the students' questionnaire compare closely with those of the doctors—there was only one difference in the top six specialties of each group. This therefore does not support the view of Wright *et al* that students are in danger of being unable to differentiate the palatable from the nutritious.

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SIR,—In the 24 March issue (p 826) there is a letter from Professor June Lloyd summarising paediatric training for doctors. This is eight to 12 weeks of the undergraduate curriculum. In the preregistration year there may be more. Yet people say that 30% of the time of the general practitioner is occupied in paediatrics. In the same issue (p 805) an article on "What shall we teach undergraduates?" by Professor V Wright and others gives 28 subjects taught in the medical curriculum, from anaesthetics to venerology. Paediatrics is placed as a very high priority by the vast majority of those who responded to the questionnaire. But one of the remarkable phenomena is that among these 28 subjects there is no mention of nutrition.

The Department of Agriculture, Fisheries, and Food has produced a handbook¹ of 135 pages, of which one-third of a page is devoted to malnutrition. Nutrition depends not just on food but on the consumer. Most of us who have spent much time working with children recognise that the training of doctors and nurses in nutrition in this country is grossly defective both in time and in subject matter. The subjects that are especially inadequate in nutrition are clinical nutrition, organisation of services, the training of staff, and family health (in co-operation with health visitors).

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¹ Department of Agriculture, Fisheries, and Food, *Manual of Nutrition*. London, HMSO, 1978.

Fats and atheroma

SIR,—I am sure that many of your readers will be as delighted as I am at the prospect of a heated controversy between Sir John McMichael (31 March, p 890) and Dr J I Mann (17 March, p 732). For controversy is the life-blood of science. Not only does it heighten the drama of a problem but it nearly always leads to new experiments and new evidence. I make the following remarks in the hope that they may add fuel to the flames of this promising battle.

I have never found the dietary hypothesis, favoured by Dr Mann, easy to accept. There is no doubt that fatty deposits can be produced in the intima of rabbits and other animals by feeding cholesterol. But the lesions in man are not at all similar. Dr Louis Katz at my request once showed me the coronary arteries of the chickens in which he had produced what he called atherosclerosis (literally hardening through the agency of porridge or grits) by feeding them cholesterol. The intima and adventitia were literally stuffed with cholesterol, as was the liver. I had never seen anything like it in human atheroma. In the human lesion the fat is not superficial in the intima: it is deep. Moreover, the outstanding clinical feature of the human disease is thrombosis, and thrombi are not prominent

in cholesterol-fed animals. It has long seemed to me that the most probable explanation of the human disease is that it is a thrombotic disease throughout. This hypothesis was fathered by Rokitsky and greatly advanced by Duguid. But the thrombi they had in mind were composed of fibrin. Evidence which I collected in my Thomas Lewis Lecture of 1964¹ suggested strongly that the thrombi were platelet-fibrin-leucocyte thrombi. These seem to occur episodically on the arterial wall. They may remain in situ, eventually lose their cellular identity, and become amorphous and indistinguishable from fibrin. They are then organised to produce the fibrous or fibro-fatty plaques. One of the striking pieces of evidence for this hypothesis is the appearance of platelet leucocyte thrombi as emboli in the retinal arteries, arising apparently from nodules in the carotid.

This hypothesis supposes that the fibrous and fibro-fatty plaques which are the essential feature of atheroma arise from organisation of these thrombi. This would accord with the episodic nature of atheromatous disease in man in territories such as that of the heart, the brain, the legs, and the kidneys. It would be natural to suppose that two factors are concerned in their causation: a general factor favouring the formation of platelet thrombi and a local factor determining their actual site. This is in conformity with clinical experience, which shows that the risk factors in myocardial infarction are not identical with those in cerebral infarction.

