of myocardial infarction,^{11 12} together with the relationship between the incidence of PVF and early admission in the hospital series,⁷ suggests electrophysiological disturbance within the heart leading to ventricular fibrillation but clearing within 24 hours.

Thus, although it is true that the heart at 17-18 hours after the onset of symptoms may not be especially vulnerable to serious arrhythmias and that they do not at this stage constitute an independent risk factor, the same conclusion cannot be drawn when these serious arrhythmias occur within the first two hours.

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¹⁰ Surawicz, B, Gettes, L S, and Ponce-Zumino, A, *American Journal of Physiology*, 1967, 212, 1519.

¹¹ McNeill, R H, and Pemberton, J, *British Medical Journal*, 1968, 3, 139.

¹² Fulton, M, Julian, D G, and Oliver, M F, *Circulation*, 1969, 39-40, suppl No 4, p 182.

SIR,—I was very interested to read the article by Dr J M Roland and others (1 September, p 518) on the effect of beta-blockers on arrhythmias during six weeks after suspected myocardial infarction. I would be in general agreement with their conclusion that beta-blockers in the dose used by them did not materially influence arrhythmias.

I fail to understand, however, why they concluded from their work that so-called serious and less serious ventricular arrhythmias have no part to play in the aetiology of ventricular fibrillation or death. Ninety-three patients were studied after definite or probable myocardial infarction and, as expected, the incidence of arrhythmias fell and became equal to that in non-infarct patients during follow-up. Hence "serious" arrhythmias are related to recent definite or probable myocardial infarct. We all know that it is patients with recent myocardial infarction who develop ventricular fibrillation, with decreasing frequency related to time after onset. It should, however, be noted that ventricular arrhythmia, even in these groups of patients, while occurring in a large percentage appears only infrequently in most patients. In this study (although their recordings did not start until 17 hours after onset of symptoms) 25 of the 49 episodes of ventricular tachycardia occurred in only one of the 31 patients taking placebo, implying that there were only 24 episodes in the remaining 30 patients—presumably only one or less episode occurring during the period of recording in a given patient. Nobody has ever claimed that every single ventricular ectopic or R-on-T phenomenon results in ventricular fibrillation.

As the authors themselves admit, the patients monitored in the coronary care unit in their study represented a good-risk group. In this group one would expect a mortality of approximately 1% if haemodynamically they belonged to the group with a cardiac index of more than 2 litres a minute and a left ventricular end-diastolic pressure of less than 18 mm Hg—

as one must assume most of their patients did. No conclusions can therefore be drawn from five deaths, three of which were in patients who had had serious arrhythmias recorded; nor can any conclusions be drawn from one patient with ventricular fibrillation who did not die and did not have any serious arrhythmia recorded, since after all the number of episodes in a given patient was infrequent during the recorded period and it is well known that arrhythmias vary in frequency from time to time.

Since the number of arrhythmias in a given patient was infrequent, conclusions regarding the efficiency or otherwise of beta-blockers are unsafe. There are a number of papers which suggest that patients differ in their response to a given dose.

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Dangerous antihypertensive treatment

SIR,—Beta-blockers and diuretics act by influencing different controlling systems in the body, but Drs O W Barritt and A J Marshall may have given the impression in their recent letter (8 September, p 606) that the hypotensive effects of the two agents in combination may be predicted by summing the falls in blood pressure achieved with the individual drugs. This is not the case.

In a study by Castenfors and Danielsson¹ 25 patients were given placebo for four weeks and then allocated to treatment with either 200 mg metoprolol or 25 mg hydrochlorothiazide for six weeks. They were then transferred to treatment with two tablets of Co-Betaloc, (a fixed combination of metoprolol, 100 mg, and hydrochlorothiazide, 12.5 mg) for a further six weeks. It was found that the blood pressure reduction, compared with placebo, was equivalent with metoprolol and hydrochlorothiazide (16/8 and 14/8 mm Hg), although the number of patients satisfactorily controlled was somewhat higher in the metoprolol group. When Co-Betaloc was given a further reduction in blood pressure was achieved in both groups (22/15 mm Hg compared with placebo), but the fall obtained with combination therapy was appreciably less than the theoretical maximum (30/16 mm Hg) deduced from adding the effects of the individual drugs.

Drs Barritt and Marshall also imply that the use of beta-blockers and diuretics in combination doubles the chances of producing unwanted side effects. On the contrary, the use of high-dose monotherapy often leads to dose-related side effects which may be minimised by the use of a fixed low-dose combination product. This was illustrated in a recently completed multicentre hospital trial with Co-Betaloc (to be published), in which 140 hypertensive patients were treated for eight weeks. In this study only two patients were withdrawn owing to side effects. One patient complained of cold extremities, which was not surprising in view of the fact that the study ran from October to April during the coldest winter for over a decade. The other patient experienced profound muscular weakness resulting from a fall in serum potassium concentration from 4.3 to 3.0 mmol(mEq)/l. However, it transpired that this patient was also suffering from chronic glomerulonephritis, and the symptoms of weakness disappeared

when the patient was transferred to a combination of metoprolol and the potassium-sparing diuretic amiloride.

