of a rectangle measuring 5×3 mm and was read at 48-72 hours with induration as the sole criterion; this was coalescent and spread out with the rectangle for at least 2 mm. We were not concerned with the lesser degrees of "positivity" which are characteristic of previous BCG vaccination, and these we therefore recorded as negative.

Our "positive" children were confirmed on investigation, which included chest x-ray, ESR, and culture of three gastric washings. Those with a "negative" reaction of less than 2 mm around one or more puncture sites may well have produced a positive reaction to a 1/1000 (10 TU) Mantoux test, and this would have allowed a measure of true reversion rates. To be meaningful, however, it would be necessary to relate the tuberculin reaction to the age of the child and time of BCG vaccination, and we were not concerned with this point.

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Atropine or thymoxamine for chronic asthma?

SIR,—Patients with bronchial asthma have bronchial musculature which is underreactive to continuous beta-adrenergic relaxatory stimuli, so that parasympathetic-induced bronchoconstriction can predominate. Thus atropine might be beneficial. At the same time it is claimed that bronchospasm that is refractory to routine beta-mimetic drugs can be relieved by blocking alpha-adrenergic receptors. Moreover, sodium cromoglycate may have an alpha-blocking effect.

In a small but detailed study I have monitored seven patients with chronic refractory asthma, who continued with their routine therapy consisting of salbutamol and sodium cromoglycate inhalations and either salbutamol or diprophyllyne tablets, while in addition they used an atomiser to deliver in a double-blind trial either water 0.3 ml four-hourly or atropine sulphate (1/1000) 0.25 mg four-hourly or the alpha-blocker thymoxamine 1.5% 0.3 ml four-hourly. By the end of the study each patient had spent two separate weeks on their basic therapy plus water and one week on additional atropine and yet another week on thymoxamine. During this time they attended twice weekly for ventilograph studies before and after inhalation and also before and after exercise. They also filled in a questionnaire designed to assess subjective impressions and at the same time any spontaneous improvement or deterioration in their condition (eg, due to infection).

In retrospect three patients claimed no benefit from either atropine or thymoxamine, one claimed symptomatic benefit from thymoxamine which was not confirmed by the FEV₁ and VC, and three patients claimed an improvement with atropine which was confirmed by the ventilograph tests. It is significant that these three were those with bronchorrhoea. They also noted dryness of the mouth.

Thus I have to conclude that atropine inhalation can improve refractory asthma when there is excessive production of secretions, but that otherwise its side effects may make it intolerable, and that thymoxamine in the dosage used is ineffective. Thymoxamine

is also expensive and caused some patients to have headache.

I am grateful for the help of Sister Moffett who performed the ventilograph studies in the chest clinic and to Miss M Gladwin, pharmacist, at Sunderland Royal Infirmary.

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Factor VIII and chronic renal failure

SIR,—Dr M Kazatchkine and others (11 September 1976, p 612) have shown that in patients with chronic renal failure (CRF) decreased plasma levels of factor-VIII-related von Willebrand factor (VIIIWF) were accompanied by high factor-VIII-procoagulant activity (VIIIc) and factor-VIII-related antigen (VIIIa). It was suggested that a selective abnormality of the portion of factor VIII molecule involved in platelet function might be responsible for the impairment of primary haemostasis expressed in these patients by a prolonged bleeding time. Our studies, carried out in 31 patients with CRF due to various primary renal diseases undergoing periodic haemodialysis for periods varying from 2 months to 10 years, are at variance with those of Dr Kazatchkine (see table). Both VIIIa (immunoradiometric

Plasma levels of VIIIa and VIIIWF in 32 normals and 31 patients with CRF

Test	Subjects	Mean ± SD	Range
VIIIa (U/ml)	Normals (32)	0.97 ± 0.24	0.57-1.64
	CRF patients (31)	2.30 ± 0.94*	0.93-4.76
VIIIWF (U/ml)	Normals (32)	0.93 ± 0.24	0.53-1.35
	CRF patients (31)	2.15 ± 0.8*	0.87-3.99

*P<0.001.

assay¹) and VIIIWF (washed platelet assay¹) were markedly increased and highly correlated (r=0.86; P<0.001); the mean VIIIa: VIIIWF ratio, which can be taken as index of discrepancy between the two measurements, was 1.07±0.20 (range: 0.75-1.62). It appears, therefore, that the factor-VIII-related properties are concomitantly increased in patients with chronic renal failure, and that the component necessary for normal platelet function is not impaired.