Whatever the hypothesis there is surely a great deal of evidence that the state of the blood lipids themselves acts as a risk factor in the pathogenesis of atheroma. There is not only the case of the familial xanthomatosis instanced by Dr Mann but all the evidence collected by the Framingham and other surveys. There is now quite a lot of evidence that suggests that a genetic factor is concerned, though I must confess I am unhappy with the view of Goldstein and Motulsky that many of the survivors from myocardial infarction have in fact a Mendelian dominant lipid disorder. When my colleagues and I had our argument with Platt it proved quite impossible to analyse our families on the either/or basis which is demanded by Mendelian inheritance. When I tried to perform this analysis on the Goldstein-Motulsky families I found it just as difficult. Fortunately there is still a good deal of work to be done.

Scientific research reminds me of gambling on the stock exchange or betting on a horse. I would put my money on the thrombotic hypothesis: the dietary hypothesis would be for the birds.

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¹ Pickering, G, *British Medical Journal*, 1964, 1, 517.

Myocardial infarction imaging

SIR,—If a new diagnostic test attempting, for instance, to differentiate between myocardial infarction and not myocardial infarction is compared with an imperfect old one it is not possible to show that the new one is better than the old.^{1 2} It may well be that imaging of the myocardium with ^{99m}Tc-imidodiphosphate does permit a more definite diagnosis of infarction in patients for whom electrocardiographic (ECG) and enzyme data are uncertain, but I submit that the design of the study by

Dr S P Joseph and others (10 February, p 372) did not allow this to be shown. From their data there is no way of telling whether the patients who had positive scans and equivocal ECGs or enzyme data, or both, had or had not had myocardial infarctions.

Demonstrating the value of myocardial imaging requires a data base for the subjects consisting of clinical history, ECG data, enzyme data, myocardial imaging data, and definitive evidence for the presence or absence of myocardial infarction. The definitive evidence for myocardial infarction could be obtained either in the postmortem room or by demonstrating irreversible incoordinate contraction of the left ventricle. A subject should be included in the data base only if his or her clinical history, ECG data, enzyme data, and myocardial imaging data have been interpreted separately and by observers unaware of the interpretations made for that subject's other investigations.

With such a data base investigators could then determine the sensitivity and specificity of clinical history alone, ECG data alone, enzyme data alone, myocardial imaging data alone, or of any combination of the four. It would thus be possible to assess how much of an improvement in the diagnosis of myocardial infarction can be obtained by adding myocardial imaging to the physician's armamentarium.

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¹ Buck, A A, and Gart, J J, *American Journal of Epidemiology*, 1966, 83, 586.

² Rautaharju, P M, and Smets, P, *Computers and Biomedical Research*, 1979, 12, 39.

Detection of deep venous thrombosis by ^{99m}Tc-labelled red-cell scans

SIR,—One cannot but agree with the criticisms raised by Mr P C Chan and others (24 February, p 552) concerning the conclusions of the investigations of Dr W Beswick and others into the detection of deep vein thrombosis using ^{99m}Tc-labelled red blood cells (13 January, p 82). It seems illogical that there should be any reluctance to submit patients to conventional x-ray phlebography on the basis of results obtained from an experimental procedure whose reliability was under investigation. The absence of objective criteria for positivity, despite the sophisticated imaging system of a gamma-camera and its associated technology, does little to engender faith in the technique as a viable alternative to phlebography.

In the current state of the art it is unlikely that any nuclear medicine investigation can ever yield comparable information to conventional x-ray phlebography in terms of the degree of fixity of the thrombus, condition of the vessel wall, and other aspects of prognostic significance. The assertion that the use of ^{99m}Tc-labelled red cells is an alternative to x-ray phlebography is therefore unacceptable.

Some time ago my colleagues and I¹ reported a procedure which, it appears, would fulfil Mr Chan's criteria of acceptability. Our technique used ¹³¹I-MAA (macroaggregates of albumin) with a detector system composed of a 2.54 cm iodide crystal, photomultiplier tube, and portable, battery-operated ratemeter. The choice of radiopharmaceutical was prompted by the demonstrable affinity of MAA for blood clot.² The isotope permitted the proce-

ture to be used without providing nuclear medicine facilities. The simplicity of the technique enables it to be performed at the bedside at any time by anyone with a minimum of training in the use of radioisotopes and with the least inconvenience to the patient.