Although one must be aware that combination therapy implies less flexibility and the consequent risk of over-treatment in patients who could have been satisfactorily treated with one of the components, this study indicates that a relatively low dose of hydrochlorothiazide in combination with metoprolol, given once a day, constitutes a simple, effective, and well-tolerated treatment for patients with essential hypertension.

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¹ Castenfors, J, and Danielsson, M, *Current Therapeutic Research*, 1979, 25, 228.

Routine exercise testing in angina pectoris

SIR,—Dr J A Raffo and others (4 August, p 295) have reported on the diagnostic value of routine exercise testing in hospital patients with angina pectoris. They claimed that their method "predicted the existence of radiologically demonstrable lesions with greater accuracy than other reported methods" and that "this improvement was achieved merely by carefully selecting the patients."

In their study 132 selected patients with angina pectoris underwent exercise testing on a bicycle ergometer. The results of tests on 32 patients were discarded because heart rate did not increase to 85% of the predicted or there was a lack of agreement in interpretation of the record. The results from the remaining 100 patients indicated that the response to exercise correlated well with abnormalities of the coronary arteries detected by angiography. Although this establishes the significance of an adequately performed exercise test, a fairer assessment of the clinical value of the test should include the 32 patients who were excluded. The results would then be less favourable.

We have assessed exercise testing in a similar group of patients but with a maximal treadmill test and a 12-lead recording system for the electrocardiogram.¹ Our study and those of others²⁻⁴ show that in patients with angina pectoris the sensitivity of the multilead exercise test is greater than that of single-lead systems. The use of multiple leads also has the advantages that the site of ischaemia can be localised and that multi-vessel disease is associated with abnormalities in a greater number of leads^{1 2} and with the sum of the ST segments in all leads.¹ This additional information is important since coronary artery bypass surgery may prolong life in patients with disease of all three coronary arteries or the left main coronary artery.

A 12-lead electrocardiogram during and after a treadmill exercise test is more expensive than a single-lead test because of the need for a three-channel recorder, the extra time needed to attach the electrodes, and the price of electrodes (£1.50 per patient). This cost is, however, relatively trivial when compared with that of cardiac catheterisation and coronary angiography. While agreeing with Dr Raffo and his colleagues that exercise testing is useful in the management of patients with angina pectoris, we believe that the additional information obtained from a

multiple-lead recording system is cost effective and provides greater accuracy in diagnosis than a single-lead system.

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¹ Baron, D W, Poole-Wilson, P A, and Rickards, A F, *British Heart Journal*, 1979, **49**, 364.

² Chaitman, B, et al, *Circulation*, 1979, **59**, 560.

³ Phibbs, B P, and Buckels, L J, *American Heart Journal*, 1975, **90**, 275.

⁴ Mason, R E, et al, *Circulation*, 1967, **26**, 517.

Increased production of urea and heart failure

SIR,—In a recent paper Dr Julia Lowe and her colleagues (11 August, p 360) concluded that the most common adverse reaction to frusemide is a reduction of the volume of extracellular fluid "manifested clinically or as a raised blood urea concentration." This assumes that the association between frusemide and a raised urea is one of cause and effect.

The most common cause of a raised plasma urea concentration in hospital patients is heart failure.¹ In a recent study² we confirmed the suggestion of Domenet and Evans³ that this rise in plasma urea was often due to an increased production of urea rather than a reduction in glomerular filtration rate.

We do not underestimate the potential seriousness of volume depletion. However, we suggest that increased production of urea has been largely ignored as a feature of heart failure, that it is a major factor in the rise in plasma urea in heart failure, and that it may explain the relation between plasma urea and prognosis in heart failure.³

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¹ Morgan, D B, Carver, M E, and Payne, R B, *British Medical Journal*, 1977, **2**, 929.

² Thomas, R D, Newell, A, and Morgan, D B, *Postgraduate Medical Journal*, 1979, **55**, 10.

³ Domenet, J G, and Evans, D W, *Quarterly Journal of Medicine*, 1969, **38**, 117.

Two geriatric cases

SIR,—I was interested in your article "Two geriatric cases" (30 June, p 1768), especially in the second case. But to my mind it is an amazing situation that brains are studied at necropsy and conclusions made without the arteries leading to the brain ever being examined. Despite the basic research done by Yates and Hutchinson,¹ the carotid and vertebral arteries are seldom examined at necropsy when the brain is found to be atrophied. These same pathologists would never think of passing an opinion on the cause of gangrene of the foot without examining the femoral arteries leading to the foot, and yet atrophy of the brain is equivalent to gangrene of the foot.

This matter is not simply academic, because if the cause of the atrophy of the brain is impaired circulation the treatment is certainly different. For instance, in the second patient mentioned in the article the carotid arteries may have been totally obstructed and that may have been the cause of the atrophy. My own research² has led to an effective way

of increasing the blood supply to the brain in many patients by the use of anticoagulant therapy, which in many of the patients has not only been able to arrest the course of the disease but has resulted in dramatic improvement.

