myocardial infarction, and ischaemic gangrene. By immunohistochemical techniques, electron microscopy, and tissue culture the evidence indicates that the underlying mechanisms include migration of low-density β -lipoproteins through the arterial wall and stimulation of multipotential smooth muscle cells in the media, with their resultant proliferation and migration into the intima.

Previously, in Iowa, Armstrong *et al*^{7, 8} demonstrated that, in more cellular lesions produced by a stronger dietary stimulus, considerable lipid depletion, condensation of fibrous tissue, and widening of the lumen resulted after returning to a natural diet. This has now also been shown in Chicago.

Interestingly and very importantly, if these primates are fed on what is now termed a "prudent" diet and recommended by many physicians for patients with coronary disease and those at high risk very little atherosclerotic change develops. The difference between the normal and the prudent diet is a reduction in total calories, saturated fat, and cholesterol, with partial replacement of saturated by polyunsaturated fat. Interestingly too, there is individual variation in susceptibility, as in man, and some animals are immune.

What more could one want? Surely, to doubt the relevance of this work to man is stretching incredulity beyond reasonable bounds. Of course, observations such as these in groups of humans are impossible. New techniques may be developed, but at present there is no possibility at all of conclusive evidence being obtained in man by long-term prospective intervention studies in free-living populations on account of the logistics, let alone the prohibitive costs.

RICHARD TURNER

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- ¹ Wissler, R W, and Vesselinovitch, D, in *Advances in Lipid Research*, vol 6, p 181, New York, Academic Press, 1968.
- ² Wissler, R W, and Vesselinovitch, D, *Annals of the New York Academy of Sciences*, 1968, **149**, 907.
- ³ Wissler, R W, *Journal of Atherosclerosis Research*, 1968, **8**, 201.
- ⁴ Wissler, R W, and Vesselinovitch, D, in *Pathology Annual*, 1969, New York, Appleton-Century-Croft, 1969.
- ⁵ Wissler, R W, *et al*, *Circulation*, 1971, **44**, 57.
- ⁶ Wissler, R W, in *The Myocardium: Failure and Infarction*, ed E Braunwald, New York, H P Publishing Co, 1974.
- ⁷ Armstrong, M K, Warner, E D, and Connor, W E, *Circulation Research*, 1970, **27**, 59.
- ⁸ Armstrong, M K, and Megan, M B, *Circulation Research*, 1972, **30**, 675.

These papers contain references to the work of many others in this field.

Antenatal diagnosis of the mucopolysaccharidoses

SIR,—In 1973 I was co-author of a method for the measurement of glycosaminoglycans (acid mucopolysaccharides) in amniotic fluid and urine.¹ While we appreciated that the ultimate diagnosis should depend on demonstration of the specific enzyme defect, it was hoped that analysis of glycosaminoglycan cell-free amniotic fluid would offer a more practical means of diagnosis.

In two cases with hysterotomy fluids taken respectively at 25 weeks' and 24 weeks' gestation the technique yielded results consistent with a San Filippo syndrome² and a Hurler syndrome. In the second case, however, a previous amniotic fluid sample analysed at 16 weeks' gestation gave normal results. Enzyme analysis and sulphate uptake studies

performed by other workers on cultured amniotic cells from the earlier amniocentesis revealed that the fetus was affected by Hurler's syndrome. I therefore consider that the only possible value of the method for glycosaminoglycan analysis described would be in later gestation samples where enzyme and sulphate uptake studies might not yield results soon enough. Currently it appears that the best means of diagnosis is by enzyme analysis and sulphate uptake studies undertaken on cultured amniotic cells obtained at 16 weeks' gestation.

Provision of a grant from the Advisory Committee on Medical Research to this department has enabled the technique of enzyme analysis to be instituted on cultured amniotic cells supplied by Professor M A Ferguson-Smith, of the medical genetics unit at these hospitals. The analyses now available include those concerned in the diagnosis of mucopolysaccharidoses types I*, IIIa, IIIb, V*, VI, and VII. The opportunity to analyse cultured cells from known or suspect cases from outside Glasgow would be welcomed.

