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.

² Walsh, A C, and Walsh, B H, *Journal of the American Geriatric Society*, 1969, **17**, 477.

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