Natural Hepatotoxins

SIR,—The juxtaposition of your recent leading article (15 May, p. 1261) on natural hepatotoxins with that on communication difficulties inherent in the increasing proliferation of specialist journals ("Too Many Words," p. 1264) was timely. For the question, "Are these toxins in any part responsible for the chronic liver disease which is so widespread in the tropics?" will only be answered by teamwork on the part of mycologists, biochemists, epidemiologists, and others.

Considering that fungal hepatotoxins have been discussed intermittently in medical journals for several years, I am surprised to find no communication preceding my own¹ reporting the finding of such toxins in grains offered for human consumption in an area where cirrhosis and primary liver cancer are endemic; for, as Forgacs² has pointed out, the incriminated fungi can be found in any grain stored without proper drying.

Now that we have in aflatoxin an "index fungal toxin" fairly readily identifiable by routine biochemical procedures, should it not be possible to screen the grain staples in endemic regions? Bio-assay might then be applied to suspect batches.

The pyrrolizidine-containing herbs present, admittedly, a rather different problem, calling perhaps for the skills of a botanically trained anthropologist—or an anthropologically minded botanist. None the less, defective grain-storage practices in developing countries (which might be greatly improved if enough favourable publicity were given to simple techniques already worked out for the smallholder) invite comparisons with the Broad Street pump-handle; and an interested layman³ has drawn attention to the "Gross National Waste" as an insufficiently considered factor in the malnutrition which afflicts so many developing countries. Is not the possibility of killing two evil birds with one stone worthy of the attention of all those who make the health of the developing world their concern? If those doctors who have seen, as I have seen, what a grievous burden chronic liver disease is in so many countries can bring pressure to bear on the appropriate international and national agencies for a "cross-discipline" study, not only might the problem of fungal hepatotoxins be elucidated but the principal of serendipity might pay unexpected dividends.—I am, etc.,

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A. COADY.

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Serum Creatine Kinase and Exercise

SIR,—May I comment briefly on one or two points arising from the paper of Drs. A. Vejajiva and G. M. Teasdale (26 June, p. 1653) and the subsequent correspondence (Drs. J. M. S. Pearce and P. D. Griffiths, 17 July, p. 167).

As Dr. Pearce points out several of Drs. Vejajiva and Teasdale's subjects had pre-exercise serum-creatine-kinase activities outside the usually accepted normal range, but this surely does not invalidate their observa-

tions that some forms of exercise can induce a rise in serum-creatine-kinase activity. It would have been interesting, however, to know rather more about their pre-exercise state, that is, how long since their last rugby game or spell of rowing, and also what their "out of season" serum-creatine-kinase activities were. One further point regarding Dr. Pearce's letter, significantly raised serum-creatine-kinase levels do seem to be found occasionally in cases where other evidence points to a neurogenic lesion.¹

I am interested to hear of Dr. Griffiths's group of "enzyme-labile" subjects, as re-examination of my own data for adult males does suggest the possible existence of a separate group of normals with somewhat higher activity than the majority. In my own group the data for females did not exhibit this feature, which perhaps explains the rather greater difference between males and females which I reported at that time,² compared with subsequent reports.^{3,4}

Some clearly defined basal state in which to collect blood for serum-creatine-kinase determinations is obviously desirable, particularly when trying to detect Duchenne carriers, but in practice a satisfactory one may prove difficult to attain. Thus, although a period of rest would be a convenient way of achieving this end, according to the recent report by Stephens and Lewin⁵ differences between carriers and normals tend to diminish when the subject is rested. Normal activity may still be the best compromise, if the complications are remembered.—I am, etc.,

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Paroxysmal Nocturnal Dyspnoea

SIR,—With frusemide and ethacrynic acid the profession has acquired new powerful diuretic agents which have in common the properties of very rapid but short-lived activity; this can be calculated at around four hours after an oral dose. These properties can be put to advantage not only in the treatment of established pulmonary oedema but also in the prevention of paroxysmal nocturnal dyspnoea, as the following consecutive four cases show:

Case 1.—A woman aged 66 with long-standing hypertensive heart disease had been troubled for months by paroxysmal nocturnal dyspnoea, in spite of the usual measures and night sedation. She had uninterrupted sleep since put on frusemide 40 mg. in the evening.

Case 2.—A man aged 64, with long-standing ischaemic heart disease but with no frank congestive failure, reported at a follow-up visit in out-patients that for the past month he had regularly woken at about 2 a.m. by typical paroxysmal nocturnal dyspnoea. He did not respond to digitalis and thiazide diuretics given in the morning, but became free from symptoms after frusemide 40 mg. was given at 6 p.m., four hours before his usual time for retiring to bed.

