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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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

1893, 100 years after Jenner's pioneering cowpox experiments in the English countryside. My grandfather would have been gratified to learn that his method for purifying the lymph containing the virus had remained essentially the same for almost another century (surely a medical therapeutic record?). During this time one of the most loathsome of communicable diseases has been extirpated and is medical history. Those of us from the medical schools of St Thomas's and Westminster, where Monckton Copeman was student and pedagogue, have another reason to be proud.

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High-carbohydrate diets and insulin-dependent diabetics

SIR,—I read with interest the article "High-carbohydrate diets and insulin-dependent diabetics" by Dr R W Simpson and others (1 September, p 523).

It is possible that the improvement noted in the 24-hour blood glucose concentrations and the other parameters of diabetic control noted in the diabetics on the high-carbohydrate diet may have been due to a difference in the fibre content of the two diets. A valid conclusion on the beneficial effects of a high-carbohydrate diet in diabetics in this study could be drawn only if the fibre content of the two diets was known to be equal, as dietary fibre content is known to be relevant in diabetic control.

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Pathogenetic mechanisms in legionnaires' disease

SIR,—Your recent leading article on legionnaires' disease (14 July, p 81) indicates an emerging picture of a multisystem disease that attacks the lungs and often involves several tissues and parts of the body. We, like others,¹ have suggested an endotoxin (or an endotoxin-like substance) as a possible pathogenetic mediator of these multiple changes.

Many described manifestations (for example, high fever, profound hypotension, propensity to acute renal failure, hepatic abnormalities, gastrointestinal disturbances, neurological disorders, thrombocytopenia, and sometimes disseminated intravascular coagulation) are characteristic also of endotoxin shock. On the other hand, from some recent work²⁻⁴ there is increasing evidence that *Legionella pneumophila* possesses some of the in-vivo and in-vitro biological properties associated with Gram-negative bacteria (that is, pyrogenic response, *Limulus* gelation, Shwartzman skin reaction) even if with different potency.⁵ There are difficulties in correlating the endotoxin content of Gram-negative organisms during infection with the pathological effects, but this does not mean that no correlation exists.⁶ Unfortunately, as in the case described by Edelstein *et al*,¹ despite the bacteraemia one cannot assume this correlation without endotoxin assay.

Further detailed investigations are necessary

to characterise more clearly the biochemical profile⁷ and the biological properties⁸ of the bacterium and to determine whether the endotoxin acts independently or collaborates with other bacterial products, so increasing the damage to the host. In this connection, some recent findings concerning an exotoxin activity⁹ offer a challenge for future research: a complex interaction between endotoxin and haemolysin (suggested as the pathogenetic mechanism in *Aeromonas* infection¹⁰) might trigger disease production. Solving the problem of bacterial products could lead to an assessment of the immunological aspects of the disease. Finally, new stratagems for increasing host defences may emerge from such researches—which could also result in the eventual development of a safe, active, and effective immunogenic procedure to protect against the disease.¹¹

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¹ Edelstein, P H, Meyer, R D, and Finegold, S M, *Lancet*, 1979, **1**, 750.

² Fumarola, D, *Bollettino dell'Istituto Sieroterapico Milanese*, 1978, **57**, 680.

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⁴ Fumarola, D, *IRCS Medical Science*, 1979, **7**, 304.

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⁶ Shands, J W, *jun*, *Microbiology*, 1975, **2**, 330.

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⁹ Baine, W B, *et al*, *Journal of Clinical Microbiology*, 1979, **9**, 453.

¹⁰ Rigney, M M, Zilinsky, J W, and Rouf, M A, *Current Microbiology*, 1978, **1**, 175.

¹¹ Wong, H K, *et al*, *Seventy-ninth Annual Meeting of the American Society for Microbiology* (Los Angeles, 1979), abstract E(H)3, p 78.

