Changing social-class distribution of heart disease

SIR,—Dr M G Marmot and others (21 October, p 1109) have reported that changes in "consumptions of sugar and, to a lesser extent, milk" may be related to changes in social-class mortality from heart disease (non-valvular and hypertensive)—not in prevalence, as the title of the article might suggest. Their food data from the National Food Survey Committee do not take into account possible social-class differences and changes in food consumption outside the home. Global epidemiological evidence on total consumptions indicates that milk is more likely than sugar to be aetiological implicated in ischaemic heart disease.¹

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¹ Segall, J. J., *British Journal of Preventive and Social Medicine*, 1977, **31**, 81-5.

SIR,—The paper by Dr M G Marmot and others (21 October, p 1109) shows correlations which might account for the continuing change in the social-class distribution of coronary heart disease mortality. The most striking increase is seen since 1951 in men aged 35-44 in classes IV and V. Unfortunately no information is given as regards country of origin or race of the population studied and a large number of classes IV and V in the younger age groups can be expected to be immigrants from overseas and Ireland. If this is so, other, to me more likely, explanations for the changes in the prevalence of coronary heart disease in the different classes are possible than dietary sugar, fibre, or cigarette smoking.

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Frusemide and renal enzyme excretion

SIR,—The pages of the *BMJ* have recently carried articles on the value of the estimation of urinary *N*-acetyl- β -glucosaminidase (NAG) activity in renal disease,¹ gentamicin nephrotoxicity,² and renal artery stenosis.³ We have carried out an investigation of the effect of the combination of cephaloridine and frusemide on renal function and found a hitherto unreported effect of frusemide on NAG excretion.

Six male volunteers (age 25-34) received single intravenous injections of 1.5 g cephaloridine with and without 80 mg oral frusemide in a controlled experiment. No abnormal values for indices of renal tolerance were found with cephaloridine alone, but abnormal values were found with frusemide alone. In particular, there was a marked outpouring of NAG in the first 4 h after dosing with frusemide, as shown in the table. A similar but less marked effect was found with cephaloridine plus frusemide.

There is a wealth of literature to indicate that frusemide is not nephrotoxic, and this finding of raised NAG excretion is presumably related to frusemide's normal action on the renal tubule. It is therefore likely that other drugs may raise enzyme excretion without causing damage. Indeed, Raab and Hohenegger found an increased urinary excretion of leucine aminopeptidase and lactate dehydrogenase in rats given large amounts of penicillin.⁴ They also found urinary excretion of these enzymes to be transiently raised in rats and in man after frusemide administration.⁵

One must therefore be wary of concluding that raised urinary enzyme levels indicate renal damage. Interpretations of "spot" urine samples for NAG estimation in hypertensive patients or in patients with renal disease must include consideration of drug therapy, in particular frusemide usage.

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¹ Wellwood, J M, *et al*, *British Medical Journal*, 1975, **3**, 408.

² Wellwood, J M, *et al*, *British Medical Journal*, 1975, **3**, 278.

³ Mansell, M A, *et al*, *British Medical Journal*, 1978, **1**, 415.

⁴ Raab, W, and Hohenegger, M, *Clinica Chimica Acta*, 1968, **20**, 95.

⁵ Hohenegger, M, and Raab, W, *Clinica Chimica Acta*, 1970, **28**, 61.

Adverse reactions to intravenous induction agents

SIR,—Dr H L Thornton (23 September, p 897) suggests that the role of Cremophor El should be investigated in adverse (anaphylactoid) reactions to the intravenous anaesthetic induction agent Althesin. This powerful detergent is used in other drug formulations, such as Epontol (oily injection of propanidid) and also (but not recommended by the manufacturers) for the solubilisation of diazepam. We agree with Dr Thornton's comments and have ourselves previously drawn attention to possible problems associated with Cremophor El.¹⁻³ It is, however, worth pointing out that Cremophor El is not a single well-defined compound but a mixture of some 50-60 compounds.

While in the dog Cremophor El alone causes direct histamine release,⁴ this does not occur in man and reactions to Cremophor-containing drug formulations may occur from the adjuvant effect of the detergent in presenting pharmacologically active drugs more directly to cells concerned with the reaction mechanisms.

Anaphylactoid response to a variety of intravenous compounds (anaesthetic drugs, muscle relaxants, and plasma expanders) may occur by one or more of several quite distinct mechanisms; these aspects were considered in detail at an international symposium held in Sheffield in June 1978.^{5,6} The factors predisposing to an anaphylactoid response are equally complex.^{5,6} Identification of the active

agent is extremely difficult except in that small minority of cases where only a single drug has been administered. There is at present no satisfactory single clinical or laboratory procedure for investigating these reactions and few of us working in the field would claim their absolute reliability. We would disagree most strongly with Dr R H Jago (7 October, p 1022) that skin testing proved *conclusively* that alphaxalone/alphadolone and not Cremophor El were involved in his case. There is no proved correlation between intradermal skin testing and systemic response and such tests can only be regarded as presumptive evidence for the involvement of a particular agent.

