radius or ulna, or both. Head injuries comprised one case of concussion, seven lacerations of the face or scalp, and three contusions. Six patients were admitted as acute cases: two with fractures of the tibia and fibula, one with a compound fracture of the radius and ulna, one with a possible infective arthritis secondary to an infected abrasion, one with a head injury, and one with a fractured femur. In this same department this winter during the nine-day spell of snow there were over 50 attendances and eight admissions due to sledging accidents.

These injuries are as nothing when compared with the 154 admissions over a two-year period at the Radcliffe Infirmary, Oxford, which were due to horse-riding accidents.¹

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¹ Barber, H M, *British Medical Journal*, 1973, 3, 532.

Bleeding gastric erosion after oral zinc sulphate

SIR,—We were very interested to read Dr Ray Moore's report (25 March, p 754) of a case of bleeding gastric erosion following oral zinc sulphate therapy. It is reasonable to suggest that this complication was a direct irritant effect of the zinc salt given during the previous week. Zinc chloride is a very powerful caustic and is likely to be formed by the action of gastric hydrochloric acid on zinc sulphate whether given as capsules or effervescent tablets. However, we believe that the time of administering this drug in relation to meals could have been more important than the form in which it was dispensed. The occurrence of epigastric discomfort after each capsule in Dr Moore's patient would suggest that zinc was taken on an empty stomach.

Patients should always be instructed to take zinc only after meals. In our department, where this is the practice, there have been no side effects in patients receiving zinc sulphate either in capsule form (Zincomed) or in a syrup. Patients with acrodermatitis enteropathica have been maintained trouble free on this therapy for the last four years.

Recently there has been evidence to show that food, particularly bread, binds with inorganic zinc.¹ This could be significant in minimising the irritant effect of zinc salts during their transit in the highly acidic medium of the stomach.

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¹ Ismail-Beigi, F, *et al*, *American Journal of Clinical Nutrition*, 1977, 30, 1721.

Factors affecting length of hospital stay

SIR,—With reference to Mr R Hole's letter (25 March, p 789), in which he questions the value of studying the duration of hospital stay, it is well recognised that this varies according to the idiosyncrasies of the surgeon¹ as well as the day of week of operation and age and sex of the patient. However, it may not be a question of just "a day or two longer."

In a study of 1426 cataract operations in seven area health authorities in Wales in 1975, using the Hospital Activity Analysis, I found that the mean duration of stay for men ranged

from 8.9 days in South Glamorgan to 17.0 days in West Glamorgan, and that for women ranged from 7.8 days in Gwynedd to 25.4 days in West Glamorgan. The recommended length of stay is of the order of six days.²⁻⁴ There is a low incidence of complications after cataract surgery,^{3,5} and it is difficult to account for these differences: it seems unlikely that patients benefit from prolonged hospitalisation in this instance. Indeed, one ophthalmologist³ has suggested that old people are suffering "merely by virtue of the fact that they were in hospital."

The cost of cataract surgery in Wales, based on the cost per inpatient week,⁶ ranged from £155 per patient in Gwynedd to £504 per patient in West Glamorgan, and the total cost for Wales in 1975 was nearly £400 000. This may not be a very large amount in relation to the total NHS expenditure, but there must be other fields in which there are elective surgical procedures for which there are similar discrepancies in the duration of stay in hospital. Mr Hole is alarmed at the cost of collecting the information on which such studies are based, but data are already being collected for the Hospital Activity Analysis on HMP 1 forms. Perhaps the administrative costs of utilising this available information might be outweighed by the reduction in cost per patient for an elective procedure; there must be some hospital administrators who earn less than the £214 per inpatient per week cost in 1975 in the University Hospital of Wales.

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¹ Dugmore, W N, and Raichand, M, *British Journal of Ophthalmology*, 1972, 56, 671.

² Mills, P V, *Transactions of the Ophthalmological Society of the United Kingdom*, 1972, 92, 637.

³ Jackson, C R S, *Transactions of the Ophthalmological Society of the United Kingdom*, 1967, 87, 779.

⁴ Galin, M A, *et al*, *Transactions of the Ophthalmological Society of the United Kingdom*, 1975, 95, 42.

