auxiliaries with little formal education. But we could never guarantee a 24-hour nursing presence and patients could count themselves fortunate if at any time there was one nurse for four patients.

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¹ Sanders, R K M, *et al*, *Lancet*, 1977, 1, 974.

² Vakil, B J, *et al*, Proceedings of the Fourth International Conference on Tetanus, Dakar, Senegal, p 423. Lyon, Foundation Merieux, 1975.

³ Sanders, R K M, *et al*, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1969, 63, 746.

Prophylaxis of tetanus

SIR,—I was interested in the article "Intensive care in tetanus" (26 May, p 1401) describing the history and treatment of 100 cases at Leeds General Infirmary during 1961-77.

It states that, of those patients who did seek medical attention for their injury, 25 were given tetanus toxoid and 21 prophylactic antibiotics, but none received antitetanus serum, either equine or human. During my 37 years of practice in a rural area I had to deal with a large number of wounds where it was necessary to provide prophylaxis against tetanus. I have always maintained that for patients who had not been previously immunised with tetanus toxoid it is not enough to treat them with toxoid or antibiotics at the time of injury but that they must have antiserum. I may say that in a long experience I have fortunately never had a case of anaphylaxis due to this procedure, although I have encountered mild reactions—mostly urticaria. I would add that I gave a minimum test dose in case of reaction, and then waited a quarter of an hour before giving the full dose.

I should be interested to hear other people's views on this matter as I know it is now common practice to give toxoid with or without an antibiotic to patients with wounds potentially infected with tetanus. Indeed I know of one case in my own practice, which occurred after I had retired, in which a patient who had not been previously immunised was given toxoid for a wound incurred in her garden and subsequently developed tetanus, from which she fortunately recovered in hospital.

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Antibiotic-induced interstitial nephritis?

SIR,—With reference to Dr C T Flynn's repudiations (16 June, p 1628) of the conclusions in our paper (5 May, p 1182), we would like to reinforce the following points.

Firstly, one of us (DJR) effectively managed all three episodes of acute renal failure in this patient and performed the renal biopsy following the administration of gentamicin. All the original renal biopsy material from 1974 has been re-examined and it confirms as stated the presence of acute interstitial nephritis temporally related to the administration of gentamicin. The subsequent rapid response to high-dose intravenous methylprednisolone serves as confirmatory evidence.

Secondly, gentamicin levels were kept within recommended limits as documented. Gentamicin was first administered on 23 July 1974 in a dose of 80 mg twice daily commensurate with the patient's renal function. Peak

gentamicin levels were if anything low at 4.0 µg/ml (24 July) and 4.5 µg/ml (25 July). Treatment was stopped on 26 July because of the decline in renal function and was not given on this date.

Thirdly, the remarks by Dr Flynn with reference to co-trimoxazole serve to demonstrate why so many cases of drug-induced acute renal failure probably go unrecognised. This patient had been repeatedly told not to take any antibiotic without prior consultation. The history of co-trimoxazole ingestion was, in fact, obtained from his wife, for whom the drug had been prescribed. As he was so ill initially, confirmation was only obtained from the patient during his recovery. There was no question of reluctance to admit taking the drug, merely embarrassment at his folly. We can only emphasise the importance of careful and repeated history taking. How many of us have toiled for years to obtain a true drug history from patients with analgesic nephropathy?

The object of our short report was to record not only that gentamicin can cause acute interstitial nephritis but also that multiple episodes due to different antibiotics can occur in the same patient. It was also our intention to underline the importance of early renal biopsy and high-dose steroid therapy in these cases.

D SALTISI

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Collaborating with the pharmaceutical industry

SIR,—I write to support the point of view expressed by Dr B N C Prichard (17 March, p 747) on the relationship between the pharmaceutical industry and university departments such as haematology or medicine.

