apparently *de novo* translocation, and certainly amniocentesis could be offered to such parents to monitor any future pregnancy.

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This letter was shown to Dr Hon Fong Mark who writes: 'I am grateful to Dr Wilroy *et al.* for their comments and am in complete agreement with their views.'

On the relation between malaria and G-6-PD deficiency: a reply

SIR,

We appreciate the opportunity to respond to the communication of Bottini *et al.* (p. 363 of this issue), especially as we feel that the apparent differences between these authors and ourselves are semantic to some extent. We hope here to clarify our views on the relation between G-6-PD deficiency and malaria.

Bottini *et al.* go to some pains to document the fact that G-6-PD-deficient haemolytic crises in hemizygous males were extremely serious events before modern medical treatment, and that the added stress of malaria could hardly have made the condition selectively advantageous. We agree. In our previous communication (Huheey and Martin, 1975) we drew an analogy between G-6-PD deficiency and sickle cell disease, with respect to resistance to malaria. Though all analogies may be pushed too far, we believe that ours is a useful one in understanding the selective forces at work on what, at first glance, may appear to be a strictly deleterious gene. To look for positive selection for the gene for G-6-PD deficiency in

hemizygous males undergoing haemolytic crises is as hopeless as looking for positive selection for the haemoglobin S gene in homozygous subjects undergoing the crises of sickle cell anaemia. Rather, those people who will receive the most positive selection will be those in whom the manifestations of the disease are minimal and, perhaps, clinically undetectable. Clearly, we never intended that the haemolytic crisis *per se* was a positive, selective factor. Indeed, we pointed out in our previous communication (Huheey and Martin, 1975) that the interaction between favism, in the broad sense of the word (taken to mean a set of genes necessary for the disease), and G-6-PD deficiency could operate in the exoerythrocytic stages of the life cycle, such as in the recurrent infection of the parenchyma cells of the liver by *Plasmodium vivax*.

The balanced polymorphism of haemoglobin A/haemoglobin S is maintained by strong, positive selection for heterozygotes having erythrocytes that do not sickle under normal conditions, but which apparently cannot support an infection of *Plasmodium*. Similarly, one should look for positive selection for the gene for G-6-PD deficiency among heterozygous subjects, which in the case of this sex-linked trait must be females. Indeed, Bottini *et al.* cite precisely this type of evidence. Luzzato *et al.* (1969) found that in the erythrocyte mosaicism that occurs in heterozygous females, the parasite rate was from 2 to 80 times higher in normal cells than in the deficient erythrocytes. This is precisely the kind of protective effect predicted by the G-6-PD hypothesis.

Finally, we cannot disagree with the statement of Bottini *et al.* to the effect that natural selection involves the interaction of the entire environment upon the total genome of the individual. In this regard, we think that the study of the mutual interaction of the genes responsible for sickle cell disease and other traits thought to be related to malaria, such as G-6-PD deficiency, β -thalassaemia, haemoglobins C, E, etc., will prove especially fruitful in the future.

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