⁵ Strachan, I M, and Bowell, R E, *Transactions of the Ophthalmological Society of the United Kingdom*, 1972, 92, 629.

⁶ Welsh Office, *Health and Personal Social Services Statistics for Wales*, No 3. Cardiff, HMSO, 1976.

Recurrent aphthous ulceration and jejunal biopsy

SIR,—Surprised at the report of the high incidence of coeliac disease in patients with aphthous stomatitis,¹ we obtained biopsies of the jejunum with a Crosby capsule in 26 patients who had had recurrent aphthous ulceration for 1-40 years, most for more than eight years. Two had major ulceration with multiple scars. There were no other complaints of alimentary origin. Half of the patients were referred from the Edinburgh Dental Hospital.

Each biopsy specimen was examined by conventional histology, intraepithelial lymphocytes were counted,² and concentrations of disaccharidases were measured. Of the 26 biopsies, in only one was there villous atrophy with an increase in intraepithelial lymphocytes. There was also no maltase, and lactase concentrations were reduced. One patient with rosacea had no sucrose and low lactase concentrations.³

The patient with villous atrophy was a 14-year-old girl. She had had mouth ulcers for nine years. Serum and red cell folate, serum B₁₂, and iron concentrations and iron-binding capacity were all normal. After five months on a gluten-free diet there was no change in her mouth ulcers.

Our results do not confirm the importance of performing a jejunal biopsy in patients with aphthous stomatitis as previously suggested,

and there seems little justification in routinely subjecting aphthous ulcer patients to this procedure.

We are grateful to Mr I T MacPhee for permission to study patients under his care.

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¹ Ferguson, R, *et al*, *British Medical Journal*, 1976, 1, 11.

² Ferguson, A, and Murray, D, *Gut*, 12, 988.

³ Paton, E, Murray, E, Watson, W C, *British Medical Journal*, 1966, 1, 459.

Vincristine-induced neuropathy in lymphomas

SIR,—The article by Drs Sylvia M Watkins and J P Griffin (11 March, p 610) on vincristine-induced neuropathy compares the incidence found in 23 patients with lymphoma and 37 with other malignant disease. This second group, however, is very heavily weighted by the inclusion of 23 female patients with breast cancer, while there is the expected male preponderance among the lymphomas, 18 male patients versus 5 female patients.

It would be interesting to know the incidence of vincristine neuropathy in the two sexes, since this factor on its own might account for the difference between the lymphomas and the other group.

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Haemodialysis during cyclophosphamide treatment

SIR,—We are interested in the report by Drs R A V Milsted and M Jarman (1 April, p 820) but cannot agree with their conclusions. From the six pairs of data for plasma concentration and dialysate concentration of cyclophosphamide it is possible to calculate the dialysis clearance of unmetabolised drug. This is 78 ml/min.

The total amount of drug cleared during the six-hour dialysis can also be calculated by integration of the area under the dialysate concentration/time curve for cyclophosphamide and multiplying by the dialysate flow rate. This is calculated as 429 mg in the six-hour period or 71.5% of the 600 mg dose (calculations available from MRB). Thus, although the concentration of unmetabolised cyclophosphamide in dialysate is an order of magnitude lower than the concentration in plasma, the total clearance is very high. This apparent anomaly is dependent on the high flow rate of dialysate used in a Gambro 1 m² dialyser (21-36 l/h).

Milstead and Jarman found a plasma half life of cyclophosphamide of 2 h 35 min for their patients on dialysis.¹ Bagley *et al*² report a mean plasma half life of cyclophosphamide of 6.45 ± 1.1 (range 3.9-8.2) hours in twelve of their patients on no other treatment. These patients had normal renal function. Only two of their 43 patients had a half life of less than 2 h 35 min and both of these had been receiving diphenylhydantoin prior to the study.