It is likely that co-operation is to the mutual benefit of both parties and, as far as I am aware, those of us following this practice have seldom transgressed the important considerations of propriety or objectivity in joint investigation. It seems to me, as to Dr Prichard, that the critical evaluation of a new product is often best carried out in a department where particular interest and expertise is already available and where objectivity is therefore likely to be at its highest. In the best traditions of scientific medicine neither the investigator nor any reputable company would wish that anything but the truth emerge from such collaboration. Certainly my experience has been that free interchange with scientific officers in company research establishments may improve trial design, substantially contribute to critical analysis of data, and clarify the presentation of results.

It has been of particular interest to observe that the number of collaborative efforts are steadily increasing: many individuals and departments who previously resisted such associations appear to be shifting their position. It would be my hope that this reflects the ever-increasing acceptance of the fact that association with the pharmaceutical industry in areas of obvious common interest does not automatically bias results. In the final analysis the viability of this desirable interaction between academic medicine and colleagues in drug development comes down

to the scientific reputation of the two parties and, from my own experience, is a collaboration to be strongly encouraged and further developed.

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Proteinuria at high altitude

SIR,—Drs A R Bradwell and J Delamere (21 April, p 1083) questioned the significance of altitude in producing proteinuria and thought that my investigation¹ did not distinguish between exercise and altitude as causes.

Recently, four fit and experienced climbers made ascents of three mountains of heights of 3400 to 3600 m in the French Alps at successive two-day intervals. On each occasion urine was tested with the Multistix strip test for protein concentration in samples taken immediately after the climb and also 24 hours later after discarding the first morning urine. Out of the total of 12 urine samples tested immediately after the climb there was a trace of albumin in four specimens and 30 mg in two specimens. Twenty-four hours later there was a trace of protein only in four specimens; no protein was detected in the remaining six specimens.

Thus within the limits of this investigation exercise produced little proteinuria and only traces were present 24 hours later. This is in contrast to the mean urine concentration of protein of over 100 mg/100 ml taken 24 hours after climbs of up to 5890 m in similarly fit climbers.¹ Thus altitude does seem a significant factor in the production of proteinuria.

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¹ Pines, A, *British Journal of Diseases of the Chest*, 1978, 72, 196.

Renal enzyme and protein excretion after induction of a diuresis

SIR,—Different results have been recently reported in the *BMJ*^{1,2} on urinary *N*-acetyl-β-glucosaminidase (NAG) excretion following 80 mg oral frusemide. In the first letter some doubts were also being raised on the use of urinary enzyme determinations as sensitive indicators of renal damage after drug administration.

We³ have investigated in eight healthy volunteers the urinary excretion of α-glucosidase, lysozyme and β₂-microglobulin after induction of a diuresis by administering tap water (500 ml by mouth in 30 minutes in the first day), frusemide (20 mg intravenously on the fifth day), and 20% mannitol (500 ml intravenously in 60 minutes on the ninth day). Urine samples were collected for two nights after mannitol administration. α-Glucosidase⁴⁻⁶ is a lysosomal enzyme, which is present as NAG in tubular cells and absent in plasma and which increases in urine after a tubular damage. Lysozyme and β₂-microglobulin are microproteins, whose increase in urine suggests a reduced tubular reabsorption of filtered microproteins ("tubular proteinuria").

Our results³ do not show any significant effect of water, frusemide, and mannitol administration on α-glucosidase excretion. Urinary lysozyme and β₂-microglobulin excretion, however, was increased by diuresis. The increase was significant for lysozyme after water and for β₂-microglobulin after frusemide administration. A more striking effect of water, frusemide, and mannitol administration on enzyuria and proteinuria was observed in

four patients with liver cirrhosis, in which a renal impairment is often present. After administration of osmotic agents (mannitol, dextran)⁷ or radiological contrast media⁸ the increase of urinary enzyme and protein excretion is more evident in patients with chronic renal diseases than in subjects with normal renal function.