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¹ Ruggeri, Z M, et al, *British Journal of Haematology*, 1976, **33**, 221.

Fractures of the tibia

SIR,—I would like to comment on Mr R W Griffiths's observations (12 February, p 440) on Mr J E M Smith's article (15 January, p 152) on the treatment of tibial fractures.

I would agree with Mr Griffiths that reference should have been made to a very serious aspect of tibial fractures, namely, the exposure of bone resulting from skin loss. Further, he rightly stresses the serious sequelae of failure

to secure primary or delayed primary skin cover. However, I note that the methods advocated to secure this cover include cross-leg flaps, with abdominal tube pedicles and free flap transfers with micro-anastomoses mentioned as possible alternatives, although the timing of the latter two methods is not made quite clear.

It is surprising that no mention is made of a method which is generally successful in providing primary or delayed primary cover, preventing the onset of chronic osteomyelitis, securing the healing of compound fractures where treatment has failed, and is often successful in the treatment of chronic osteomyelitis, even where this is accompanied by non-union. I refer to the management by debridement, muscle transposition, and delayed skin graft of the muscle.¹⁻¹⁰ This method has been in use over the last 13 years and is infinitely simpler than the suggested alternatives, whose disadvantages are well known. Further, with the possible exception of free flap transfers, whose successes are few and dependent on the expertise of a relative few, other methods are wrong in principle in that they rely on the pathologic area for their survival.

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¹ Ger, R, *American Journal of Surgery*, 1966, **111**, 659.

² Ger, R, *Surgery*, 1968, **63**, 757.

³ Ger, R, *Journal of Trauma*, 1970, **10**, 112.

⁴ Ger, R, and Efron, G, *Clinical Orthopaedics*, 1970, **70**, 165.

⁵ Ger, R, *Journal of Trauma*, 1971, **11**, 6, 502.

⁶ Ger, R, *Current Problems in Surgery: The Surgical Management of Ulcerative Lesions of the Leg*. Chicago, Year Book Publishers, 1972.

⁷ Ger, R, The closure of defects of the lower extremity by muscle flaps, in *Reconstructive Plastic Surgery*, ed J M Converse. (In press.)

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⁹ Pers, M, and Medgyesi, S, *British Journal of Plastic Surgery*, 1973, **26**, 313.

¹⁰ Mathes, S J, McCraw, J R, and Vasconez, L O, *Surgical Clinics of North America*, 1974, **54**, 1337.

Alcoholic liver disease in women

SIR,—The paper by Dr Marsha Y Morgan and Professor Sheila Sherlock (9 April, p 939) raises once again the interesting question whether women are more susceptible than men to the physical consequences of alcoholism. The basis for asking this is the occurrence in their series of more severe liver disease and nutritional disorders in female problem drinkers than in men.

One possible explanation of this observation is a sex difference in the hepatic handling of ethanol. However, the most recent studies in which the subjects' sex is stated fail to show significant male-female disparity in respect of alcohol metabolism rate¹ or liver biopsy alcohol dehydrogenase content.² Epidemiological evidence is likewise unhelpful. In one comprehensive review of US experience the relationship between national per caput consumption of alcohol by sex and the incidence of cirrhosis is similar for males and females until the early 1960s.³ After this date an excess of female cirrhosis begins to appear, probably reflecting a change in diagnostic habits.