Gastric and duodenal ulceration after burns

SIR,—Without sufficiently differentiating between ulceration of the stomach and of the duodenum after burns, your leading article (1 September, p 512) states that the condition is common. We would agree that superficial gastric erosions commonly occur in the early days after burn injuries but these rarely give rise to serious complications. The dangerous lesions are the deeply penetrating ulcers of the duodenum and these alone should be termed Curling's ulcers. It is difficult to know the incidence of this ulcer in patients who survive burn injuries, but what we can say with certainty is that the number of patients who show clinical evidence of Curling's ulceration during life is very small indeed.

In an extensive inquiry in this country in 1974¹ we found that only 18 examples of severe gastroduodenal haemorrhage had occurred during the treatment of over 32 000 children and adults in 13 centres treating major burns. An extensive search of the literature showed that in reports of over 14 000 patients treated in Denmark, Sweden, Italy, and Czechoslovakia the incidence of alimentary haemorrhage was 0.2%.

You contrast these low European figures with the much higher incidence of haemorrhage and perforation (11.7%) reported from the United States Army Burns Centre in Texas and consider this difference to be unexplained. It is worth noting that the centre does not admit children or women² and it seems likely that it admits a highly selected population of severely burned men, so perhaps this very

high figure is not representative of burned patients in general.

There is at least one other possible reason for the difference in incidence in this country and in the United States. In Britain it is general policy to give relatively large volumes of colloid during early fluid replacement, whereas in the USA the policy is to give large volumes of electrolyte solution with little or no colloid. This latter type of management is often associated with low blood volumes and a high haematocrit and blood viscosity.³ These are conditions likely to be associated with poor blood flow in the visceral microcirculation, which must increase the likelihood of gastroduodenal ulceration.⁴

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¹ Muir, I F K, and Jones, P F, *British Journal of Surgery*, 1976, **63**, 60.

² McAlhany, J C, Czaja, A J, and Rosenthal, A, in *Burns—A Team Approach*, ed C P Artz, J A Moncrief, and B A Pruitt, p 513. Philadelphia, Saunders, 1979.

³ Moyer, C A, and Butcher, N R, *Burns, Shock and Plasma Volume Regulation*, p 262. St Louis, Mosby, 1967.

⁴ Friesen, S R, *Surgery*, 1950, **28**, 123.

Offspring of phenylketonuric parents

SIR,—Professor D Kutter and Dr J Thoma in their paper "Management of maternal phenylketonuria" (PKU) (28 July, p 272) raise an interesting problem, if I understand the figures from their world literature review correctly. Fourteen homozygous offspring from 62 pregnancies (if that is what they mean), on the assumption that the homozygous parents chose mates at random, would imply a carrier rate of nearly one in 2.2, which is clearly absurd as this would give an incidence of PKU in the general population of about one in 20.

There are at least three other possible explanations (separately or in combination) for their review figures: (a) The literature has under-reported cases of PKU parents producing normal (heterozygous) offspring. (b) Assortative mating has occurred, possibly on the basis of olfactory discrimination, or (as with the deaf) by meeting in select social groups such as clinics. (c) Incest has occurred at least in some cases.

The first possibility is highly likely unless all the review cases were selected before the birth of the offspring. The second possibility is more speculative. The third possibility is not as improbable as one might at first suspect, particularly in the case of dull or mentally handicapped mothers. Although hard evidence on this point is difficult to come by, I suspect that incest between fathers and mentally handicapped daughters (and perhaps also brothers and mentally handicapped sisters) is not rare. As in the case of child abuse, objective possibilities may be overlooked because of naive assumptions about family behaviour.

The four PKU fathers producing three homozygous offspring are, despite the small numbers, most interesting. The mates are obviously identified and therefore their genotype should be known. If, as expected, they are heterozygous and are not blood relatives, then selective reporting or assortative mating (or both) must be operating. Only prospective studies can determine the true incidence of PKU offspring of PKU parents,