represented in the "for" and "against" replies. Perhaps the Medical Defence Union could give a public breakdown of these replies.

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SIR,—We all have recently become aware of the 70% increase in the standard subscription rates to the medical defence bodies, with the prospect of American sized premiums on the horizon. The societies point out that we are paying less for our cover than comparable professionals such as architects and solicitors, but for these groups the cover may be a practice expense.

This premium falls unfairly on the hospital doctor, who does not have this option, and to whom it is a substantial expense. The time has come for our employing authorities to take over the responsibility for paying the subscription, as they do for the non-medical staff they employ. In the past there has been resistance to this from doctors not wholly employed in the NHS, but for them the health authority could contribute a proportion of the premium depending on the number of sessions they are employed for.

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SIR,—The recent 70% increase in medical defence subscriptions announced by the Medical Defence Union and the Medical Protection Society may be no surprise to those who are aware of the outcome of recent medical malpractice cases but still comes as a shock to most junior hospital doctors. The considerable recent rise in the cost of insurance has effectively reduced our meagre salary increases by 20-30% and there is little reason to believe that this trend will not continue. The time has surely come for some more positive action.

Firstly, the NHS appoints its own doctors and must hold responsibility for its choices. Furthermore, junior hospital doctors are contractually obliged to work full time for the NHS but to obtain and pay for their own medical insurance. The British Medical Association and allied organisations should insist that the NHS should bear this cost, as it does for nurses and as hospitals do in the USA for their residents.

Secondly, legal malpractice suits take many years to be carried through so that, in a sense, today's doctors are having to pay for "the sins of their fathers." Certain groups of doctors, such as pathologists, rarely call on the services of the medical defence societies—nor did their predecessors. These organisations should be prepared to review their approach to such doctors. If they do not the continuing rise in defence society subscriptions will ensure the appearance of realistic competition.

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Vitamin B6 concentrations in patients with chronic liver disease and hepatocellular carcinoma

SIR,—Dr S N Zaman and colleagues (19 July, p 175) measured serum pyridoxal and pyridoxal-5'-phosphate, the two main forms of vitamin B6 in the circulation. In their controls the proportion of the pyridoxal-5'-phosphate varied from 50 to 100% of

the two vitamers while in patients with cirrhosis the proportion of serum pyridoxal-5'-phosphate was significantly lower.

We also examined ratios of pyridoxal-5'-phosphate to pyridoxal in serum from 14 women, none of whom were receiving vitamin B6 supplements but who showed a wide range of serum pyridoxal-5'-phosphate concentrations when measured enzymatically.¹ We were interested to see whether those sera with low pyridoxal-5'-phosphate concentrations had increased amounts of pyridoxal, a metabolite of vitamin B6 which is not detected by enzymatic measurements. The pyridoxine vitamers were separated by thin layer chromatography and measured fluorometrically but we could not determine any difference in the proportion of pyridoxal between those with high and low pyridoxal-5'-phosphate concentrations, and in all but two of the women the ratio was >1.5 with an overall median of 4.0.²

However, the importance of our observations and those of Dr Zaman and colleagues is questionable, for published reports disagree over the normal relative amounts of pyridoxal-5'-phosphate and pyridoxal in blood. In agreement with our own studies² and those of American workers who report a fourfold to fivefold excess of pyridoxal-5'-phosphate in control subjects,^{3,4} Dr Zaman and his colleagues report that pyridoxal-5'-phosphate is more abundant in the serum. Others, however, have reported pyridoxal to be in a threefold to fourfold excess over pyridoxal-5'-phosphate⁵⁻⁷ or in roughly equal amounts to pyridoxal-5'-phosphate.⁸

There are differences between the methods used by the different workers, but the explanation for the different ratios is not immediately apparent. In all cases fluorometric methods were used, and opposite results for the proportion of pyridoxal-5'-phosphate in controls were obtained by Dr Zaman and colleagues from those of Smith *et al.*,⁶ whose method they used.

These differing values for the pyridoxal-5'-phosphate ratio probably reflect the rapid turnover of pyridoxal-5'-phosphate in human plasma. Pyridoxal-5'-phosphate is bound to albumin and does not easily cross the cell wall, in contrast to pyridoxal. Pyridoxal-5'-phosphate is hydrolysed to pyridoxal by alkaline phosphatase, and it has been suggested that pyridoxal is the transport form of vitamin B6 available to the tissues.⁹ Plasma pyridoxal-5'-phosphate is rapidly influenced by the dietary intake of pyridoxine,⁵ and the ratio of the two may reflect not only dietary supply and demand for vitamin B6 within the tissues but also the proximity of the last meal. Dr Zaman and colleagues, in common with most others, do not give this information but it is unlikely to be the complete explanation; high ratios have been observed in both fasting³ and non-fasting² subjects.