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¹ Duncan, D M, *et al*, *Clinica Chimica Acta*, 1973, **45**, 73.

² Harper, P S, *et al*, *Journal of Medical Genetics*, 1974, **11**, 123.

*Phenyl iduronide substrate kindly made available by Drs E F Neufeld and B Weissman (NIH-NIAMDD 73-2205).

First aid in acute myocardial infarction

SIR,—Your excellent leading article with this title (14 February, p 356) did not in fact discuss first aid. I believe that specific first-aid measures may reduce the mortality and morbidity caused by myocardial ischaemia and can be undertaken by anyone before the doctor arrives.

While working in a factory medical unit I have frequently seen patients within minutes of the onset of symptoms. Sometimes there is a resemblance to a vasovagal syncope episode with bradycardia, a weak, thready pulse, pallor or cyanosis, and collapse or even unconsciousness. Presumably these manifestations are caused by parasympathetic over-activity. Well-meaning friends and helpers usually prop up the patient in a chair or leave him slumped across a desk. Placing the patient on the floor and raising the feet, together with instructions to breathe deeply, often produce a remarkable improvement. Of course, the airway of an unconscious person must be ensured. Administration of oxygen (or Entonox if the pain is severe) also appears to help. It is not unreasonable to assume that by ensuring adequate venous return and full oxygen saturation of the haemoglobin, and possibly dissolving a small additional amount of oxygen in the plasma, fibrillation of the anoxic myocardium might be prevented.

In my experience most patients with acute chest pain from myocardial infarction or angina have shallow respiration. Indeed some of them appear to have respiratory depression, which could reduce oxygen saturation of the haemoglobin and the supply of oxygen to the myocardium. Therefore I believe that all patients with symptoms of acute myocardial ischaemia should lie flat with the feet elevated and be

instructed to take deep breaths. It is our usual practice to wait until the patient's condition stabilises before transporting him or her to hospital, and oxygen or Entonox may be administered during the journey.

Analysis of blood gases in the early moments following the onset of symptoms would make a fascinating study. Reduced oxygen tension of the blood from physiological factors could account for some of the early mortality.

D P MANNING

Southport, Lancs

SIR,—In your leading article (14 February, p 356) you mention important recommendations for the early care of patients with myocardial infarction. However, the following statement could be misinterpreted: "For a patient in jeopardy from tachycardia . . . both intravenous practolol (5-10 mg) and verapamil (10 mg) are relatively safe drugs. . . ." This advice could possibly lead to the successive administration of both drugs if one of them was ineffective or even to the simultaneous administration of the two drugs.

Nayler and Szeto¹ reported that beta-adrenoceptor blocking agents and verapamil both possess calcium-antagonistic properties acting through different mechanisms, and both exert a mild negative inotropic effect. According to various authors the combination of a beta-blocker with parenteral verapamil may be harmful. Benaim² reported a case of asystole after administration of 20 mg of practolol intravenously followed within half an hour by 7 mg of verapamil intravenously. Krikler and Spurrell³ observed severe bradycardia and hypotension following administration of verapamil in patients receiving oral propranolol or practolol. In addition, a few cases of serious interactions of a similar type have been reported to our adverse reactions department in which pindolol was used in association with verapamil. These observations suggest that combined medication with beta-adrenoceptor blocking agents and verapamil should be avoided.

P JERIE

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¹ Nayler, W G, and Szeto, J, *Cardiovascular Research*, 1972, **6**, 120.

² Benaim, M E, *British Medical Journal*, 1972, **2**, 169.

³ Krikler, D M, and Spurrell, R A J, *Postgraduate Medical Journal*, 1974, **50**, 447.