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¹ Watkins, J, *et al*, *British Journal of Anaesthesia*, 1976, **48**, 881.

² Padfield, A, and Watkins, J, *British Medical Journal*, 1977, **1**, 575.

³ Watkins, J, Allen, R, and Ward, A M, *Lancet*, 1978, **2**, 736.

⁴ Lorenz, W, *Agents and Actions*, 1975, **5**, 402.

⁵ Watkins, J, and Clarke, R S J, *British Journal of Anaesthesia*. In press.

⁶ *Adverse Response to Intravenous Drugs*, ed J Watkins and A M Ward. London and New York, Academic Press, 1978.

Deputising services

SIR,—Following our report on a one-in-five sample of nearly 500 000 patient contacts with 18 deputising services in 1974-5 (26 February 1977, p 560) our own university computing service carried out further analyses which uncovered a programming error made by the computer bureau which implemented, under contract, our specified computer system. Regrettably this error led, in our paper, to an exaggeration of the percentage of patients who waited long periods for a deputy visit. The relevant sentences should read:

"Of all patients seen alive by the deputies of the 18 services, 57% were seen within one hour of contacting the service (ranging from 45% at one service to 77% at another) and 1% [not 7% as originally suggested] apparently waited four hours or longer as calculated from the recorded time of receipt of the call by the service and the time of the deputy's arrival. . . Of patients diagnosed by the deputy, on arrival, as having acute myocardial infarction, less than 1% [not 5%] apparently waited more than four hours."

However, the more recent analyses also show that waiting times were considerably lengthened at holiday times, though it must be remembered that the service deals at such times with higher proportions of non-urgent calls than at other times. Thus in the afternoons (1300-1759) of five days in bank holiday periods 7% of calls received at all the centres apparently waited four hours or more and the percentage rose to 14 at one centre, which was then handling an hourly average of 20 visits as well as calls not requiring a visit. (All percentages are based on at least 100 records on the computer file.)

Waiting times were no doubt sometimes overestimated at busy periods, however. Congestion of radio space may have prevented the deputy from reporting back to the control centre after every visit and he may sometimes have forgotten to report his actual time of arrival, so that his time of reporting back to

Mean urinary NAG excretion (mIU/h) in six volunteers. Numbers of abnormal results (>120 mIU/h) in parentheses

Period after administration	No drug	Cephaloridine alone	Cephaloridine + frusemide	Frusemide alone
0-2 h	73 (0)	53 (0)	204 (5)	887 (6)
2-4 h	46 (0)	51 (0)	75 (0)	498 (6)

the control centre was recorded as the arrival time. Moreover, the centres using automatic time-stamps (the centre quoted above did not) were prevented from entering times retrospectively.

Despite these qualifications, the findings show that the resources of some deputising services, medical manpower or telecommunications or both, appeared to be stretched at bank holiday periods.

Generalisations about the quality of deputising services as a whole have in the past been misleading. It is to be hoped that the introduction of standard procedures for monitoring the operation of deputising services (DHSS Health Circular HC(FP)(78)1) will serve to diminish differences in quality among them.

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Alpha-fetoprotein in the diagnosis of hepatoma

SIR,—The ideal diagnostic test is perfectly sensitive (true-positive (TP) ratio=1) and perfectly specific (false-positive (FP) ratio=0). Dr P J Johnson and his colleagues (2 September, p 661) apparently approach the ideal in their report that a diagnostic serum α -fetoprotein (AFP) concentration of 10 IU/ml (10.5 ng/ml) has TP and FP ratios of 0.97 and 0.01 respectively in the diagnosis of hepatoma in cirrhotics. Usually as sensitivity increases so specificity decreases and the TP and FP ratios are related by a receiver operating characteristic (ROC) curve the shape of which depends on the test characteristics, the disease, and the population tested. The ROC curve illustrated was constructed from information in the literature on cirrhotic Caucasians tested for hepatoma.¹ The position X of the point TP=0.97, FP=0.01 lies well to the left of the curve derived from other studies. This discrepancy probably occurred because Dr Johnson and his colleagues derived the FP ratio from non-diseased patients who were not those in whom hepatoma had been suspected and tested for but rather those who had had a necropsy and been shown to be hepatoma-free. Indeed, the authors point out that higher FP ratios would occur in patients suffering from a variety of common disorders.