Case 3.—A man aged 57, with long-standing hypertension, was admitted to hospital in February this year with a major anterior wall

infarct complicated by recurrent pericarditis of the Dressler type. He was eventually discharged at the beginning of May on digitalis and thiazide diuretics, but reported at follow-up in out-patients that he was being troubled by paroxysmal nocturnal dyspnoea. He lost this distressing symptom when given frusemide 40 mg. four hours before retiring to bed.

Case 4.—A woman aged 56, with long-standing severe essential hypertension and left ventricular failure, who showed a poor response to a variety of hypotensive drugs, complained two months ago that she was being regularly disturbed by paroxysmal nocturnal dyspnoea. Since given frusemide, 40 mg. four hours before retiring to bed, in addition to her previous treatment, she also lost this distressing symptom.

I thought that this experience was worth while relating to the profession through your columns.—I am, etc.,

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E. MONTUSCHI.

Urbanization and Coronary Disease

SIR,—In his *National Atlas of Disease Mortality in the United Kingdom* Howe¹ showed that the mortality rate from coronary heart disease was lower in rural areas compared with urban centres of population. This situation was also noted in a nation-wide survey in the United States.² In that country Berkson and co-workers³ have shown that mortality from all cardiovascular renal diseases is approximately twice as high in Chicago as it is in rural Illinois. In Norway⁴ it has been shown that six rural centres of population had mortality rates for arteriosclerotic and degenerative heart disease and for malignant tumours only a *third* of the corresponding rates obtaining in Oslo for the period 1952–61. Evidently the toll from coronary heart disease can be much lower in country districts compared with towns. Yet this important observation, which admittedly requires much further definition, is paid little or no attention to in current textbooks of medicine. It is not mentioned in contributions on "The Anti-Coronary Club,"⁵ nor is it touched upon in recent authoritative articles.^{6,7}

It may be maintained, of course, that it is too late for most people (especially for those who have already had episodes of coronary ischaemia) to make the somewhat drastic change indicated of uprooting and moving from town to country. This "too-lateness" has often been averred, despondently, in relation to the changing of other relevant parameters. It is interesting, therefore, to note that in regard to smoking a recent investigation has shown that the persons investigated who had given up smoking had an even lower mortality rate from coronary heart disease than those who had not smoked at all.⁸

In the numerous and highly expensive studies, retrospective and prospective, which are now being undertaken on the epidemiology of coronary heart disease, it is surely legitimate to insist that adequate attention be paid to the issue under discussion. We know, for example, of the careful comparisons now being made in relation to coronary heart disease of Irish people in Boston, and of their brothers, urban and rural, in Ireland.⁹ Surely it would be worth while to make additional comparisons, not only of ubiquitous migrants from country to town but of that moiety who, for one reason or another, have

undertaken the reverse migration.—I am, etc.,

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Jaundice in Severe Infections

SIR,—The recent article in the *B.M.J.*, "Jaundice in Severe Infections" by Dr. A. Eley and his colleagues (10 July, p. 75), prompts me to report a similar patient admitted to the medical wards of this hospital in March of this year.

A 44-year-old sub-postmaster, an ex-Royal Navy cook, was admitted with a history of attacks of diarrhoea and sickness for about two months, together with increased cough and purulent, brown sputum; there was also a history of fever with rigors and sweating for the week before admission.

He gave a history of dysentery in Singapore in 1958, but denied any previous respiratory symptoms apart from a "smoker's cough" for many years.

On examination the patient appeared very ill, slightly icteric, and breathless at rest: temperature 101.4° F. (38.5° C.), pulse 124/min., irregular with occasional drop beats, respirations 24/min. The sputum was purulent, copious, and very dark brown in colour, almost resembling anchovy sauce. The physical signs in the chest revealed extensive consolidation in the right lower zone, where there were coarse crepitations. The liver margin was just palpable and was tender.

Repeated microscopic and culture examinations of stool for *E. histolytica* were negative: haemoglobin 82%; total leucocyte count 14,750/c.mm., with 89% polymorphs, 8% lymphocytes, and 3% monocytes; E.S.R. (Westergren) 120 mm. in the first hour. Serum bilirubin 2.0 mg./100 ml., alkaline phosphatase 4 K.-A. units, thymol turbidity 5 units, total proteins 5.5 g., albumin 2.7 g., globulin 2.8 g. The urine showed a trace of albumin and contained bile salts and pigments. Blood culture and urine culture were sterile. Sputum cultures, though initially showing normal flora, were later shown to grow a coagulase-positive staphylococcus on one occasion and *Str. faecalis* on another. Radiograph of chest disclosed complete consolidation of the right lower lobe. All investigations for tuberculosis and malignancy were negative.

The patient was treated with a variety of antibiotics, including benzylpenicillin (Crystamycin), erythromycin, tetracycline, fusidic acid (Fucidin), ampicillin, and cloxacillin. His condition, clinically and radiologically, improved slowly and the liver-function tests eventually returned to normal.