An additional factor that may have influenced the ratios in the cirrhotic patients of Dr Zaman and colleagues is therapy. Some drugs may interfere with the fluorometric assay, while others, such as penicillamine and isoniazid, may affect vitamin B6 metabolism. Penicillamine was possibly used by the authors to treat the cirrhotic patient with Wilson's disease and this drug has also been used to treat chronic active hepatitis and primary biliary cirrhosis. Penicillamine is known to bind both with pyridoxal and particularly strongly with pyridoxal-5'-phosphate.¹⁰

The only conclusion which can be drawn from these results is that the factors responsible for controlling the pyridoxal-5'-phosphate:pyridoxal ratio in plasma are not fully understood and the widely different ratios reported clearly indicate the importance of measuring both vitamers in assessing pyridoxine status.

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Ethics of predictive testing for Huntington's chorea

SIR,—The article by Doctors D I O Craufurd and R Harris (26 July, p 249) struck a familiar note, in particular the references to the shortcomings and responsibilities of predictive testing.

As one who has been concerned in identification of the fragile X syndrome in Ireland I found that, although the hunt for affected individuals is of considerable interest, in many cases it leads to more problems than it answers. Of these probably the greatest is what to do when a combination of family pedigree and chromosomal studies suggests that the abnormality is segregating in a family. Ultimately the advice that can be offered to the family must be guarded because of the as yet limited amount of information available on the prevalence of the fragile X and on its effects on those individuals in whom it is found. While it is possible to outline to a female carrier of the chromosome the likelihood of her producing male offspring with the fragile X it is not possible to say with any certainty what the status of these offspring will be—whether they will be severely mentally handicapped, for example, or, as has been sometimes found, of normal measured intelligence.^{1,2} Equally, given that some female carriers appear to be affected by the existence of the abnormality,^{3,4} it is not possible to say that female offspring will be of normal intelligence.

This situation arises because, as with the case of the marker for Huntington's chorea, it is not known exactly what is the strength of association between the presence of a fragile X chromosome in an individual and the existence of mental handicap.

However, and this is the real dilemma, the information on this subject will not be forthcoming without adequate population studies. As an explanation must be given to the subjects of these studies, the risk exists of provoking needless anxiety, especially in those families where cases are discovered.

It would be possible, of course, to perform a study on the understanding that the information would be made available to the participants only if it appeared to be of relevance—that is, in families where isolation of the defect appeared to be associated strongly with the genotypal abnormalities. This would, however, place an unreasonable burden on the researchers. It has been my own experience that, even with adequate briefing on the background for the study, families still express concern and ask for advice which will be incomplete.

It seems that the only really satisfactory solution is to offer chromosomal studies to members of those families where there appears to be a familial

pattern of mental handicap, with an explanation about the as yet limited predictive value of these.

The problems with predictive testing are a further example of the ethical difficulties which beset research workers. It is becoming increasingly obvious that the division between clinical and research work is not clear and that the guidelines for the research worker's responsibility to his clients need better definition.

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Use of molar units for drugs and toxins?

SIR,—Professor D N Baron's leading article (5 July, p 2) calling for the use of trendy molar units for drugs and toxins echoes similar previous demands by clinical biochemists.¹⁻³ Such a change would have implications reaching far beyond the narrow service involvement of clinical biochemists in therapeutic drug monitoring and emergency toxicology. It seems that little thought has been given to the much wider consequences or the adverse effects that the change would have on medical practice and the welfare of patients. Clinical chemists should recognise that many specialties other than their own are concerned with drugs and their clinical measurement, and the views of those who are responsible for the development, manufacture, marketing, prescription, administration, and investigation of drugs must be taken into account.

Apart from the inconvenience, confusion, and increased risk to patients which would result from the introduction of molar units for clinical drug measurement the clinical biochemists go further to propose seriously that drug doses should also be changed to molar units.^{1,4,5} This would indeed be a logical and necessary sequel if only to avoid the absurd situation which would arise if drug concentrations were measured in one system of units while drug doses were administered in another.^{6,7} A change to molar units for drugs and toxins would cause little inconvenience to clinical biochemists but it would have enormous repercussions on the medical and nursing professions, medical education, clinical pharmacology and toxicology, pharmacy, and the pharmaceutical industry. It would be very expensive and the confusion which would occur during and for long after the change-over is unimaginable. Such a drastic and painful move could be justified only by an overwhelming advantage of molar over mass units.