The optimal diagnostic concentration or operating position on the ROC curve is determined by the prevalence of disease in the tested population and the "costs" of misdiagnosis.² If a disease is common and the course of action indicated by a positive test curative and without side effects a sensitive test is best—a position high on the curve (B). If the disease is uncommon and the course of action of less value and with more side effects a specific test is best—a position low on the curve (A). Benefits and costs are difficult to define, but in the cirrhotic patient with a hepatoma the benefits of action are marginal and the optimal position is largely determined by the disease prevalence.¹ Dr Johnson and his colleagues work in a liver unit, where the prevalence of hepatoma may be higher than usual, but generally the prevalence in patients tested for hepatoma is low (for example, 3%) and the less sensitive, more specific diagnostic concentration is appropriate. However, different centres have different prevalences and

ROC curve for different diagnostic serum AFP concentrations.

may also have different disease patterns and test methodologies. Ideally each laboratory performing serum AFP estimations would construct its own ROC curve for the class of patients tested using past data and modifying the curve as more data became available. Then TP and FP ratios could be reported as well as the actual result and the physician could use his first estimate of disease probability (PD) and Bayes's formula to obtain a revised estimate of disease probability:

$$\frac{PD \times TP}{(PD \times TP) + (1 - PD) \times FP}$$

Alternatively, the laboratory could report the results of a test as positive or negative at a level decided upon by cost-benefit analysis. Such help from the laboratory is especially important for rare diseases like hepatoma because the individual physician may not have seen many (or any) cases to provide a basis for his assessment of a test result. This need for advice is shown by the clear difference between serum AFP results from patients with and without cirrhosis tested by the method of D Johnson and his colleagues. At the same serum AFP concentration very different TP ratios occur.

It must be tempting for the practising physician to accept a diagnostic level which apparently has a high TP and low FP ratio, but we suspect that in most centres the routine use of the serum AFP concentration of 10 IU/ml (10.5 ng/ml) in the diagnosis of hepatoma in deteriorating cirrhotics would lead to an unacceptably high number of false-positive results.

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¹ Phillips, P J, *et al*, *Journal of Clinical Pathology*, 1977, 30, 1129.

² Swets, J A, Tanner, W P, and Birdsall, J G, in *Signal Detection and Recognition by Human Observers*, ed J A Swets. New York, Wiley, 1964.

How to raise funds

SIR,—I would like to add a few comments to Dr A K Thould's advice on fund-raising (14 October, p 1065). Doctors have a head start as they are trusted in their community and they must have some patients who would be concerned to help them apart from their personal friends. A bank manager told me

seven years ago to aim at making my charity worth one-tenth of a million, and this is what has been accomplished by delegating to non-professional people. My view is that few people read pieces of paper unless these are handed to them in person and in this way stamps have been saved. (And the ladies' room is a good place to sell Christmas cards!) I receive 2000 printed newsletters each year free of charge, stating that the accounts are available for inspection. No member of the public has ever asked to see them but these newsletters are in the waiting rooms of my colleagues and I consider they have provided a source of interest and support.

I found, like Dr Thould, that my first visit to the Charity Commissioners was very important, and all their suggestions have been most constructive. The mayor of the local borough can be an important ally and his secretary is invaluable as she provides continuity throughout the years. It is important to find out which grant-making trust is interested in your particular charity and to keep the influential person informed of what you are doing and why. I have avoided self-advertisement by insisting that my local newspaper refers to me as "the founder" of my charity and it is only when I write to my professional journals that I sign my name.

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Intensive iron-chelation in thalassaemia

SIR,—We have read with interest your leading article (16 September, p 782) about subcutaneous infusion for iron-chelation in thalassaemia.

We are at present following 56 thalassaemic patients (40 boys and 16 girls) ranging from 18 months to 17 years; they are kept on a high-transfusion regimen (keeping haemoglobin at 9-14 g/dl) and receive intramuscular desferrioxamine 20 mg per kg per day. In the last few months we have been offering these patients the option of receiving, during their hospital stay for transfusions, desferrioxamine by either intravenous or subcutaneous infusion by means of a portable (166 × 53 × 23 mm) syringe driver. While the intravenous infusion was disliked almost unanimously, the subcutaneous pump, quickly nicknamed the "transistor," was enthusiastically accepted by 32 of the 34 boys selected to try it on the basis of age and number of previous transfusions. They welcomed the switch from the dreaded daily intramuscular injection to the little painless stitch; they would watch TV, sleep, and even engage in ball games while wearing it. On the other hand, 13 of 15 girls did not accept it so easily: many cried, a few even refused to try it, and all of them seemed to be most aware of the bulky, unsightly object that reminded them of their difference from others. Two of the girls on this occasion questioned their parents for the first time about the cause and prognosis of their disease. The two boys who have so far refused subcutaneous infusion were already showing signs of psychological distress and came from families that had not yet learned how to cope with the disease.

So far 21 families have decided to administer subcutaneous infusion at home. Although we are aware that the long-term benefits of this form of therapy have yet to be demonstrated,