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¹ Yates, P O, and Hutchinson, E C, *Cerebral Infarction: The Role of Stenosis of the Extracranial Cerebral Arteries*, Medical Research Council Special Report Series No 300. London, HMSO, 1961.

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Neutropenia associated with metronidazole

SIR,—Metronidazole is widely used in clinical practice and is particularly valuable in anaerobic infections. We have recently observed acute neutropenia occurring in a man on long-term azathioprine who was treated with metronidazole.

A 66-year-old man with pyoderma gangrenosum had been treated for three months with azathioprine, 150 mg daily. His white cell count remained normal during this period. Because of an offensive smelling slough at the margins of two skin lesions, anaerobic infection was suspected and he was started on metronidazole, 200 mg six hourly, for two weeks. By the end of this treatment his polymorph count had dropped from $3.0 \times 10^9/l$ to $1.78 \times 10^9/l$. Both drugs were discontinued and prednisolone, 10 mg daily, was commenced. The polymorph count fell further, to $1.2 \times 10^9/l$, seven days later, recovery occurring over the next 10 days. Azathioprine was then recommenced in a dose of 100 mg daily with no adverse effect on the white count.

Metronidazole is a nitroimidazole and chemically related to levamisole, an immunomodulating drug and a recognised cause of neutropenia. Metronidazole has been noted occasionally to cause a transient leucopenia, though not to the degree shown here.¹ It seems probable that the combined effect of azathioprine and metronidazole was responsible for the neutropenia in this case. Since patients on immunosuppressive therapy are more susceptible to infection requiring antibacterial chemotherapy it is important to monitor the white count closely in such patients during treatment with metronidazole.

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¹ Lefebvre, Y, and Hesseltine, H C, *Journal of American Medical Association*, 1965, **194**, 15.

Needle aspiration of the breast

SIR,—Commenting on the paper by Dr Helen L D Duguid and her surgical colleagues (21 July, p 185), Mr A John Webb considers that a 20-ml syringe is far more reliable than a 10-ml syringe to obtain an adequate yield in aspiration biopsy (25 August, p 491). It may be that, apart from other considerations, a 20-ml syringe is more convenient for his one-handed "braced-thumb" technique. However, it is not generally realised that, although it is possible to achieve an ejection pressure of several atmospheres when pushing a syringe plunger, it is physically impossible to achieve a

suction greater than 1 atmosphere when pulling the plunger. The suction is the pressure difference between the inside of the syringe and the environment and it is this pressure which drives the tissue sample into the needle.

Suction approaching the 1 atmosphere limit can be achieved with most sizes of syringe, but the required pull on the plunger to attain a given suction is directly proportional to the area of the syringe plunger—for example, a pull of about 29 N (6.4 lb force) on a typical 20-ml syringe, 16 N (3.7 lbf) on a 10-ml syringe, and 5.3 N (1.2 lbf) on a 2-ml syringe. It is futile to attempt to pull harder.

The suction attained depends on the presence of any water in the syringe, on the dead volume (that is, the air present in the system before suction is commenced), and on any leakage past the plunger. If there is even a tiny amount of water in the syringe, the maximum suction is limited to 98% of atmospheric pressure owing to water vapour pressure in the syringe (17 mm Hg at 20°C). Syringes of 20 ml, 10 ml, and 5 ml can readily attain a suction of 98% atmospheric pressure. The dead volume of a fully closed syringe fitted with a needle is in the range 0.05 to 0.15 ml, and this affects the suction achievable with 2-ml and 1-ml syringes, but only slightly (97% and 93% of atmospheric pressure respectively). With such small dead volumes, progressive withdrawal of the plunger has a rapidly diminishing effect on the suction produced. The dead volume is sometimes deliberately increased by partially withdrawing the syringe plunger before connecting the needle in order to give better control over the suction applied. This is particularly useful, for example, in reducing haemolysis when sampling venous blood. However, increasing the dead volume does reduce the maximum attainable suction and is therefore undesirable in tissue biopsy. Leakage occurring at the syringe plunger could significantly reduce the suction, but this is unlikely to be a problem with new syringes.

Flow of material up the aspiration needle and into the syringe is dependent on the suction; but, as shown above, this suction is limited, and the flow rate is much more dependent on the bore (and length) of the needle and on the nature of the material.

Syringe size should be chosen to suit the handling technique employed. The use of a larger syringe will not significantly increase the amount of suction.

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Smallpox vaccination

SIR,—On 8 September, p 617, you proclaimed a triumph for epidemiology: the elimination of smallpox from the globe. Then, two years after the last recorded case of smallpox, you announced the imminent availability of a freeze-dried vaccine, which might suggest we are unlikely to be startled by the slamming of the door after the bolting of the proverbial horse (or might it be a calf or "vacca"?).

I wonder how many dozens of millions of doses of glycerinated calf lymph have been used to vaccinate mankind since its inventor, S Monckton Copeman, presented its virtues before the Royal Society in the summer of