forms of malignant disease occur less frequently in those with a history of "allergic diseases" than in those without such a history.^{1,5}

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¹ Rimington, J. *British Medical Journal*, 1971, 2, 273.

² Holland, W. W., et al. *Archives of Environmental Health*, 1965, 10, 338.

³ Read, J., and Selby, T. *British Medical Journal*, 1961, 2, 1104.

⁴ Fisherman, E. W. *Journal of Allergy*, 1960, 31, 74.

⁵ Gabriel, R., Dudley, B. M., and Alexander, W. D. *British Journal of Clinical Practice*, 1972, 26, 202.

Risks of total hip replacement

SIR,—The purpose of my letter (31 May, p 498) which was commented on by Mr N E Shaw and Dr M W Johnstone (13 September, p 651) was not so much to discuss the pharmacology of methylmethacrylate monomer (MMA) as to get some indication of the frequency of cardiac arrest currently being encountered in total hip replacement.

Experience in my own unit would give the impression that no problem exists at all. Out of 10 356 total hip operations performed between January 1963 and June 1975 there have been two fatal arrests, but in one of these there were features which challenged the responsibility of MMA. However, the response which I have had to my letter suggests some disquieting possibilities.

I received only three replies, but these related to four incidents of cardiac arrest. Two were fatal. The medullary cavity was vented in three but not stated in one. The disquieting feature was that all these arrests had occurred recently (one had happened only two weeks before the appearance of my letter) and I received the impression that it was coincidence rather than incidence which prompted the replies. One correspondent, an anaesthetist, said, "I can assure you that difficulties still arise at the time when cement is put into the body."

From my reading of published experimental work and my own clinical experience I am inclining to the view that cardiac arrest in these operations must occur in patients whose hearts are already poised for arrest from unrelated causes and that the final stimulus for arrest is not specific for MMA. Thus in a heart poised for arrest the stimulus could equally well be the sudden injection into the blood stream of fat, bone marrow, and air, and all with the added effects of neurogenic impulses. Cases are encountered in which an arrest takes place before the cement stage of the operation is reached.

The idea that a fall of arterial pressure would precipitate cardiac arrest is a possibility, but the clinical picture does not fit: quite severe falls of pressure are not uncommonly encountered at all stages in these operations but they do not often end in arrest. Most often the picture is one of a fall of pressure occurring more or less simultaneously with arrest and without any warning. Hypersensitivity to MMA also does not explain the situation, because hypotension can occur at one operation but not at a subsequent procedure on the opposite hip and vice versa. From experimental work on animals there is no evidence suggesting that MMA can produce cardiac arrest. Transferred to man the fatal dose for dogs

would require about 6 g of MMA to be given intravenously in 90 seconds.

Because of the disquieting deductions which could be made from my attempt at inquiry I think that some official body should circulate orthopaedic consultants for their experiences over the past two years; we should then know whether the matter deserves more serious study.

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More battering

SIR,—A particularly sad form of violence is that inflicted by patients on their relatives. I have seen this particularly in cases of stroke, but I believe that it occurs also in other forms of extensive brain damage. Most of the cases which I have seen occurred six months or more after partially successful rehabilitation from an extensive stroke, more often after right hemiplegia with language disturbance. One or two of the patients had previously been of a violent nature, but in most cases there had been a change in the patient's personality from a previously placid temperament. The violence was nearly always directed against the person devoting most care and attention to the patient, usually the wife. She was often the victim of abuse and foul language and of blows on the head and body. All the patients whom I interrogated denied the assault.

I know of no direct way of dealing with this situation; but a club for victims of stroke has proved to be of some value in giving the patient at least some social outlet, and a club for relatives has allowed these unhappy experiences to be shared with others who could understand them.¹

I wonder if others have encountered this form of battering?

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¹ Isaacs, B., Neville, Y., and Rushford, I., to be published.

Interactions with monoamine oxidase inhibitors

SIR,—As probably the longest user and most consistent advocate of the monoamine oxidase inhibitor (MAOI) drugs in Britain for over 12 years now, I agree with Dr J M McGilchrist (6 September, p 591) about their safety, provided that a minimum of essential precautions are taken. Patients will sometimes get some frightening headaches but very rarely die—I have had no deaths in 12 years and only one small brain haemorrhage, and even in this case the patient, now more careful of his diet, has been back on Parstelin (tranylcypromine and trifluoperazine) for five years.

But it is essential for the patient to be told not to eat cheese, because it is fermented milk, Marmite, which is also a strongly fermented food, and all other foods that have fermented or gone bad. One can get a headache, for instance, from rotten bananas but not from fresh ones.

