Not So Benign Sick-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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- 1 Levin, W. C., Baird, W. D., Perry, J. E., and Zung, W. W. K., *J. Lab. clin. Med.*, 1957, **50**, 926.
- 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.,

A. L. WOOLF.

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REFERENCES

- 1 Zülch, K. J., *Dtsch. Z. Nervenheilk.*, 1954, **172**, 81.
- 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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B. E. FINCH.

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

- 1 Woodliff, H. J., *Blood and Bone Marrow Cell Cultures*, 1962, Ph.D. thesis, Cambridge.

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

psychiatric disability such that the offence would have been committed even if the offender had become aware that he was certain to be caught and punished?"

It is doubtful whether psychiatrists would show any greater measure of agreement among themselves by their answers in individual cases than they do now, but there would be the satisfaction of knowing that the source of the difficulty lay in the complexities of psychiatric illness and not in the dubious nature of the fundamental concept.—I am, etc.,

JAMES WARNER.

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Single-handed G.P.s

SIR,—Most general practitioners like myself must have been gratified and heartened to read the account of Dr. Davies's timely report to Council on the action of the G.M.S. Committee regarding G.P. remuneration (*Supplement*, November 16, p. 162).

As the pleas for increased rewards and incentives gather momentum, however, I do hope that our negotiators will take note of the position of the single-handed G.P. He is, of consequence, far more tied to his practice and therefore has less free time, works longer hours, and finds greater difficulty in arranging and getting holidays because of shortage of locums and expense in providing them. The financial load of providing secretarial or ancillary help must be far greater for the single-handed.

The group practitioner, on the other hand, has much more free time to devote to himself, his family, or to hospital, industrial, or other appointments, etc., and must find holidays longer, easier, and more certain. But, more important than this, especially when there is so much talk of the good doctor who provides a better service for his patients, is the fact that ancillary help in the form of nurse, receptionist, or secretary is much more readily available to group practitioners, as the cost of these per doctor must be one-third to one-sixth that prevailing on the single-handed doctor. Let us not forget that the very fact that he is single-handed makes even more important his need for ancillary help and appointment systems.

Consequently, when devising new distribution schemes and considering possible capital provision for premises, etc., I do hope that the interests of single-handed G.P.s will be borne in mind by our negotiators.—I am, etc.,

Mitcham, Surrey.

TREVOR SILVER.

The Title of "Dr."

SIR,—The correspondence about the title "Doctor" is always of interest as it recurs from time to time.

The degree of Doctor of Medicine is, in the British Commonwealth, the highest degree granted by our universities in the Faculty of Medicine. It is obtainable only after the presentation of original work which has been deemed to constitute an advance in medical science. It is

not lightly bestowed and is entirely different from the qualifying licences and diplomas in status. It would be ridiculous to permit everyone on the *Medical Register* to use the letters "M.D." or any other letters suggesting academic standing to which he or she is not entitled. The doctorates in other faculties are, one must assume, rather jealously protected.—I am, etc.,

"M.D., M.Ch."

Cancer and Date of Birth

SIR,—Attention has recently been drawn¹ to an observation made on lung cancer patients in Holland. In studying the distribution of 330 cases by year and month of birth, Dijkstra² has found variations which he considers significant; in particular, he notes an excess of cases born in February and March. From this observation he deduces an enhanced susceptibility to lung cancer in persons born in late winter, and he suggests that this may be due to an irreversible metaplasia of the lungs caused by a lack of vitamin A following birth, both human and cow's milk being deficient in this vitamin in late winter.

If generally applicable to lung cancer, Dijkstra's observation regarding month of birth would clearly be of great interest. However, his sample is small, and the first essential is to repeat his survey on a larger scale.

A study is in progress which, when complete, will provide information on the dates of birth of approximately 4,000 men and 800 women dying with certified primary carcinomas of the lung in southern England during the period 1959–61. This sample will comprise roughly one-twentieth of all certified lung cancer deaths in England and Wales during these years. The analysis is at present complete in respect of the months of birth of 2,042 men dying in 1959 and 1960, and the results are shown in the Table below, with Dijkstra's figures for comparison.

Distribution by Month of Birth of 330 Lung Cancer Cases in Holland (Dijkstra's Series), and of 2,042 Men Dying of Lung Cancer in Southern England in 1959 and 1960

Month of birth	Dijkstra's series	Male deaths in Southern England
January	23	170
February	36	169
March	50	173
April	29	173
May	19	162
June	22	158
July	21	158
August	20	189
September	26	185
October	28	165
November	29	172
December	27	168
All Months	330	2,042

The results from this comparatively large sample do not support Dijkstra's observation, no significant variation between months being revealed.

We must conclude that there is at present no evidence that lung cancer in this country is in any way related to month of birth. Speculations regarding the role of vitamin-A deficiency in the newborn as a cause of lung cancer, or

of dried milk as a prophylactic,¹ appear premature in the absence of such evidence.—I am, etc.,

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- ² Dijkstra, B. K. S., *J. nat. Cancer Inst.*, 1963, 31, 511.

Tetanus Prophylaxis

SIR,—Dr. Colleen A. Cox, Professor J. Knowelden, and Mr. W. J. W. Sharrard (November 30, p. 1360) are to be congratulated on three counts. They have, firstly, conducted excellent surveys on tetanus cases and reactions to tetanus antitoxin. Secondly, their paper is lucid, controversial, and contains helpful tables. And thirdly, they have had the courage to abandon antitoxin in the prophylaxis of tetanus. I believe that this policy may well be justifiable in an industrial city like Sheffield: well-equipped and well-organized accident departments can rapidly cope with accident cases from modern factories with industrial medical officers and experienced first-aid staff. Speed and efficiency ensure that an injured person can be examined, given antibiotics (when indicated), and operated on in the shortest possible time.

How very different is the plight of the casualty officer in a small country hospital when confronted by a farmer who, four days previously, ran a fork into his foot and arrives with manure still in his penetrating wound. It would take great courage to withhold tetanus antitoxin in such a case.

Time will tell whether the Sheffield experiment can succeed; I hope it will, because every effort should be made to cut out antitoxin when antibiotics plus swift, efficient surgery will suffice to prevent tetanus. But I believe that circumstances do and will continue to occur where it is essential to give antitoxin (with all due precautions) in an attempt to offset tetanus. It is acknowledged that tetanus can occur (and kill) despite prophylactic antitoxin, but how many times has antitoxin saved a life?

Active immunization of more and more of the community is obviously the answer. It is interesting that in Sheffield the casualty department, recognizing its responsibility to complete active immunization after an injured person has been discharged, recalls its patients with reminders. It would be more interesting to learn how successfully this scheme operates. Some patients might prefer to have their own doctors complete the course. Some local authority clinics are anxious to help in this work. The chief worry about such divided responsibility would be ensuring that all three sets of records (hospital, general practitioner, and clinic) are completed and notified to each other. In any discussion on tetanus prophylaxis one always comes back to one of the keys to the whole problem—records, personal and other.—I am, etc.,

Beckenham, Kent.

D. A. CANNON.