Though it was initially thought, from the patient's past and present history of dysentery, enlarged liver, and very dark brown sputum, that he might have developed an amoebic abscess of liver which had ruptured into the lung, all the tests for amoebiasis were negative, and because of the extensive lung involvement it was decided to treat the patient as a case of lobar pneumonia.

The patient ultimately made a good recovery, but the original clinical condition with jaundice was misleading.

I am grateful to Dr. D. H. Smith for permission to report this case and for his helpful criticism.

—I am, etc.,

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M. K. TANDON.

Management of Cerebrovascular Disease

SIR,—I was a little surprised to note that Sir John McMichael in his review of my book (24 July, p. 217) should state that the average age of my patients on hypotensive therapy was 41 years, whilst for my controls it was 59 years, without also stating that the groups were standardized for age before comparison of their life expectancies was made.

I was also surprised that he should make use of the controls in the largest American series of transient ischaemic attacks treated with anticoagulants I tabulated, as these controls were selected in a manner which makes it highly likely that they carried a poorer prognosis than average, a fact I pointed out in my text. The two smaller series I tabulated were free from this defect and remain the best factual evidence we have to date about the place of anticoagulant therapy in transient ischaemic attacks. They show that anticoagulants reduce the frequency of transient ischaemic attacks but do not provide evidence that these drugs protect against a future cerebral infarction. I did not refer to the excellent work of Acheson and Hutchinson as my manuscript was with the printers before their paper appeared in October last year.

I was sorry Sir John could not find any references to transient strokes in association with disturbance of cardiac rhythm and myocardial infarction; they are on pages 121, 122, and 128.—I am, etc.,

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Provident Association Forms

SIR,—We regret that the motion moved by Dr. B. D. Morgan Williams at the A.R.M. at Swansea ["That this Meeting deprecates the threatened action of the B.U.P.A. to remove the general-practitioner sanction clause from their claim form"] was lost (*Supplement*, 17 July, p. 45).

The majority of consultants and the majority of subscribers to provident associations are honest people whose conduct is ethical, but there are, unfortunately, some who are always prepared to take advantage of anything in the nature of insurance, thereby defeating justice being done to the general body of subscribers.

If general practitioners require a reasonable fee for completing provident association certificates, subscribers able to pay for private specialist treatment wholly or partly through insurance should not resent their general practitioner asking a fee. The Western Provident Association and the Bristol Hospitals Fund are immensely grateful to general practitioners for much unpaid, unselfish, and valuable help in the conduct of their affairs.

We have always understood that the profession adheres to the principle that specialist advice and treatment should only be given on the advice of the patient's family doctor. There are, unfortunately, members of the profession willing to ignore this principle. We therefore regret the apparent desire of the B.U.P.A. to abandon the chief safeguard they, and all provident associations, have against abuse of their rules.

The certificate is, in our view, an essential safeguard if justice is to be done to the vast majority of honest subscribers. Without this safeguard it is impossible to prevent abuse of waiting periods for benefits. To pay claims to new subscribers on account of undisclosed adverse conditions existing at the date of application for membership is unjust to the general body of subscribers, apart from its financial dangers for the associations.

Provident associations are of immense value to consultants, because without them there would be very few private patients left. It would be a retrograde step in the provident movement for general practitioners' certificates to be abandoned.—I am, etc.,

JOHN DODD,

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and Nursing Home Services,
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Gut-secreted Calcium

SIR,—Many workers in the field of calcium metabolism must have been as puzzled as I was by the paper of Dr. G. A. Rose and his colleagues (13 March, p. 690). The authors compared net calcium absorbed, calculated by subtracting faecal from dietary calcium, $d-f$, with true amount absorbed, $a.d$, a being the fraction of orally administered ^{45}Ca absorbed, estimated by measuring faecal excretion of isotope. The correlation coefficient for the regression of $a.d$ on $d-f$ was so high (+0.95), as to suggest that net secreted calcium was virtually equal to total secreted calcium and was independent of absorption.

As this conclusion contradicts much other data—e.g., Heaney,¹ Nordin *et al.*²—the high correlation coefficient was worrying. I attempt to show here that the contradiction is due to the way in which the authors represented their results and that the latter are in reality compatible with those of most other authors.

Before proceeding I should note one further criticism. The authors ignored ^{45}Ca rescreted into the gut, assuming that the error so introduced would not be great enough to influence their conclusions. DeGrazia and Rich³ have shown that the underestimate introduced by this approximation is variable but seldom less than one-tenth of the value obtained by the unmodified isotope method. All the results for percentage absorption of Dr. Rose and his colleagues are therefore in error by an amount which is hardly negligible.

Two symbols are necessary to the discussion:

s = that fraction of the secreted calcium which is capable of reabsorption in the same proportion as dietary calcium, mg./day.

s' = that fraction of the secreted calcium which cannot be reabsorbed, mg./day.

The assumption I (and most workers, I think) make about the secreted calcium is that it is all represented by $s+s'$.