We conclude that the urinary excretion of α -glucosidase and probably of other renal glucosidases is not influenced in normal subjects by the induction of a diuresis and may be considered a reliable and sensitive index of tubular damage after drug administration. In patients with underlying liver or renal diseases, however, the possible administration of diuretic agents must be taken into account before drawing any conclusion. One must be cautious in normal subjects too when determining enzyme or protein indexes of tubular proteinuria such as lysozyme and β_2 -microglobulin. Conversely, the determination of tubular enzyme excretion after induction of a diuresis (chiefly after an osmotic load) might be used as a sensitive test of underlying renal diseases, as suggested also by Burchardt *et al.*⁷

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¹ Harding, S, and Munro, A J, *British Medical Journal*, 1978, 2, 1431.

² Petersen, J, *et al*, *British Medical Journal*, 1978, 2, 1790.

³ Guarnieri, G F, *et al*, *Clinical Enzymology Symposia*, vol 2. Piccin Medical Books, in press.

⁴ Ceriotti, G, and Guarnieri, G F, *Proceedings of the Sixth International Symposium on Clinical Enzymology*. Milan, Kurtis, 1974.

⁵ Guarnieri, G F, *et al*, *Enzymes in Health and Disease*, p 186. Basel, Karger, 1978.

⁶ Guarnieri, G F, *et al*, *Enzymes in Health and Disease*, p 193. Basel, Karger, 1978.

⁷ Burchardt, U, *et al*, *Zeitschrift für Medizinische Laboratoriums-Diagnostik*, 1977, 18, 190.

Vaginal microbial flora in normal young women

SIR,—I was interested to read the careful study of vaginal microbial flora in normal young women in Edinburgh (2 June, p 450) but feel that it may not fully reflect the situation in all parts of Britain.

In particular, I feel that *Trichomonas vaginalis* is, at least in Cleveland, a more frequent pathogen than the Edinburgh study suggests. Analysis of the findings in 1000 cervical smears received consecutively by this laboratory in January and February this year from family planning clinics shows that *Trichomonas vaginalis* was positively identified (by at least two observers) in 70 (7%). In addition, cytological features suggesting trichomonas infestation were present in a further 61 in which the parasite could not be identified with certainty. Inflammatory changes were present in all but three of those 131 smears and vaginal discharge was recorded on the accompanying request form in 107 (82%). By contrast, *Candida* organisms were identified in only 24 of the 1000 smears, though cytological features suggestive of candidiasis were seen in a further 12. Comparison with a similar study made in 1969 showed that the findings are relatively constant in this area.

While I admit that a cervical smear is an inferior technique to culture in demonstrating vaginal candidiasis, there is no doubt that examination of a smear is an effective way to demonstrate trichomonas infestation and that

this pathogen is a major cause of vaginal discharge. Though there clearly may be differences in selecting the patients studied here and in Edinburgh, it is difficult to account for the different frequency of *Trichomonas vaginalis* in cervical smears in Cleveland (at least 7.0%) and Edinburgh (1.2%) except by postulating a difference in prevalence. It would be of interest to know the position in other parts of Britain.

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Uterine rupture after intra-amniotic injection of prostaglandin E₂

SIR,—We wish to report a case of uterine rupture following intra-amniotic injection of prostaglandin E₂ and hypertonic saline in order to induce abortion.

The patient, aged 39 years, had had three previous vaginal deliveries and requested abortion at the 20th week of pregnancy. This was induced by an eventful transabdominal amniotic injection of 5 mg prostaglandin E₂ and 100 ml of 30% hypertonic saline following the removal of 150 ml of clear liquor. Contractions commenced after four hours but after 11 hours the patient developed continuous lower abdominal pain and a pulse rate of 120 beats per minute. Abdominal examination revealed a tender suprapubic mass, equivalent to a 16-week gestation and a separate firm mass, 8 cm in diameter, in the right hypochondrium. A diagnosis of ruptured uterus was made and at laparotomy there was a rupture at the junction of the upper and lower segments involving the anterior wall and both lateral walls of the uterus. The intact gestation sac was bulging through the deficit. Total abdominal hysterectomy was performed and the postoperative course was uneventful. The cervix was normal.

