Correspondence

Letters to the Editor should not exceed 500 words.

Oral Contraceptives

SIR,—At a time when the Dunlop Committee on Safety of Drugs has just reported on the contraceptive pill and has, albeit with reservations, put a "safe" level on it, I for one am feeling more and more uneasy about prescribing it. The excellent paper by Drs. E. R. Bickerstaff and J. MacDonald Holmes (25 March, p. 726) prompts me to report a case of my own.

The patient, a woman of 29, a married State-registered nurse with two children, was supplied with a popular brand of the "pill" in October 1966. She attended again in December 1966 complaining of headache, dizziness, and faintness after having taken only "a few of the pills." She wished to try another brand. She had had a similar attack three years previously when she had been given hormones to help her conceive. I should add here that both the previous prescriptions had been supplied by different doctors.

I had heard similar complaints from other patients during their first month on the "pill," none of which had come to anything, and in any case this patient had complained of "dizzy spells" in the past when not taking the "pill." I therefore prescribed another contraceptive pill, one with which I was more familiar and which has a lower oestrogen content than the first. I saw her one month later for evaluation. She had been well, and I therefore gave her a prescription to last six months.

Her husband attended surgery on 3 April 1967, one week after I had read the paper by Drs. Bickerstaff and Holmes, and mentioned that his wife had had further dizzy spells. I therefore obtained a full history from her which I now state in chronological order.

In May 1963 her doctor gave her hormone tablets (? nature) to help her conceive. After two weeks' treatment she fainted, was aphasic and completely blind for two days, and had a severe frontal headache. (Her mother has migraines and the patient herself has had occasional severe frontal headaches.) Haemoglobin was found to be very low, and she was given intramuscular injections of Imferon (iron dextran) and the hormone tablets were stopped. She was completely well after one week, and in fact began to improve immediately the tablets were stopped. She conceived three months later.

In October 1966 she was supplied with a course of contraceptive pills. On the tenth day she fainted three times, became dysarthric, and then completely aphasic. She had blurring of vision, numbness and loss of power in the right hand and arm, severe frontal headache, and sharp stabbing pain in the occipital region. She took two codeine tablets and went to bed. She had a little blurring of vision the next morning which passed off and then she was quite well. She had withdrawal bleeding on the eleventh day. Haemoglobin at this time unknown, but three months earlier it was 13.5 g./100 ml.

In December 1966 she was supplied with a different contraceptive pill by myself; this she had been taking for three months without any trouble. On Easter Sunday (26 March) she felt dizzy and faint; numbness and loss of power developed in her right hand and arm; she became dysarthric; and then aphasic. She had a severe frontal headache and sharp stabbing

occipital pain which occurred at about half-hourly intervals. She stopped the "pill" and was well by the next day.

This patient was obviously suffering from cerebral arterial insufficiency, and as far as I am concerned there seems little doubt that all the attacks were due to the administration of hormones. I have advised her never again to take the "pill."

At the time of writing I have not the advantage of having read the official report on the "pill" made by the Committee on Safety of Drugs (see 8 April, p. 68). I make my comments only on what I have gleaned from the Press. We are told that women on the "pill" are only running a risk equal to that of a pregnant woman (less risk if one includes the act of childbirth itself and the puerperium). Pregnancy is certainly a natural state of affairs—but one lasting, say, 20 years?

I do not know in what proportion iatrogenesis has increased with the increase in number and complexity of drugs now available to us. I do know that without such reports as that by Drs. Bickerstaff and MacDonald Holmes to guide us the proportion would be greater and we in the front line of medicine and our patients would be very poorly placed. One of my clinical teachers used to say (and I quote): "When I go to bed at night I ask myself, 'Have I done anybody any good today?', and then 'Have I done anybody any harm?', and if I have done neither I have not done too badly." His statement did not mean quite so much to me then as it does now. It goes without saying that a committee such as that headed by Sir Derrick Dunlop is absolutely essential, but often as in this case the committee finally leaves it up to the individual practitioner.

I shall continue to prescribe the "pill." All other things being equal, and in the light of the findings I do not believe I have the right to withhold it from my patients. I shall certainly take more care to whom I prescribe it.—I am, etc.,

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Post-transfusion Hepatitis

SIR,—Dr. A. J. Salisbury (25 March, p. 756) has drawn attention to the value of a plasma protein solution as a transfusion fluid which is free of the risk of transmitting hepatitis from donor to recipient. Until, and even when, this material is more generally available, greater use should be made of plasma substitutes, such as dextran or dextran 110, both of which are safe and effective plasma volume expanders when limited in total volume in cases of blood loss to not more than 1,000 ml. Besides being free of the risk of transmitting hepatitis, dextran solutions have the advantage that they are less expen-

sive than plasma protein solution, plasma, or whole blood, as well as being more readily available.

A recent experience suggests that not all cases of post-transfusion hepatitis are being reported to directors of Regional Transfusion Services. Following a recent report in this region of a patient who had developed hepatitis following a transfusion of plasma, it was found that plasma from the same batch had been given to four other patients of whom three had become jaundiced (which had not been reported). In one of these the doctor had considered the diagnosis, but had decided that the patient was "too mildly affected to be suffering a post-transfusion hepatitis." Because of the delay in the detection of this infected plasma many of the donors whose plasma was included in this pool have been bled again. The recipients of their blood are under follow-up observation to determine whether any will show evidence of hepatitis. It would clearly have been far more desirable to have detected the carrier donor(s) sooner than inadvertently to have exposed other recipients to the risk of acquiring hepatitis.

May I offer a reminder through your columns that whenever a patient is found to be suffering from hepatitis he should be asked whether he has received a transfusion of blood or blood products during the preceding six months, and that if this is so the possibility that his may be a case of post-transfusion hepatitis must be reported without delay to the director of the appropriate Regional Transfusion Service?—I am, etc.,

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Malaria, Glucose-6-phosphate Dehydrogenase Deficiency, and Hb S

SIR,—Attention has been drawn in your columns recently (25 February, p. 496, and 7 January, p. 49) to the incidence of malaria in Great Britain. It has been pointed out that in any patient presenting with unexplained fever who has recently returned from the tropics the differential diagnosis of malaria must be borne in mind.

Without minimizing the importance of this observation, I should like to draw attention to a related problem which, because of the numbers of people involved, may eventually prove to be of greater importance in this country. There are now in our midst people who previously lived for generations in areas that are endemic for malaria. These ethnic groups show a high frequency of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and/or of Hb S—both being genetic traits capable of presenting certain syndromes in themselves. As the immigrant population continues to rise, the problem imposed by these phenomena will require increasing attention. West Indians or Asians living in Britain are unlikely to consult their doctor on account of malaria, but in any condition for which they seek treatment the possibility

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