper published in 1975, Huheey and Martin put forward the hypothesis that favism and G-6-PD deficiency interact synergistically, providing an increased protection against malaria compared to that provided by G-6-PD deficiency alone. Though acknowledging the fact that in many areas there is only a poor correlation between G-6-PD deficiency and malarial prevalence, the authors maintain that in populations afflicted by favism, G-6-PD deficiency shows the highest prevalences and there is a good correlation with the incidence of malaria. In order to explain this 'apparent paradox', they suggest that 'the stress imposed on the erythrocyte by haemolytic favism may act synergistically with the already unfavourable G-6-PD levels to eliminate parasitized erythrocytes'. Therefore, while 'in the absence of the enhancement of protection against malaria by favism, pressures from migration, mutation, and/or genetic drift could be responsible for the erratic G-6-PD frequencies', in populations which include Vicia Faba in their diet positive selection on the allele for G-6-PD deficiency would be stronger, and the relation with malaria more likely to be detectable.

Recently, also, Modiano (1976) has suggested that haemolysis may not be a negative factor among the selective forces acting upon G-6-PD deficiency.

In the present paper we discuss some points concerning these hypotheses and present our view on the problem of the relation between malaria and G-6-PD deficiency.

Prevalence of G-6-PD deficiency and past malarial morbidity in Italian populations

In Sardinia and in the area of the Po Delta, malaria has been highly endemic until recently, and, moreover, Vicia Faba is a current foodstuff. As reported in a previous paper (Palmarino *et al.*, 1975), however, the correlation between prevalence of G-6-PD deficiency and past malarial morbidity in these populations is very low.

In 52 Sardinian villages surveyed by Siniscalco *et al.* (1966), a correlation coefficient of -0.07 was found between the frequencies of G-6-PD deficiency and past malarial morbidity as reported by Fermi. In 11 villages of the Ferrara province (near the Po Delta), Gandini *et al.* (1969) found a correlation coefficient of 0.15 . More recently, in 14 villages of the central area of Sardinia, we found a correlation coefficient of 0.62 between G-6-PD deficiency and past malarial morbidity (Palmarino *et al.*, 1975). Both in Siniscalco's sample and in ours, a good correlation was found between altitude and G-6-PD deficiency (correlation coefficients -0.59 and -0.73 , respectively) sug-

gesting that other environmental factors, such as barometric pressure, partial pressure of O_2 , humidity, temperature, and quantity and quality of Vicia Faba used in human diet, may have been more important than malarial diffusion in determining the G-6-PD frequencies in the Sardinian villages. An important role of other factors besides malaria is strongly suggested also by the fact that, though both Sardinian lowlanders and inhabitants of the Po Delta were heavily afflicted by malaria, and made widespread use of Vicia Faba for their alimentation, G-6-PD deficiency shows a very high prevalence in Sardinians (up to 0.35), but a low prevalence in the population of the Po Delta (<0.05).

Therefore, on the basis of the observations on Italian populations, the main argument supporting the hypothesis of Huheey and Martin (1975) (that is, the good correlation between G-6-PD deficiency and malarial prevalence in populations affected by favism) appears questionable.

Haemolysis and protection against malaria

It is unlikely that a protective action of G-6-PD deficiency against malaria could take place in association with the typical severe episode of haemolytic favism usually occurring in male children during the first decade of life.

Before the introduction of transfusional therapy, in populations afflicted by malarial endemicity a mortality of about 15% was recorded in these cases. We have seen many such episodes in populations free from malaria, and on the grounds of clinical common sense we think that, in the absence of therapy, the association with such a severe disease as malaria should logically reduce the survival rate.

Haemolytic episodes, usually moderate, are often seen in female carriers. These episodes, frequently not recognised, are associated with the destruction of a portion of the G-6-PD-deficient erythrocytes, and usually do not need therapy. Luzzatto *et al.* (1969), however, observed that in heterozygous females, the parasite rate is much higher in normal erythrocytes than in G-6-PD deficient ones. Therefore, it is unlikely that in a heterozygous female affected by malaria the destruction of the less parasitised red cells could represent an advantage.

More generally, if haemolysis protected against malaria, one would expect selection in favour of G-6-PD variants associated with constant and continuous haemolysis, independent of environmental factors. In fact, the variants associated with malaria are not of this kind. On the contrary, the haemolysis is occasional, inconstant, dependent on environmental factors, and occurs only during short seasonal periods.

It seems unlikely, therefore, that haemolysis by itself

could represent an advantage in a malarial environment. It is more reasonable to assume that the negative effects associated with haemolysis represent the price that must be paid for some strong, positive effect of G-6-PD deficiency that is still largely unknown in its mechanism.

Interaction of G-6-PD deficiency with genetic and environmental factors

Siniscalco *et al.* (1961) showed that the presence of the thalassaemia trait makes G-6-PD-deficient individuals less liable to acute haemolysis from *Vicia Faba*. In 1971, we described an association between favism and the phenotype of erythrocyte acid phosphatase in G-6-PD-deficient males in Rome and Sardinia (Bottini *et al.*, 1971).

More recently, we confirmed this association in the area of the Po Delta. The data suggested that the susceptibility of G-6-PD-deficient subjects to haemolysis is highest in the carriers of P^a and P^c alleles of acid phosphatase. Moreover, we also observed that the presence of the thalassaemia trait in Sardinian G-6-PD-deficient males with a positive history of favism is negatively associated with the P^a allele. This indicates that the protective action of the thalassaemia trait towards haemolytic favism takes place mainly (or only) in subjects carrying the P^a allele. A survey of 14 villages located in the central area of Sardinia has shown that the frequency of the P^c allele is positively correlated with the altitude and with G-6-PD deficiency (Palmarino *et al.*, 1975).

A correlation between G-6-PD deficiency and adenosine deaminase gene frequencies has also been described by our group in Sardinia (Lucarelli *et al.*, 1971).

The heterogeneity of β -thalassaemia is well known. Recently, a high prevalence (0.95) of the β^o variant in the area of the Po Delta has been shown (Conconi *et al.*, 1976). In this type, the synthesis of β -globin is completely lacking. Since G-6-PD deficiency interacts with thalassaemia, differences in the prevalence of various β -alleles between Sardinia and the Po Delta may have contributed to the present striking differences in the frequency of G-6-PD deficiency between the two areas.

In conclusion, the data suggest a complex interaction between G-6-PD deficiency and various genetic

and environmental factors. Therefore, the selective values of G-6-PD genotypes seem to be dependent on several genetic and ecological variables. This could explain the lack of a simple linear relation between malarial endemicity and the prevalence of G-6-PD deficiency recorded both in the Mediterranean area and in other parts of the world. Further analysis of these interactions of G-6-PD deficiency, carried out at biochemical, clinical, and population levels, may help to clarify the mechanisms by which G-6-PD deficiency has been selected positively in malarial environments.

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N.B. Professors Huhey and Martin comment on this paper on page 407 of this issue.