Since ^{131}I -MAA was initially described as a lung scintiscanning agent, it is ideal for extension into a formal lung scan, permitting evaluation of perfusion deficiencies in cases of suspected pulmonary emboli.

Nuclear medicine is an expensive pastime, but the procedure, as we have described it, demands little in expertise, special skills, or manpower. In comparison with other nuclear medicine investigations it is inexpensive. It could become widely available but has the disadvantage of requiring pretest blockade of thyroidal uptake by sodium iodide. Sensitivity (88%) and specificity (91%) are comparable to those of similar techniques for detecting deep-vein thrombosis. Even with this technique, however, the information yielded cannot be considered on a par with that of conventional α -ray phlebography. Although we have not undertaken any clinical studies, there would appear to be no objection to using ^{125}I -labelled MAA, with the consequent lowering of radiation dose to the patient. At the time of the original work ^{125}I -MAA had not become available.

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¹ D'Auria, D, *et al*, *British Journal of Surgery*, 1973, **60**, 908.

² Webber, M M, Webb, R, jun, and Craggin, M, *Medical Radioisotope Scintigraphy*, 2, p 773, Vienna, IAEA, 1969.

Driving after anaesthetics

SIR,—As an anaesthetist who has volunteered many times for brief experimental nitrous oxide and oxygen anaesthetics, and who has followed up 81 outpatients anaesthetised for orthopaedic procedures,¹ I would like to add a few observations to the discussion about residual effects of general anaesthetics (10 and 31 March, pp 686 and 891).

Subjective and objective changes in mood and behaviour induced by nitrous oxide may outlast retention of appreciable quantities of this gas. For example, a tendency to hypoxaemia induced by nitrous oxide in the lunch hour may be commented on by one's spouse in the evening, without knowledge of the precipitating circumstances. When nausea has resulted malaise has persisted. A lunch-time inhalation of 80% nitrous oxide with oxygen only up to the point of no response to repeated auditory stimuli may leave the volunteer subjectively aware of slight difficulty in assessing traffic speed while waiting at a T junction in the evening. Although residual effects were not noticed 24 hours after anaesthesia, the fact that they appeared to outlast the presence of the causative agent should warn against simplistic predictions of recovery.

Nine of the 81 patients felt nauseated or actually vomited after outpatient anaesthesia and it is noteworthy that this was often precipitated by the journey home. Two patients felt nauseated or "sickly" for about two to three days. Two patients felt very tired for 24 hours.

If anyone takes up Dr Ogg's suggestion of a

study of volunteers or patients subjected to driving tests at 24 and 48 hours after anaesthesia it might help to design driving tests to deliberately stimulate the semicircular canals, and to seek subjects who have a low threshold to general anaesthetics and who are easily nauseated. Duration of the driving test may also be relevant.

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¹ Smith, W D A, *Outpatient anaesthesia with particular reference to nitrous oxide*, appendix E. MD thesis, University of London, 1969.

Sex determination and the H-Y antigen

SIR,—Your lucid and comprehensive leading article (17 March, p 704) on H-Y antigen nevertheless omits certain evidence from one crucial abnormality of sexual development. As you mention, H-Y antigen is expressed in true hermaphrodites, yet by definition such patients have ovarian as well as testicular tissue. Moreover, the two types of gonads exhibit lateralisation, testes being preferentially situated on the right and ovaries on the left side.^{1 2} This asymmetry is strong evidence in favour of the involvement of an epigenetic factor in the gonadal differentiation of these patients. Clearly, if this epigenetic factor could be pinpointed, this might be expected to throw light on the general problem of gonadal differentiation.

A useful pointer comes from an observed asymmetry in the development of normal gonads. In human fetuses the two gonads differ in size and cell number, those on the right being on average somewhat larger, and containing more cells, than left-hand gonads.³ Furthermore, testes are markedly larger than ovaries in fetuses of similar crown-rump-length.³ If we make the assumption that fast growth is a prerequisite for testicular differentiation, the asymmetrical distribution of testes and ovaries in hermaphrodites is simply explained: testes tend to develop on the right because the gonad on this side is naturally faster growing than its partner on the left, and vice versa for the preferential location of ovaries on the left.

