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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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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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