In our opinion, the short half life of cyclophosphamide of this one patient on haemo-

dialysis¹ is most likely to be due to the high dialysis clearance of unmetabolised drug. This also explains why the peak plasma level of cyclophosphamide is within the range previously reported in patients with normal renal function.³

The action of cyclophosphamide depends on biotransformation in the liver⁴ to aldophosphamide⁵ and other active metabolites with alkylating activity. For a given dose, in a patient with chronic renal failure we would predict much higher plasma availability of both cyclophosphamide and active metabolites on days when the patient was not on dialysis. These observations have particular relevance to the renal transplant patient being given cyclophosphamide as immunosuppression.

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¹ Milstead, R A V, and Jarman, M, *British Medical Journal*, 1978, **1**, 820.

² Bagley, C M, Bostick, F W, DeVita, V T Jun, *Cancer Research*, 1973, **33**, 226.

³ Jarman, M, et al, *Clinical Chimica Acta*, 1975, **58**, 61.

⁴ Brock, N, and Hohorst, H J, *Arzneimittel-Forschung*, 1963, **13**, 1021.

⁵ Hill, D L, Laster, W R Jun, Stuck, R F, *Cancer Research*, 1972, **32**, 658.

Staphylococcus aureus in raw human milk for neonates

SIR,—Dr A Lucas and others (25 March, p 781) understandably take us to task on the subject of acceptable limits for *Staphylococcus aureus* in raw human milk.

We should like first to point out that, unfortunately, an error appeared in our paper (18 February, p 393). Under the heading "Raw milk" on p 395 we give three main criteria for the acceptance of human milk to be fed raw. The second of these appears as: "It should not contain more than 10×10^5 colony-forming units of *Staphylococcus aureus*/l." The figure of 10×10^5 is repeated twice more in the same paragraph. In all three cases it should be 10^5 colony-forming units/l (that is, 10^2 /ml). After experience with more sensitive methods, we eventually chose to use a screening test employing a standard loop (0.01 ml of milk), with the result that 10^5 colony-forming units/l is the lower limit of sensitivity of our method.

It is not easy to obtain human milk that does not contain small numbers of *Staphylococcus aureus*. The organism is hardly likely to be derived from the alimentary tract since it is not a common intestinal pathogen, and its presence therefore would not indicate the likelihood of faecal contamination, which is the case with the enterobacteria. In addition, there are good reasons for thinking that all human milk possesses antistaphylococcal properties.¹ The protective effect of human milk against *Staphylococcus aureus* may extend throughout the gut of breast milk fed infants, since in a study of the faecal flora of seven-day old full-term breast fed infants *Staphylococcus aureus* was much less frequent as a significant component of the faecal flora than in an equivalent group of formula-fed infants (5% as against 34%).² It is well known that a high proportion of newborn infants rapidly become nasal carriers of *Staphylococcus aureus*³ and small numbers of these organisms must

normally pass into the intestinal tract. These factors convince us that the feeding of carefully selected raw milk containing at most only small numbers of this organism is unlikely to present a hazard to the infant's health. We would agree, however, that further investigative work is necessary to clarify the situation more fully.

Our reasons for using raw milk are partly nutritional and partly immunological. Pasteurisation, it is true, preserves part of the antimicrobial components of milk, but these are more fully retained when untreated breast milk is deep frozen.⁴ It is difficult to reconcile the misgiving of Lucas *et al* that immunological properties retained by raw milk may on the one hand be deleterious and yet be beneficial if the milk is pasteurised. It is also difficult to be sure of what "foreign (? undesirable) cellular components" (apart from a strictly defined number of bacteria) are present in deep-frozen raw milk that are not found in pasteurised milk.

We feel that, until proved otherwise, careful collection methods and bacteriological surveillance such as those we advocate should be rigorously applied by anyone thinking of establishing a milk bank. Reliance on pasteurisation itself to render the milk safe may not be adequate if bacteriological screening is postponed until after the procedure. Unless one can be reassured by prior screening that the count of *Staphylococcus aureus* in the milk is low prior to pasteurising, enterotoxin production may constitute a cause of unexpected gastrointestinal problems such as those we are all trying to avoid.

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¹ Gyorgy, P, *American Journal of Clinical Nutrition*, 1971, **24**, 970.

² Hewitt, J H, and Rigby, J, unpublished observations.

³ Williams, R E O, et al, *Hospital Infection*, 2nd edn, p 54. London, Lloyd Luke, 1966.

