correlation between the vaginal hormonal state and the body weight. During treatment (which was nutritive, not hormonal) in all but one case there was a significant alteration in the vaginal hormonal cytological pattern in that appearance of a cyclic character could be demonstrated although menstruation had not yet returned.¹ We find this method very useful, particularly as it can be repeated frequently.

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¹ Bosze, P., and Oö, M., *Magyar Noorvosok Lapja*. In press.

Cryotherapy for piles

SIR,—In the past three years reports have appeared of the management of piles by cryotherapy, the claims being that treatment could be carried out in an outpatient department or consulting room; that, being painless, anaesthesia was unnecessary; that subsequent morbidity was minimal; and that complete symptomatic relief was almost invariable.^{1,2}

By courtesy of a grant from the East Anglian Regional Health Authority I have been able to test the effect of cryotherapy on piles. The apparatus is expensive—£600 or more. Liquid nitrogen is the cooling agent and at the probe tip a temperature of -180°C is achieved. Exposure of tissue to this temperature for about half a minute or less produces an inflammatory reaction but, usually, not necrosis. Exposure for long periods kills tissue and this is necessary to produce an appreciable effect on piles. A slough forms and is shed in due course, leaving an ulcer which heals by granulation and epithelialisation. An uninfected lesion on normal skin, about 1 cm diameter, was not completely healed until around the 56th day. In the anal canal infection always occurs and healing takes rather longer.

External piles can be treated by cryotherapy without anaesthesia. Freezing is followed by first a watery then a purulent discharge; the piles slough and become very smelly and rather tender. The patient is advised to have daily warm baths and wear an anal pad. After about six weeks the reaction has subsided and the external skin tags will have disappeared.

I have been unable adequately to expose internal piles for application of the probe without dilating the anal sphincter and inserting a speculum. For this day-case anaesthesia or very heavy sedation is necessary. Following application of the probe internal piles slough and are eventually shed. There is considerable discomfort, amounting frequently to pain. Patients remain in bed or away from work for from three to seven days. In all respects the clinical course is not dissimilar from that following spontaneous thrombosis of piles and the amount of analgesic sedation needed is comparable. After six weeks or so the end result is good and I have had no serious complications in 10 cases.

My impression from this investigation is that this is a cumbersome and expensive method of treatment. Pain, morbidity, and time incapacitated are no less, and in many cases longer, than can be achieved by other modern methods. For the conservationists this is manual dilatation of the anus.³ For

abolitionists like myself it is rubber-band ligation for small to moderate internal piles,⁴ while for internal piles which are either very large, covered with squamous metaplasia, or fibrosed by previous thrombosis a conservative excision using multiple transfixion ligatures for each pile is used.⁵ Careful use of these techniques and good judgment in the selection of method have produced results which, by all criteria, are equal to or better than those achieved by cryotherapy.

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- ¹ Lewis, M. J., *Diseases of the Colon and Rectum*, 1972, 15, 128.
- ² Lloyd Williams, K., Haq, I. V., and Elm, B., *British Medical Journal*, 1973, 1, 666.
- ³ Lord, P. H., *British Journal of Hospital Medicine*, 1973, 9, 347.
- ⁴ Barron, J., *American Journal of Surgery*, 1963, 105, 63.
- ⁵ Tagart, R. E. B., *Practitioner*, 1974, 212, 221.

Perforation of small intestine and Slow-K

SIR,—Dr B B Scott (13 September, p 649), commenting on our case report (26 July, p 206), draws attention to the often described ulcers of the small bowel which are believed to occur secondary to vascular disease.

Unfortunately our case report had to be pruned to meet the requirements for publication as a "short report" (4 October, p 6). Originally it included a longer report of the operative findings, including the facts that no arterial disease was apparent in the mesenteric vessels (which were easily inspected as there was little fat) and that histological examination showed no evidence of arteriolar disease, the factor cited in the sources quoted by Dr Scott. We note with interest that the authors of one of these papers¹ were attempting to cast doubt on what was to become a well-recognised association between enteric-coated potassium preparations and small-bowel ulceration.

