Not So Benign Sickle-cell Trait

SIR.—The occurrence of splenic infarcts in persons with the sickle-cell trait travelling in unpressurized aircraft is well known. Experimental evidence demonstrating sickling *in vivo* in carriers of the sickle-cell trait exposed to simulated altitudes of 7,000 to 8,000 ft. (2,133 to 2,438 metres) was provided by Levin *et al.*¹ Using similar techniques Basu and Woodruff² have now shown that sickling can also be induced in such persons by pyrexia, thus lending support to the clinical observations made by myself (October 19, p. 976) and others.

The vulnerability of the sickle-cell trait to high altitude and infection now seems established beyond doubt, and Dr. J. R. B. Williams's letter (November 23, p. 1342) indicates a further potential hazard—namely, under-water swimming. The long-held concept of the benignity of the sickle-cell trait is no longer tenable, and its detection in negroes and persons of Mediterranean origin exposed to such risks is of obvious importance, and may even be life-saving.—I am, etc.,

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REFERENCES

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- 2 Basu, A. K., and Woodruff, A. W., *Lancet*, 1963, **2**, 1088.

Spinal Cord Ischaemia

SIR.—Although there were many puzzling features in the fascinating case of spinal cord ischaemia presented at the clinicopathological conference at Stoke by Drs. E. C. Hutchinson and A. J. McCall (November 9, p. 1186), the final sensory level at D4 with the pathological observation of a "very thin" spinal artery at this level requires perhaps a little more emphasis. Zülch¹ has stressed repeatedly that D4 is a critical segment in spinal-cord ischaemia, lying as it does at the watershed between the areas supplied by the large root arteries topping up the anterior spinal artery at C6 and D9. Whenever there is a fall in systemic (aortic) blood-pressure, whether from Stokes-Adam seizures (as in one of Zülch's cases) or other causes, even in the absence of local vascular disease, the ischaemic lesion in the cord (if it is a single one) is most likely to be found at D4. The blood-pressure in Dr. Hutchinson's case fell from 210/100 to 100/60 in two days. This would presumably cause a halving of the blood flow along the root arteries but a much more severe decrease in the blood supply to the critical segment D4 in accordance with Schneider's¹ "last field" irrigation analogy. It does not, therefore, seem necessary to postulate embolism of a lumbar vessel. It is to be hoped that Dr. McCall will publish the histological findings in the cord in this case in detail as

such reports are scarce and vital to our understanding of the blood supply of the cord.—I am, etc.,

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- 2 Garcin, R., Zülch, K. J., Lazorthes, G., and Gruner, J., *Pathologie Vasculaire de la Moelle*, 1962, p. 102. Masson, Paris.

Antihistamines and the Ovum

SIR.—In his letter (November 16, p. 1268) Professor M. C. Shelesnyak discusses the lack of absorption of antihistamines by the uterus, and the absence of anti-nidation effect when these are given by the systemic route.

However, as he states, he has been dealing only with rats, monkeys, guinea-pigs, and rabbits. Absorption of antihistamines varies from species to species, with even selective absorption appearing in different members of the same species. Thus in rats the absorption is minimal, whereas in humans it may be maximal.

I feel, therefore, that one must reconsider the use of antihistamines and other related quaternary compounds in those cases of idiopathic infertility and in women about to start a family.—I am, etc.,

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Effect of Drugs on Cells in Vitro

SIR.—Increasing numbers of studies of the effects of drugs on cells *in vitro* are being published. In comparing these one is confronted by difficulties due to the different methods of expressing the concentrations of the agents used.

Drs. Dorothy M. Easty and J. A. H. Wylie (June 15, p. 1589) have used "g. per ml." We feel a preferable system would be to express the concentrations as a molarity. This allows drugs of differing molecular weight—for example, mustine hydrochloride (mol. wt. 192.53) and melphalan (mol. wt. 305.2)—to be compared on a molar basis. We suggest, therefore, that all workers express their concentrations in this way whenever possible.

Some of the drugs tested by Drs. Easty and Wylie on gliomata *in vitro* have been studied in our laboratory for their effect on the oxygen uptake of leukaemic cells using the Warburg apparatus. Mannitol busulphan used at concentrations ranging from 1 millimol (mM) to 100 mM had no effect on the oxygen uptake of chronic granulocytic leukaemia cells, whilst the above workers report a cytotoxic effect on gliomata at concentrations ranging from 2.5×10^{-5} to 2.5×10^{-3} g./ml. (0.074 to 7.4 mM). Melphalan used at 10 mM concentration produced marked inhibition of the oxygen uptake of chronic lymphatic leukaemia cells, but at 1 mM concentration there was inhibition in some cases but not in others. This compares with the cyto-

toxic effect on glioma cells *in vitro* at concentrations ranging from 2.5×10^{-6} to 2.5×10^{-4} g./ml. (0.0082 to 0.82 mM).

Chlorambucil at 1 mM concentration inhibited the oxygen uptake of chronic lymphocytic leukaemia cells in six of eight cases studied. However, at 0.1 mM concentration the cells were resistant in all cases. This also compares with the cytotoxic effect of this drug on glioma cells at concentrations ranging from 2.5×10^{-6} to 2.5×10^{-4} g./ml. (0.0086 to 0.86 mM).

Methotrexate at 1 mM concentration has previously been found to inhibit the oxygen uptake of some, but not all, human and mouse leukaemia cells.¹ Drs. Easty and Wylie found this drug to be uniformly lacking in cytotoxic effect at concentrations greater than 25×10^{-6} g./ml. (>0.55 mM) in their system.—We are, etc.,

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REFERENCE

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Psychiatry and the Law

SIR.—A healthy well-fed man who steals a loaf of bread is responsible for his theft. His hypothetical twin brother deprived of food for a fortnight would not generally be considered "responsible" for a similar act. Between the two extremes we could picture a range of bread thieves—slightly hungry, hungry, very hungry, nearly starving—the responsibility of each diminishing with the blood-sugar level.

But Dr. H. M. Holden (November 9, p. 1201) may be correct to say that the concept of diminishing responsibility has no meaning other than a moral one, and Baroness Wootton (July 27, p. 197) is right in suggesting that "the doctor (along with everybody else except the Almighty) is not well cast as an authority upon responsibility."

I suggest that to help our re-thinking of this complex problem we need a clumsy neologism—the concept of "detrability." Humane considerations would preclude experiment, but it is reassuring to rational thought that here is something which, hypothetically at least, could be measured, albeit crudely. Our fairly hungry bread thief would desist when threatened by a ten-shilling fine. The very hungry one would need a deterrent of perhaps six months' imprisonment, while the starving man who had to steal to save his life would not be deterred by the threat of the most severe of punishments. Deterrability is closely allied to our general idea of responsibility.

When faced by a psychiatrically ill offender, the judge, the jury, and psychiatrists should have in their own minds, in addition to the McNaughton Rules, this question: "Is the nature of the