Support for varicose veins

SIR,—Since publication of our article on this subject (31 January, p 254), our attention has been drawn to inaccuracies in the manufacturers' technical descriptions of the garments that we obtained for the study. The correct descriptions of the garments should read: (a) nylon-covered, elastane support tights, average denier 227; (b) nylon-covered, 0.2-mm rubber core, National Health stockings; (c) nylon-covered, elastane support stockings, average denier 150; (d) nylon-covered, elastane support tights, average denier 75; (e) non-supporting tights, average denier 20.

However, we must point out that the average denier of the different fibres used in the manufacture of a garment is only a crude guide to the relative strength of the garment.

The pattern of construction is also important in determining the support provided. Indeed, this information gives so little true guidance regarding the compression provided by a garment when it is worn by an individual patient that it further emphasises the need for methods such as we described.

The particular need for this letter is to point out that since, in the light of new information, the average denier of garments (c) and (d) was different as well as their pattern of construction, readers should not infer that our paper demonstrated a difference in the support provided by tights and stockings. Indeed other work on tights and stockings made to specification (a) demonstrated no difference in the support provided.

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Cost of phentermine preparations

SIR,—It has been drawn to my attention that I made an error in estimating the monthly cost of the currently available anorectic agents in the table that was published with my article on the management of obesity (14 February, p 388).

The cost of Ionamin was overstated by a factor of 3. According to the February 1976 issue of *MIMS* the cost for 30 days' treatment of Ionamin is now £1.05 and of Duromine £1.10. It follows that of the two proprietary preparations of phentermine available Ionamin is marginally the cheaper.

J F MUNRO

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Curability of breast cancer

SIR,—In my view Mr M Baum (21 February, p 439) is right in considering that, if the current generation of clinicians is to reduce mortality from breast cancer, it must reject the obsolete concept of the nature of the disease that has led to more and more aggressive local treatment.

If the statistics (which Mr Baum is not alone in struggling to make sense of) show anything, it is that in the majority of cases breast cancer is a systemic disease when first diagnosed. It follows that the treatment required is systemic treatment aided by the removal of the visible tumour mass. At the stage of first presentation of the disease, the most suitable systemic therapy to accompany surgery would seem to be with the drug ICRF 159, which has little or no cytotoxicity but is effective in preventing metastases from establishing a blood supply.¹ However, it would be desirable to use any surgical sample obtained for in-vitro studies to identify the hormones on which the individual tumour depended,² so that specific anti-hormone drugs could be held in reserve in case further treatment should prove necessary.

An alternative primary systemic treatment could be with small doses of a combination of cytotoxic drugs, but it would seem preferable to hold these in reserve also until the efficacy or inefficacy of ICRF 159 has been established, since all cytotoxic drugs have inhibitory effects on the body's natural immune defences.

Future research lies in determining the necessary duration of systemic therapy re-

quired. In my own case two months' treatment with ICRF 159 proved insufficient after mastectomy and was followed by development of an isolated cerebral metastasis. Treatment for this was local destruction of the lesion by radiotherapy, accompanied by a radiation menopause, and two years of systemic drug treatment aimed specifically to reduce oestrogen and prolactin stimulation. Its success has belied my therapist's gloomy prediction (between three and six months to live) and has led to three years' survival with no trace of disease, no ablative operations, and no cytotoxic drug therapy.

A single successful case has no statistical value, but it is the only case I am able to present (being non-medical). I can only hope that it will encourage the current generation of clinicians in the new approach to breast cancer as a systemic disease.

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- ¹ Le Serve, A W, and Hellman, K, *British Medical Journal*, 1972, **1**, 597.
² Hobbs, J R, et al, *British Journal of Surgery*, 1974, **61**, 785.