Attention has already been drawn to the hazards in clinical toxicology caused by the premature use of molar units by some laboratories,^{6,8} and the pros and cons of the two different systems of units have been debated at some length.^{1,3,6-11} Despite the superficially persuasive arguments put forward by clinical biochemists, it is obvious that there would be no practical clinical advantage if molar units were introduced for drugs and toxins. The outstanding disadvantage of molar units is that the molecular weight of the compound must be known to give any physical reality to the value in question. It would be impossible to cope in this way with the enormous range of drugs and toxins of differing molecular weight which are encountered in clinical practice.

Everyone agrees that standardisation of units for drug measurement is necessary, but it is presumptuous, if not arrogant, of clinical biochemists to attempt to force a change to molar units without wide consultation and the majority agreement of all those who are likely to be affected. It is proposed to prepare a definitive document reflecting the official position of clinical, industrial, and other specialty interests in this matter. In the mean time I hope that common sense will prevail and that clinical biochemists will appreciate the reasons for the resentment and depth of opposition to their proposals.

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Diabetic renal disease: differences between Asian and white patients

SIR,—D A Samanta and colleagues recorded a significantly higher prevalence of proteinuria in Asian (Indian) diabetics than in white diabetics, which they believed to be due to microvascular disease (9 August, p 367). We have reported a high prevalence (18%) of microvascular complications in 85 South African Indian patients with non-insulin dependent diabetes in the young.^{1,4}

The 18% prevalence of microvascular complications contrasts with the findings of most workers reporting on non-insulin dependent diabetes in young white patients, who have highlighted the rarity of vascular complications in their patients.^{4,8} However, Fajans has reported a similar frequency of microvascular complications in such patients.⁹ While most patients with microvascular complications in Fajans's series (16 of 17) had had diabetes for over 15 years, in accordance with the data of Dr Samanta and others, half of our South African Indian patients with microvascular complications had had diabetes for less than 10 years. Thus in addition to Indian diabetics having a much higher prevalence of microvascular complications than whites they also seem to have a shorter duration of diabetes.

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SIR,—Further details are required before the preliminary results of Dr A Samanta and his colleagues can be accepted.

Surely it is time for a more restricted definition of ethnic group than "Asian." They might perhaps have specified "of Gujarati origin" in their title. Although many of us have used the term "Asian" as a flag of convenience,¹ knowledge has progressed. Environmental factors affecting culturally diverse groups of British citizens originating from the Indian subcontinent cannot be assumed to be the same—let alone assuming that such groups share a similar gene pool.² Standardisation of terms is urgently needed.

As with all clinic studies, sampling biases may be large. The authors mention potential referral bias but what does "consecutive" mean for Asian and white attenders of at least one year? Was every attender from date A to date B included? What proportion of the total white attenders at the Leicester clinic do the 368 whites represent? Were they stratified by sex, accounting for the nearly even sex balance between Asians and whites?

By chance one clinic in 20 will find a "significant" ($p < 0.05$) excess (or deficit) in some variable—that may be " $p < 0.001$ " in that clinic. Confidence intervals should have been given. The 99% confidence interval ($2 \times 58 \times \text{SE}$) for the proportion of all Asians with proteinuria ($53/370 = 14\%$) is 9.4 to 18.6% and for all whites ($23/368$) 2.8 to 9.2%—for example, distributions that are only just apart. For the sexes separately 99% confidence intervals overlap with those for whites.

A further problem is that only 37.1% (135/370) of Asians were treated with insulin compared with 70.1% (258/368) of whites. This is high for a typical sample of whites of that age (mean (SD) 12). Is it possible that the proteinuria was partly due to toxicity from the oral agents—a spectre that has been raised before?³

The authors suggest that their data need confirmation from epidemiological work. We currently have a population sampling study underway among three ethnic groups (one being Gujarati) in Brent and Harrow. Unfortunately, the sample sizes and time required are too great to compare the incidence of diabetic proteinuria, which is what is needed. However, perhaps those of us with research interests in the diabetic problems of ethnic groups in the UK should discuss methods of standardising our data bases. Their combined size, properly managed, would allow pressing public health topics^{4,7} in this subject to be analysed adequately and developed for clinical trials and other preventive work.

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