If we make the further assumption that the expression of H-Y antigen is normally confined to the sex whose gonads grow faster than those of the other sex, another puzzling finding is explained. As mentioned in your editorial, H-Y antigen is expressed in the males of mammals and is associated with testicular development, but in birds the antigen is expressed in females and is likely to be associated with ovarian development. What, then, is the underlying similarity between testicular development in mammals and ovarian development in birds? When we compare the relative growth rates of testes and ovaries, it becomes apparent that whereas mammalian testes grow faster than ovaries, in chick embryos aged 8 days onwards the ovaries grow faster than the testes.^{4 5} This difference in relative growth rates finds a parallel in the fact that in mammals the testis is the dominant embryonic gonad in contrast to birds, in which the ovary is the dominant embryonic gonad.⁶

The association of H-Y antigen with the fast growing, dominant embryonic gonad provides a simple explanation for the finding that the antigen is expressed by the heterogametic sex regardless of whether this is the

male, as in mammals, or the female, as in birds. It does not provide an answer to the chicken-and-egg question, whether the antigen causes gonadal differentiation or vice versa. Whatever the precise relationship it is clear, however, that the antigen is associated not with any particular type of gonadal differentiation but with a common denominator underlying the development of mammalian testes and avian ovaries.⁷ There appears to be strong evidence that this common denominator is a relative effect which becomes apparent in a measurable difference in growth rate.

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¹ Polani, P E, *Philosophical Transactions of The Royal Society of London B*, 1970, **259**, 187.

² van Niekerk, W A, *True Hermaphroditism*. Maryland, Harper and Row, 1974.

³ Mittwoch, U, *Annals of Human Genetics*, 1976, **40**, 133.

⁴ Mittwoch, U, *et al*, *Nature New Biology*, 1971, **231**, 197.

⁵ Gasc, J-M, *Journal of Embryology and Experimental Morphology*, 1978, **44**, 1.

⁶ Jost, A, in *Organogenesis*, ed R L de Haan and H Ursprung, p 611. New York, Holt, Rinehart and Winston, 1965.

⁷ Mittwoch, U, *Journal of Medical Genetics*, 1977, **14**, 335.

Polyunsaturated fatty acids in multiple sclerosis

SIR,—Dr D Bates and others (10 March, p 683) have had the misfortune to invest much time and effort in a clinical trial (18 November, p 1390) which, so far as α -linolenate is concerned, is entirely nugatory. They did, however, from time to time receive verbal warnings that the prostaglandin E_2 (PGE_2) reaction produced by prolonged exhibition of (tartrazine-coated) Naudicelle capsules was puzzlingly out of step with those given by linoleic and arachidonic acids (LA and AA).¹

The circumscribed use of the drug advocated in my letter (10 February, p 411) and the tentative suggestion made earlier with respect to children² surely do not merit the epithets "avowed propagandist for the use of Naudicelle" and "advocate of its administration to children." I plead guilty only to putting forward a new idea.

The electrophoretic tests used^{1 2} have been validated against widely accepted indicators of lymphocyte sensitisation.^{3 4} Failure to "catch on" in "other laboratories in Britain" is immaterial since the method currently receives scholarly and unprejudiced study in the United States, West and East Germany, Italy, France, and other countries. Three international meetings are scheduled over the next six months to discuss the fully automatic and advanced laser-Doppler machines developed recently for simplified objective measurements.

Bates *et al* write in their paper that "the frequency of attacks was not significantly different between the four groups (table II)" (a difference from the original findings of Miller *et al*), though when the "attack score" is used (a statistic of their own, inadequately explained) a "significant difference" emerges between columns C and D. The deterioration of Naudicelle patients faster than controls ($P < 0.05$) is rejected by the authors as not biologically significant. I agree. But what is the P value of the difference between C and D—not given in the statistical analysis?

A retest with pure α -linolenate and adequate laboratory control throughout is needed. We know that some of the patients of Bates *et al*