This is the first reported case of uterine rupture following mid-trimester termination of pregnancy with prostaglandin E₂ and hypertonic saline, although one case has been reported following intra-amniotic injection of prostaglandin F₂ and hypertonic saline.¹ Cervicovaginal fistula, however, has been reported following 1% of terminations induced using intra-amniotic prostaglandin.² We report this case in order to draw attention to an unusual complication which must be taken into account when choosing a method of terminating a pregnancy in the mid-trimester.

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¹ Borten, M, and Friedman, E, *Prostaglandins*, 1978, 15, 187.

² Lowensohn, R, and Ballard, C A, *American Journal of Obstetrics and Gynaecology*, 1974, 119, 1057.

An open-access morbid pathology facility for GPs?

SIR,—Family doctors have often received a rap over the knuckles for inaccurate certification of death. We are as interested as are any of our colleagues in knowing why patients die, but we are often prevented from finding out.

An elderly patient dies at home after an illness in which investigation by open-access pathology requests, consultant domiciliary consultation, or a period of inpatients or out-patient surveillance has produced a variety of possible pathological diagnoses. Age, frailty, and humane considerations have precluded

further probing. The obvious need, then, is for a postmortem examination. The only way that this can be procured is by reference to the coroner and then only at his discretion. This cumbersome procedure is quite inappropriate where there is no question of foul play, where the final mode of death (but not the antecedent condition) is obvious, and where a visit from a police officer, however kindly, is an ordeal for the relatives. How many doctors can honestly say that they have not certified deaths as being due to, for example, bronchopneumonia, while knowing that a deeper cause for that has not been uncovered?

There is a clear need for an open-access morbid pathology facility for general practitioners. We should all be humbled, but enlightened, by this; and our patients would stand to gain.

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Enterotoxigenic *Escherichia coli* and travellers' diarrhoea

SIR,—Mr R J Gross and others (2 June, p 1463) reported that they isolated enterotoxigenic *Escherichia coli* (ETEC) from the faeces of 6/55 (11%) patients who developed diarrhoea during or shortly after travel abroad, and also from 1/50 (2%) patients with diarrhoea but no history of recent travel outside the UK. We have been conducting similar studies in Manchester and wish to report our confirmatory results.

We tested the toxigenicity of five colonies of *Escherichia coli* isolated from the faeces of each of 13 cases of diarrhoea in travellers returning to the Manchester area from abroad, and also in a control group of 13 patients who developed diarrhoea at about the same time but gave no history of recent travel. A group of 13 babies with diarrhoea admitted to Wythenshawe Hospital, South Manchester, were also included in this survey. In an earlier study we examined 210 strains of "specific" *E coli* isolated from cases of infantile diarrhoea by various hospital laboratories in the north-west. Heat-labile enterotoxin was detected by the Chinese hamster ovary cell assay¹ and heat-stable enterotoxin by the infant mouse gut test.² All toxigenic strains isolated were tested serologically using *E coli* O-agglutinating antisera (Wellcome) and then sent to Dr B Rowe of the Central Public Health Laboratory, Colindale, London, for further serotyping.

Our results show that 6/13 (46%) of travellers with diarrhoea were infected with ETEC, each of a different serotype. None of the control group yielded ETEC. All 13 infants from Wythenshawe Hospital were clear of ETEC. Furthermore, all the strains (210) of specific *E coli* from cases of infantile diarrhoea in the north-west were non-toxicogenic.

While confirming the conclusions drawn by Mr Gross and his colleagues, our results show a significantly higher isolation rate of ETEC from travellers with diarrhoea than their results. We note, however, that, whereas they examined only one or sometimes two "cultures" (*sic*) from each patient, we have been routinely screening five colonies of *E coli* from each patient. We feel that this may account for our higher isolation rate. We also find that in the north-west of England ETEC do not appear to be a significant cause of sporadic diarrhoea in infants or adults; this is in agreement with the results of Gross *et al* and other workers in the United States³ and Sweden.⁴

Finally, it is necessary to report that not all the toxigenic strains of *E coli* we isolated from