Fluoridation and the Government

SIR,—We are disappointed to learn from the interview with Dr David Owen (28 February, p 513) that "this is not the right time for a compulsory national decision to fluoridate." We are exhorted to stand up and campaign in our localities for fluoridation. Dr Owen can hardly be unaware that this has been going on for years and has resulted in painfully slow progress towards national water fluoridation. Ten years after Birmingham fluoridated its drinking water very few other major cities have followed the example, and only 6% of the population drink fluoridated water. Are Birmingham's children to remain among the few privileged in our community to enjoy the benefits of improved dental health? The Minister must realise the difficulty that is constantly encountered in arguing the case for fluoridation. Dogma (accompanied by cries of mass medication) is not easily met by logical scientific argument, however persuasively advanced.

Accepting that yet another government is avoiding its responsibility for introducing the necessary legislation for national fluoridation, one other major problem remains. Even if the protagonists are able to persuade the relevant health and water authorities to fluoridate where is the necessary finance to be obtained? One way in which the present Government could demonstrate its good intentions as far as preventive dentistry is concerned is to underwrite the capital costs of water fluoridation from central funds.

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JOHN MURRAY

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Normotensive pheochromocytoma with hypercalcaemia

SIR,—I should like to draw attention to the striking preoperative hypercalcaemia of 19.4 mmol (776 mg/24 h) which was ignored by Drs R S Gray and J Gillon in the discussion

of their very interesting case (14 February, p 378). The reported level was unexpectedly high for the serum calcium of 3.03 mmol/l (12.1 mg/100 ml).

The puzzle of hypercalcaemia disappearing after the removal of a pheochromocytoma was discussed elsewhere¹ but remained unresolved. Of particular relevance in this context is the work of Morey and Kenny.² They observed a woman who had a pheochromocytoma and an abnormally high level of calcium excretion which returned to normal after the removal of the tumour. In experiments in rats they showed that both adrenaline and noradrenaline caused hypercalcaemia. This effect was blocked by phenoxybenzamine and could be observed even in parathyroidectomised rats, suggesting a direct effect of catecholamines presumably on tubular reabsorption of calcium according to the concept of Talmage and Krantz.³ The hypercalcaemic effect of adrenaline in man has been known for a long time.⁴ The mechanism is not clear. A direct effect of catecholamines on the bones in pheochromocytoma has also been postulated.⁵

Although hypercalcaemia in pheochromocytoma is rare, except in Sipple's syndrome, where hypercalcaemia is a frequent finding,⁶ hypercalcaemia is probably common and its correlation with the circulating catecholamine levels deserves more attention.

PETR SKRABANEK

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- ¹ Case Records of the Massachusetts General Hospital, *New England Journal of Medicine*, 1975, **293**, 1085.
² Morey, E R, and Kenny, A D, *Endocrinology*, 1964, **75**, 78.
³ Talmage, R V, and Krantz, F W, *Proceedings of the Society for Experimental Biology and Medicine*, 1954, **87**, 263.
⁴ Inoue, T, *Japanese Journal of Medical Science and Biology*, 1924, **2**, 14.
⁵ Finlayson, J F, and Casey, J H, *Annals of Internal Medicine*, 1975, **82**, 810.
⁶ Case Records of the Massachusetts General Hospital, *New England Journal of Medicine*, 1973, **289**, 472.

Vaginal candidosis

SIR,—Your recent leading article (14 February, p 357) effectively summarises the current problems arising from the steady increase in the incidence of vaginal candidosis. However, we would like to draw your attention to an important factor which was omitted from your review—namely, the behaviour of patients on continuous unsupervised treatment.

As doctors, we too readily assume that all our patients will carry out their treatment instructions implicitly. That they do no such thing, in Scotland at least, clearly emerges from a study of the behaviour of patients on unsupervised treatment. Over the past 10 years we have noted that 4% of the patients do not even start their treatment, while almost half have ceased to follow their advised treatment course within the first 14 days. Thus disappointing therapeutic results may be a measure of human rather than drug fallibility. There seems little to choose between the antifungal preparations currently available, but in our experience the shorter the course of treatment, the better the short-term results. It seems that even feckless patients will complete or nearly complete an abbreviated course of treatment.

We believe that this is the underlying reason why clotrimazole, one pessary (100 mg) inserted nightly for six nights has given better