of enzyme deficiency or sickling must be borne in mind. Allergic reactions and haemolytic symptoms have been reported in G-6-PD-deficient subjects after administration of a number of drugs, and even salicylates have been incriminated.¹ The physician who is not on the lookout for this eventuality may consider it a complication of the original condition for which he was consulted. As probably more than 10% of these people are G-6-PD-deficient or show sickling, estimation of the enzyme and haemoglobin studies will need to become a routine investigation in any clinical laboratory.

G-6-PD is the initiating enzyme of glucose metabolism via the pentose phosphate pathway, the activity of which runs in parallel with the rate of pentose sugar production and consequently with that of nucleic acid and protein formation.² The availability of G-6-PD will thus influence the potential of the body's response to certain physiological and pathological demands.

In a recent retrospective study,³ an altered pattern of physio-pathological processes in enzyme-deficient subjects was apparent. There appeared to be a lower mortality from carcinoma, for instance, particularly in the male, which is in accordance with the mode of genetic transmission of this deficiency. This finding was interpreted with caution, however, as many other factors are operative, including environmental ones, even in a closed community. Because of this, I initiated prospective studies among these groups⁴ and these studies have revealed that females homozygous for G-6-PD deficiency seem to have some difficulty in carrying a pregnancy to term, and achieved this only after a number of miscarriages, their G-6-PD level rising after each one. Once a full-term pregnancy was achieved, subsequent pregnancies followed a normal course.

From all the foregoing it appears that while deficiency of this enzyme has definite disadvantages it may also provide some benefits. It has been suggested that G-6-PD deficiency and Hb S confer protection from malaria.⁵ In the Congo, where malaria is hyperendemic, frequencies of 20% or higher of enzyme deficiency and Hb S have been recorded,¹ but both traits are not necessarily co-existent in the same individual. In the recent study⁴ I directed in Asia with the co-operation of the medical services in each region surveyed a frequency of about 25% of G-6-PD deficiency was found in populations in two areas hyperendemic for malaria—the Caspian littoral and an area of Kurdistan—but, contrary to the findings in Africa, the frequency of sickling was only 1% in the former and none was demonstrated in the latter. This seems to suggest that the relation of Hb S to malaria may be an ethnic characteristic augmented by natural selection, while G-6-PD deficiency is an induced mutation secondary to environmental demand and reinforced by natural selection. This observation is further substantiated by a field study⁴ in the city of Yazd on the western fringe of the great salt desert in Iran. In this high, dry, malaria-free region the indigenous Farsi Zoroastrian population show a frequency of less than 1% G-6-PD deficiency. By contrast, the descendants of this same ethnic group who fled the region at the time of the Muslim conquest about a millennium ago and settled on the west coast of India—until recently hyperendemic for malaria—now

show a frequency of 17% G-6-PD deficiency.

If the maintenance of these mutations is consequent to the exigencies of environmental demand, then the gradual eradication of malaria should see a progressive diminution of their frequency over the generations.—I am, etc.,

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Haemolysis in Typhoid Fever

SIR,—I was most interested to read the article by Drs. C. Hersko and P. A. Vardy on "Haemolysis in Typhoid Fever in Children with G-6-PD Deficiency" (28 January, p. 214). It recalls to my mind a case of typhoid fever in a South African Bantu male child, aged 6½ years, who was admitted to Baragwanath Hospital in March 1953.

There was a three-day history of abdominal pain, headache, and fever. A practitioner had prescribed sulphanilamide 48 hours previously, and a total of six tablets (3.0 g.) had been taken. On the day of admission the passage of dark red-brown urine had been observed.

Blood culture grew *Salmonella typhi*. Urine-tests confirmed the presence of haemoglobinuria, which persisted for five days. Haemoglobin was 12 g.% on admission, which fell to 7.0 g.% three days later. Coombs test was negative. Maximum serum bilirubin level was 3.1 mg./100 ml. (seventh day).

Treatment consisted of chloramphenicol 250 mg. every four hours for 10 days, A.C.T.H. 15 units every six hours for three days, and blood transfusions on the third and fourth hospital days. There was a complete recovery. A test dose of 0.5 g. of sulphanilamide was given to the patient three months later without any untoward effect.

In 1962 this patient was recalled and a sample of blood was found to be G-6-PD-deficient by the screening method of Motulsky and Campbell-Kraut.¹ Therefore it would appear that both the typhoid fever and possibly the sulphonamide contributed to the acute haemolytic crisis in this G-6-PD-deficient individual. The chloramphenicol which was started on the first hospital day is unlikely to have provoked any haemolysis. The reason for this contention is that the G-6-PD enzyme deficiency in South African Bantu subjects resembles the type found in American Negroes rather than that in Caucasians. Chloramphenicol can produce haemolysis in enzyme-deficient Caucasians but not in affected Negroes.^{2,3}—I am, etc.,

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SIR,—With reference to the paper of Dr. C. Hersko and Dr. P. A. Vardy (28 January, p. 214), "Haemolysis in Typhoid Fever in Children with G-6-PD Deficiency," we would like to give our opinion on this phenomenon.

During the last 10 years we have observed about 300 cases of typhoid fever. However, a haemolytic crisis occurred in one case only (a boy 10 years old), in spite of the relatively high frequency of G-6-PD deficiency in this area.

We think that the haemolytic crisis was due to the chloramphenicol therapy and not to the infection per se, for the following reasons.

Haemolysis occurred at the eleventh day of the disease, 48 hours after chloramphenicol was administered.

Twenty days after clinical recovery a relapse did not cause haemolysis.

Five years before the patient showed haemolytic crisis during the course of gastroenteritis after the administration of chloramphenicol.—We are, etc.,

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Intrauterine Transfusion

SIR,—Your leading article on intrauterine transfusion (11 March, p. 583) cannot be allowed to pass without comment.

Exchange transfusion is clearly established in the treatment of liveborn infants, but one is on much less secure ground in claiming that premature induction has had much effect on perinatal mortality. Some stillbirths have been prevented, but it must be taken into account that prematurity has serious implications for any newborn infant; also that 30% of intrauterine deaths from Rh isoimmunization have occurred before 32 weeks' gestation.

Liquor examination, although probably the best single criterion of severity, is not infallible. In 525 patients liquor examination at 34 to 36 weeks' gestation enabled a correct forecast of severity in 82% of cases but in only 74% of 136 patients tested at 31 to 33 weeks (unpublished observation). Failures occurred both from failure to forecast very severe disease, and also from the incorrect prediction of mild disease. The decreased reliability earlier in pregnancy was mainly due to overestimating severity, and probably applies increasingly the earlier the pregnancy. As the role of intrauterine transfusion is to prolong pregnancy to a stage of gestation where conventional methods of management can be expected to give good results, selection for this difficult and dangerous procedure must be made very early in pregnancy. Selection should be stringent, and even so it is difficult to be sure that otherwise any foetus "would certainly have died." Apparent good results have been reported when cases have been selected later in pregnancy, for not only is the procedure easier but many of the very bad cases will already have resulted in intrauterine death.

Theoretically intrauterine exchange transfusion would be superior to simple transfusion in foetuses already in heart failure but