Alcohol is safe. Bottles of whisky have been drunk by some patients on the MAOIs, the only result being that they got very drunk more easily and cheaply. Even

morphine may be safe, and I know of some 10 cases with no side effects except a more prolonged morphine action. Both local and general anaesthetics are safe and thousands of general anaesthetics have been given to patients on the MAOIs for electric convulsion therapy. But Mu-Cron, for nasal congestion, can give a very nasty headache.

The Committee on Safety of Medicines is dishonest in not admitting how wrong they have been on imaginary dangers. They lose credibility, as with the halothane circular. One of the committee I know is using combined antidepressants (Parstelin and trimipramine) yet as a body the committee is officially saying how dangerous it is. One death from Sherlock's supposed MAOI jaundice has occurred in a village where there was an epidemic of infective hepatitis. I have had patients on iproniazid for over 10 years and their livers seem very healthy indeed.

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SIR,—The New Zealand Committee on Adverse Drug Reactions has had notification since 1965 of seven patients who manifested interaction between monoamine oxidase inhibitors (MAOIs) and foodstuffs, one of them fatal (from subarachnoid haemorrhage). This and two others followed the eating of cheese; one of broad beans; one of cheese, broad beans, and beer; and the two most recent ones of packet soups. These last contained hydrolysed yeast and hence monoamines, including tyramine. All of the above reactions have been accompanied by intense headache and, in five of the cases, documented paroxysmal hypertension. Only one of the reactions involved phenelzine but there seems no reason to suppose that the reactions may not involve all members of the group of MAOIs. Unfortunately we do not have recorded whether the broad beans were consumed with or without their pods, but the form in which they are eaten by at least some people in New Zealand is clearly capable of producing such reactions. The interaction with broad beans alone occurred twice in the same patient, who had been warned about cheese but not beans. The recent accession of packet soups to the range of active agents seems to merit their inclusion on any list of prohibited foods.

In the same period 14 interactions have been reported involving drugs of various kinds, with two deaths.

There could undoubtedly be debate in some of these cases as to the certainty with which a causal role could be allocated to the MAOIs, but the majority of them, including the fatal ones, are sufficiently well documented as to be beyond reasonable doubt.

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Heparin and ristocetin-reduced platelet aggregation

SIR—Drs Jeanne Stibbe and E P Kirby (28 June, p 750) reported that after the start of cardiopulmonary bypass the plasma of patients undergoing open heart surgery inhibited ristocetin-induced platelet aggrega-

tion. They attributed this inhibition to Haemacel, a plasma expander used in the heart-lung machine. We have found, however, that heparin also strongly inhibits ristocetin-induced platelet aggregation.

In our in-vitro experiments by the turbidimetric method using heparin PRP (250 U/l) aggregation due to ristocetin in a concentration of 1 g/l was completely abolished by this substance, while with 1.5 g ristocetin/l the inhibitory effect of heparin started at a concentration of 10 kU/l and was completed at 25 kU/l.

In blood obtained from 10 normal individuals after an intravenous injection of 5000 U of heparin there was a slight impairment of aggregation with ristocetin (1.5 g/l), while with 1 g ristocetin/l platelet aggregation was abnormal.

We conclude therefore that heparin as well as Haemacel must play a part in the inhibition of ristocetin-induced platelet aggregation in patients undergoing cardiopulmonary bypass.

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Serum digoxin in patients with thyroid disease

SIR,—The paper by Dr M S Croxson and Professor H K Ibbertson (6 September, p 566) was an interesting study of drug metabolism in thyroid disease.

The low serum digoxin levels in thyrotoxicosis are probably due in part to increased clearance of the drug, as suggested. But a much more important factor may be that of malabsorption, which was not adequately investigated.

It is known that a high percentage of patients with thyrotoxicosis have steatorrhoea.¹ Digoxin is a steroid molecule and poorly soluble in water. It is therefore very probable that malabsorption of digoxin accompanies the steatorrhoea of thyrotoxicosis. Unfortunately Dr Croxson and Professor Ibbertson measured digoxin excretion in only two patients with thyrotoxicosis and no control values were given, so we feel that there is little evidence to support their suggestion that malabsorption does not play an important role in the low serum digoxin levels in thyrotoxicosis. This aspect obviously needs further investigation, especially as the results may have implications for other drugs given to patients with thyrotoxicosis.

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¹ Thomas, F B, Caldwell, J H, and Greenberger, N J, *Annals of Internal Medicine*, 1973, 78, 669.