⁴ Evans, T J, et al *Archives of Disease in Childhood*, 1978, **53**, 239.

* * * We regret that " 10×10^5 " arose through an error in proof correction.—Ed, *BMJ*.

Histocompatibility antigens and urinary tract abnormalities

SIR,—The observations of Drs R R Bailey and M R Wallace (7 January, p 48) with regard to the association of HLA-B12 and vesicoureteral reflux in patients with renal failure are very interesting and similar to our findings in children.

A total of 36 unrelated Caucasians (predominantly French Canadian)—34 girls and two boys aged 3–16 years—with a history of recurring urinary tract infections (UTI) due to *E coli* were tissue typed for 25 HLA specificities. Results were compared with 188 normal random subjects. In addition, four families with a total of 16 siblings (7 with UTI, 9 normal) were also tissue typed to study segregation of reflux with HLA haplotypes. HLA-A2 was significantly reduced in UTI patients (UTI v control: 48% v 25%, $P < 0.025$). On the other hand, specificities A10 (9% v 22%, $P < 0.04$) and Bw16 (3% v 14%, $P < 0.015$) showed significant increases in UTI patients. However, when UTI patients were divided into two groups,

one with reflux (16 patients) and the other without reflux (20 patients), no significant differences between the two groups were observed with regard to these three HLA specificities. Thus, our results suggest that HLA specificities A2, A10, and Bw16 may be associated with the susceptibility to UTI due to *E coli* independent of developmental anomalies of vesicoureteral origin. Although subjects with and without reflux showed deviations in several HLA specificities (B12, A9, and A11), only Aw32 was found to be highly significant ($P < 0.0001$) in our patient population. In addition, the patients with a history of recurrent UTI but without reflux showed a higher incidence of blood group A (65%) as compared to normal controls (45%). In three of the four families studied, a pair of HLA-identical siblings had a history of recurrent UTI and reflux. Although reflux segregated with HLA haplotype in all four families, no single HLA specificity or common HLA haplotype was found to be associated with reflux. Our studies suggest that a gene (or genes) other than those governing the HLA is responsible in the genesis of reflux. However, it seems to have a close linkage with the major histocompatibility complex and may be in linkage disequilibrium with Aw32.

Segregation of ureteropelvic junction obstruction (stenosis) with HLA haplotype was also recently observed in 12 siblings of a French Canadian family. The proband was a prospective renal allograft recipient who had apparently inherited stenosis from his father (ab) via HLA haplotype a. Within the family, four other siblings (two HLA identical with the proband) who shared haplotype a with the proband were also found to have stenosis, while seven other siblings who did not receive HLA haplotype a from their father were free of this anomaly. Although there was complete segregation of stenosis with HLA haplotype, the disease had variable expressivity.

Our data suggest that HLA typing may be used as a marker within a family for the presence of certain urinary tract anomalies such as ureteropelvic junction obstruction and childhood reflux.

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¹ Sengar, D, et al, *XV International Congress of Pediatrics*, New Delhi, 1977.

² Sengar, D, Rashid, A, and Wolfish, N, *Annals of Royal College of Physicians and Surgeons*, 1978, **11**, 87.

³ Sengar, D P S, Rashid, A, and Wolfish, N M, *Clinical Nephrology*, in press.

Diseases of the respiratory system

SIR,—In his article on pneumonia, Dr C M Ogilvie (25 March, p 771) lists the antibiotics which may be of value in the treatment of pneumonia. He notes that acute fulminating pneumonia is usually caused by penicillin-resistant staphylococci or Gram-negative organisms and recommends treatment with flucloxacillin and an aminoglycoside with alternatives for patients allergic to penicillin.

In acute fulminating pneumonia, particularly if it has not responded to antibiotic therapy appropriate for a less severe pneumonia, it is important to cover as wide a range of infecting organisms as possible (one must presume that tuberculosis has been excluded). Apart from *Strep pneumoniae*, the bacteria which are likely to be lethal in pneumonia are *Staph aureus*, *Klebsiella* spp, possibly haemolytic streptococci, and also the organism of legionnaires'