We feel that in the absence of any other demonstrable intestinal disease in our patient, and bearing in mind the known risk of ulceration with Slow-K, the perforation we described was undoubtedly due to Slow-K.

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¹ Alexander, H. C., and Schwartz, G. F., *Gastroenterology*, 1966, 50, 224.

Prostaglandins and carcinoid tumours

SIR,—We read with great interest the case report by Dr J A Barrowman and others of high serum levels of prostaglandins in a case of thyroid medullary carcinoma (5 July, p 11). We have recently observed a patient who had a bronchial carcinoid tumour and very high levels of serum prostaglandins.

A 50-year-old woman had a bronchial carcinoid tumour with diffuse hepatic metastases and classical symptoms of the carcinoid syndrome. She had a permanent flush with exacerbations accompanied by profuse lacrimation and periorbital oedema. The biochemical findings were typical, with elevated serum serotonin ($3.7\text{ }\mu\text{mol}$ (0.65 mg)/l) and 5-hydroxyindole acetate in the urine ($502\text{ }\mu\text{mol}$ (96 mg)/24 h). The diarrhoea was watery in

consistency without increase in transit time, varied between 1 and 2 litres/day, and was not influenced by antiserotonin therapy (parachlorophenylalanine, cyproheptadin).

This watery diarrhoea precipitated a severe hypokalaemia with a plasma potassium level of only 1.8 mmol (mEq)/l. Levels of 3 mmol/l were never exceeded despite intravenous and oral potassium supplements of 250 mmol/day . The diarrhoea was associated with a low gastric acid secretion following pentagastrin stimulation.

There were two possible explanations for this syndrome: (1) An associated amine precursor uptake and decarboxylation tumour, but pancreatic angiography, thyroid scan, and estimation of different polypeptide hormones (vasoactive intestinal protein, thyrocalcitonin, gastrin, insulin) proved negative and no other associated tumour was found on thorough search at necropsy. (2) The secretion of a substance such as prostaglandins (PGs) by the tumour or its metastases. The plasma PG levels (in ng/l), which were measured by radioimmunoassay (Dr Dray), were as follows (normal ranges in parentheses): PGE, 18 (4.3 ± 1.4); PGE₂, 120 (4.5 ± 1); PGF₂, 86 (7.5 ± 2).

It appears from the above result and those of Sandler *et al*¹ that some carcinoid tumours secrete PGs as can other tumours such as medullary carcinoma of the thyroid.² This clinical syndrome—permanent flush, diarrhoea by hypersecretion, and gastric hypochlorhydria—is compatible with the known effect of these fatty acids.^{3,4}

It is worth mentioning that this clinical picture is particularly common in bronchial tumours.⁵ So it would appear to be worth while to estimate the plasma PG levels in cases of carcinoid tumour derived from the foregut and, when appropriate, to treat the profuse diarrhoea with PG inhibitors (indomethacin, aspirin).

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¹ Sandler, M., Karim, S. M. M., and Williams, E. D., *Lancet*, 1968, 2, 1053.

² Williams, E. D., Karim, S. M. M., and Sandler, M., *Lancet*, 1968, 1, 22.

³ Matuchansky, C., and Bernier, J. J., *Gastroenterology*, 1973, 64, 1111.

⁴ Milton-Thompson, G. J., *et al*, *Gut*, 1975, 16, 42.

⁵ Melmon, K. L., Sjoerdsma, A., and Mason, D. T., *American Journal of Medicine*, 1965, 39, 568.