Rabies

SIR,—In your leading article on the diagnosis and treatment of human rabies (27 September, p 721) you do not include the valuable evidence that can often be obtained about the animal. The state of the dog, for example, is very relevant in making a correct diagnosis. When I worked in Zambia I learnt to ask all about the "mad" dog. If it is rabid it dies

within 10 days. I checked this fact with the Liverpool School of Tropical Medicine.

When faced with a patient showing symptoms and signs suggestive of rabies there may be clear-cut evidence that the dog was ill and died of its illness. Rabies becomes probable. If the history is of no dog bite, or a bite by a dog that was not ill and that was known to be alive 10 days afterwards, rabies is nevertheless still a possibility because of the unreliability of negative evidence.

But the question whether there has been inoculation of the virus often arises when someone is bitten or has contact with an ill dog. Here the state of the animal is of essential importance. If alive it must be compounded and kept to see if it dies within 10 days. All too often a dog is killed in anger, ignorance, or misplaced zeal, although there may be circumstances when it is too mad to be caught and kept alive. It must not be destroyed or buried. A post-mortem examination is obligatory, and of course this is most likely to give reliable results if the dog has died naturally. If it cannot be proved that the dog was free from rabies, then prophylactic injections must be given to the patient and others at risk, even though they are often painful and hazardous. I raise this as only last week a patient asked about a bite from a dog "from Germany." The dog was alive and well and had been in quarantine, so I was able to reassure them that there was no danger of rabies.

Kirkham

J E PARRY

SIR,—Your timely leading article on the diagnosis and management of human rabies (27 September, p 721) was extremely interesting. However, I believe it would also be very desirable to hear from one of our veterinary colleagues on public health aspects of the disease in animals in view of the spread of rabies across Europe.

Many people think of animal rabies only in terms of the furious form of the disease, whereas in the tropical countries in which I have served I think it was the animal with the dumb form which was more dangerous because the state of the animal could not be immediately recognised.

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Controlled trial of therapy in Reye's syndrome

SIR,—Your timely leading article on Reye's syndrome (20 September, p 662) correctly emphasises the importance of considering this diagnosis in any child with convulsions and coma. Since the pathophysiology of this condition is so poorly understood the value of the various forms of therapy which have been advocated for this condition can be decided only by well-conducted controlled trials. A major problem in instituting such trials is the comparative rarity of the condition, its sporadic frequency, and its varying severity. None of the forms of therapy mentioned in the leading article have been subjected to such controlled trials. For that reason we are co-operating in a multicentre

controlled trial organised by the department of paediatrics of Yale University in conjunction with some eight units.

Four treatment regimens are being assessed, supportive treatment as outlined in your leading article being compared with similar supportive measures aided by (a) exchange transfusion, (b) peritoneal dialysis, and (c) glucose and insulin infusion.

We would be pleased to supply further details of the trial protocol to clinicians who would wish to participate in this trial. May we through your columns also ask any pathologists or clinicians to preserve serum, urine, and liver tissue from such patients, preferably at a temperature of -70°C , so that these may be available for analysis as the pathophysiology of this condition is elucidated?

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SI units

SIR,—Among doctors divorced from the hierarchy of the teaching hospitals and pure science there is an overwhelming feeling that we are being conned into accepting the introduction of SI units as an advancement in medical technique. One district after another in Kent through their district medical committees have already sent resolutions of protest and at least one district pharmaceutical committee and the area medical advisory committee have similarly protested.

There are no reasons to suppose that the introduction of SI units will benefit the patient or improve the results of investigations interpreted through SI units; indeed, the reverse is likely to occur, with possible disastrous results to the patient. The undue haste with which this scheme is being introduced will bring intolerable pressures on both the medical and nursing professions, and it seems highly unlikely that re-education of such large numbers can be completed in time. That such a scheme should be introduced at this time of financial stringency and shortage of all grades of hospital staff to meet the whims of scientific bureaucrats and none else seems quite incredible. We readily support our colleagues on these other committees and ask that in the interests of the patient and the country the introduction of SI units shall be postponed, possibly for even as long as five years.

A F CRICK

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Effects of exertion on hormone secretion

SIR,—In addition to the investigations presented in our previous letters (29 June 1974, p 726; 21 June 1975, p 685) we decided to assay plasma growth hormone (GH) before and after exertion in the remaining sera from the group of amateur Finnish marathon runners. The determination of GH was performed with a double-antibody solid-phase technique. Mean control values were 0.7 (range 0.2-2.8) $\mu\text{g/l}$ and after the run the mean value was 5.4 (range 1.3-11.2) $\mu\text{g/l}$.