Gentamicin nephrotoxicity in patients with renal allografts

SIR.—Mr J M Wellwood and his colleagues (2 August, p 278) suggest that gentamicin has deleterious effects on renal function in patients with renal allografts. We have found gentamicin to be of considerable value in the management of sepsis in the immunosuppressed renal transplant recipient and we would not wish its value to be undermined on scanty evidence. We agree that gentamicin causes ultrastructural changes in both mice and men and that urinary enzymes as studied by these authors are probably associated. However, we would challenge their view that gentamicin affects renal function significantly in any permanent way. An alternative cause—namely, transplant rejection—is discussed by the authors but they present no evidence to refute this possibility. This is surprising in view of their previous publication¹ in which they state that urinary N-acetyl β-D-glucosaminidase was abnormally high in 94% of transplant rejection episodes. In their present series the indication for gentamicin therapy in 8 of 19 cases was undiagnosed pyrexia—a phenomenon often

Effect of gentamicin on renal function (creatinine clearance) in six oliguric patients (left-hand column) and 23 patients with stable renal function (right-hand column).

associated with transplant rejection. The authors give no indication as to the renal pathology in four patients whose function deteriorated to such an extent that they required graft nephrectomy or dialysis but implied that gentamicin was the causative agent.

We suggest that there is a wide gap between the electron microscopic changes and urinary enzyme alterations induced by gentamicin and renal failure which progresses to graft nephrectomy or dialysis. The implication that gentamicin is involved in the process of total graft failure without the renal biopsy exclusion of transplant rejection is a serious one which we feel these authors have not supported with concrete evidence.

Our experience with gentamicin, guided by frequent monitoring of blood levels, has been quite different. Twenty-nine transplant patients have been treated with gentamicin, six being initially oliguric and 23 having stable renal function at different levels. The figure shows that renal function remained very low in only one oliguric patient and that in only two of the other 23 patients was there a fall in creatinine clearance during gentamicin therapy. In all three patients renal biopsy showed that the deterioration was due to severe rejection.

Taking our own results into account, we conclude that gentamicin is not a nephrotoxic drug in renal transplant patients, provided it is prescribed using a suitable nomogram and with frequent monitoring of blood levels.

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1 Wellwood, J M, et al, *British Medical Journal*, 1973, 2 261.

Heparin and acute renal failure

SIR,—The study by Dr E A Ribes and others (27 September, p 745) is of value in emphasising the hazards of full-dose heparin anticoagulation, particularly in high-risk patients, and in pointing out that obvious disseminated intravascular coagulation (DIC) carries a poor prognosis. I feel that certain comments would be of help to the general reader.

(1) The loading dose of heparin used in this study was exceptionally large.

(2) Even those who are heparin enthusiasts would be careful with obstetric, traumatic, and certain types of surgical patient. If a patient dies of a complication one cannot tell whether in that case the heparin would have been of benefit.

(3) The authors used the criteria of Colman¹ for DIC—namely, platelet count $\leq 150 \times 10^9/l$ ($\leq 150,000/mm^3$) prothrombin time ≥ 15 s, and fibrinogen ≤ 1.6 g/l (≤ 160 mg/100 ml). It is necessary to point out that these criteria select only the florid cases of DIC. Using the radiofibrinogen catabolism study I find that the catabolic rate can be increased to twice normal before coagulation criteria start to be abnormal. Indeed, the radiofibrinogen study shows that some DIC is a concomitant of almost all types of acute renal failure² and that severe DIC is commonly the result of septicæmia³ or endotoxinaemia.⁴

(4) If indeed endotoxinaemia was the principle explanation for the very high mortality in this series, then it is probably quite valid to claim that heparin only prevents cortical necrosis. In animal experiments heparin has to be in the circulation before the endotoxin for there to be any benefit. What we do not yet have are adequate endotoxin neutralising agents.⁴

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1 Colman, R W, Robboy, S J, and Minna, J D, *American Journal of Medicine*, 1972, 52, 679.

2 Wardle, E N, *Quarterly Journal of Medicine*, 1973, 42, 205.

3 Wardle, E N, *Scandinavian Journal of Infectious Diseases*, 1972, 4, 155.

4 Wardle, E N, *Quarterly Journal of Medicine*, 1975, 44, 389.

Multiple factors in the hyperlipidaemia of hypervitaminosis D

SIR,—The interesting report of an inverse correlation between serum triglyceride and calcium levels in subjects over 60 by Dr Marianne Schroll and others (26 July, p 226) does not negate the epidemiological correlation of moderate hypervitaminosis D with increased serum cholesterol reported by one of us (12 April, p 87). Clinical studies of the hyperlipaemic effects of vitamin D in healthy adults¹ are in accord with the hyperlipaemia seen in infantile hypercalcaemia,² associated with hyperreactivity to vitamin D,³ and with hypervitaminosis D in rodents.^{4,5}

Hypocalcaemia can be caused not only by vitamin D deficiency but also by magnesium deficiency. A syndrome of hypomagnesaemia-hypocalcaemia that is unresponsive to administration of either vitamin D or calcium until the magnesium deficit is repaired has been reported in neonatal infants and in adults with chronic magnesium loss or malabsorption.⁶ Magnesium deficiency has been associated with hyperlipaemia,⁶ and vitamin D excess causes magnesium loss.⁷ It is possible that magnesium deficit may have contributed to the hypertriglyceridaemia of the hypocalcaemic patients reported by Dr Schroll and her colleagues.

The lower serum lipids in patients with higher serum calcium levels suggests that they may have been on diets rich in calcium. Calcium has been shown to interfere with fat absorption, thereby lowering blood cholesterol.¹ However, in a study⁸ of dietary and serum minerals and lipids in hard- and

soft-water cities in Great Britain and the United States serum cholesterol and triglycerides were found to be higher in residents of both cities (London and Omaha) with hard water, despite the lower rates of ischaemic heart disease (IHD) there, than they were in the cities with soft water (Glasgow and Winston-Salem). In neither London nor Glasgow was the serum calcium high (2.14 and 2.18 mmol/l (8.57 and 8.70 mg/100 ml)). In both American cities the serum calcium was higher—particularly in the hard-water city (2.59 and 2.40 mmol/l (10.37 and 9.59 mg/100 ml)). Residents of both hard-water cities had higher serum magnesium levels than those of their paired soft-water cities. The difference was significant in Great Britain. (London/Glasgow, 1.25/1.07 mmol/l (2.50/2.14 mEq/l); Omaha/Winston-Salem 1.05/1.0 mmol/l (2.10/2.01 mEq/l.)) Whether the generally higher intake of calcium and vitamin D in milk in the United States than in Great Britain a contributory factor should be explored.

The possibility that magnesium deficiency might contribute both to the hyperlipaemia and the cardiovascular lesions of infantile hypercalcaemia and that deficiencies of vitamins A, B₆, and E might also participate was suggested in 1960.⁹ Reviewed elsewhere¹⁰ is further evidence that susceptibility to vitamin D excess may be intensified by deficiencies of other vitamins and of magnesium.

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1 Lindén, V, *Scandinavian Journal of Social Medicine*, In press.

2 Forfar, J O, et al, *Lancet*, 1956, 1, 981.

3 Seelig, M S, *Annals of the New York Academy of Sciences*, 1969, 147, 537.

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5 Hass, G M, et al, *American Journal of Pathology*, 1961, 38, 289.

6 Seelig, M S, and Heggveit, H A, *American Journal of Clinical Nutrition*, 1974, 27, 59.

7 Seelig, M S, in *Proceedings of First International Symposium on Magnesium Deficit*, Vitell, France, 1971, ed J Durlach, vol 1 p 11.

8 Berenbaum, M L, et al, *American Journal of Public Health*, 1973, 63, 169.

9 Dalderup, L M, *Voeilng*, 1960, 21, 424.

10 Lindén V, in *Proceedings of the Annual Meeting of the American College of Nutrition*, 1975, ed M S Seelig, New York, Spectrum Press. In press.

"Sectorisation" in psychiatric hospitals

SIR,—I cannot allow to pass without comment Dr D A Spencer's letter (4 October, p 39) in which he questions the practicability and clinical propriety of the principles involved in sectorisation. Leaving aside the sinister connotation which he senses in implied bureaucratic and dictatorial clinical direction (increasingly I wonder whether imputation of this nature is not a means of rationalising absence of desirable initiative on the part of clinicians who should be prompting change), it seems to me totally logical and to the benefit of patients that the large psychiatric hospital should be organisationally dismembered, allowing relatively discrete communities in what is so often a catchment area with extraordinary