In fact, part of the answer may well lie in the difficulty, confirmed by the Royal Free workers, of extracting an accurate quantitative drinking history from women patients of this sort. The higher incidence in women alcoholics

of personality disorder and the lack of need for housewives to conform to social drinking hours may lead to a heavier—but still historically minimised—alcohol intake than in male alcoholics. The question then becomes: *for the same degree of alcohol abuse, do women fare worse than men?*

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¹ de Cruz, A G, *et al*, *Acta Hepatogastroenterologica*, 1975, 22, 369.

² Dow, J, *et al*, *Clinical Science and Molecular Medicine*, 1975, 49, 603.

³ Brenner, M H, *American Journal of Public Health*, 1975, 65, 1279.

SOMA

SIR,—Two members of the Society of Authors, both doctors, have drawn our attention to an article by Dr I J T Davies entitled "SOMA: new hope for medical authors" in your issue of 2 April (p 887).

Dr Davies says that "most medical authors get a raw deal" and that for this and other reasons a group "has now banded together to form the Society of Medical Authors." He states that "the standard contract (euphemised to 'memorandum of agreement') drawn up between most authors of medical books and their publishers was apparently agreed by the Society of Authors and the Publishers Association" (my italics). I have no idea where Dr Davies could have got this totally incorrect information. The Society of Authors has negotiated no such contract. There is, indeed, no "standard publishing contract," though some publishers tend to imply that theirs is "standard" so as to discourage authors from any attempt to bargain.

The Society of Authors has a substantial number of medical authors among its three and a half thousand members. They are entitled to individual advice on all matters connected with the marketing of their work and, in particular, to detailed "vetting" of publishing contracts. This often enables them to negotiate considerably better terms than those originally offered.

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Paracetamol-induced acute pancreatitis

SIR,—With reference to the report by Drs I T Gilmore and E Tourvas of pancreatitis associated with paracetamol overdose (19 March, p 753), I would like to report a similar case of paracetamol overdose in which pancreatitis was associated with a lesser degree of hepato-renal failure, occurring at a different stage of the illness.

A 41-year-old machinist was admitted to hospital 48 hours after taking 25 g of paracetamol (50 Panadol tablets) with suicidal intent. She had not taken alcohol with the tablets. She had been nauseated and had vomited several times before admission. She had no abdominal pain. She had no previous history of biliary or liver disease and consumed only small amounts of alcohol.

On examination no bruising was present, she was slightly icteric but not clinically dehydrated or shocked. She had epigastric tenderness with normal bowel sounds. Initial investigations showed: Haemoglobin 15.0 g per 100 ml (15 g/dl); white cell count $6.5 \times 10^9/l$; prothrombin 20 seconds, control 13; alkaline phosphatase 125 IU/l (normal

46–190); serum glutamic oxaloacetic transaminase (SGOT) 2000 IU/l (normal 2–19); bilirubin free 45 mmol/l, conjugated 36 mmol/l, total 81 mmol/l (normal 5–17); gamma glutamyl transpeptidase 51 IU/l (normal 4–18); serum paracetamol 15 mg/ml; urea 3.4 mmol/l (normal 1.6–5).

A regimen of 50% dextrose IV giving 3000 calories a day was started controlling blood sugar with insulin via an infusion pump according to Dextrostix. Magnesium sulphate enemas and vitamin K were also given. Her initial vomiting settled with metoclopramide by the second day of admission. Her liver function tests deteriorated, with the SGPT reaching 4137 IU/l at the same time.

On the third day after admission, a further episode of vomiting occurred. She had mild abdominal pain, which worsened over the next two days, being central and radiating to the back. The abdomen became distended, with an ileus present. A diagnostic tap on the sixth day revealed turbid ascitic fluid positive for blood on ward testing with a protein content of 20 g/l and an amylase of 4000 IU. The serum amylase was 1250 IU (70–300 IU normal), calcium 1.9 mmol/l (normal 2.2–2.6), protein 55 g/l (normal 63–78), haemoglobin 12.3 g per 100 ml (12.3 g/dl), white cell count $11.5 \times 10^9/l$ with 30 000 platelets ($30 \times 10^9/l$) and urea 13.6 mmol/l. No evidence of viscus perforation on abdominal x-ray was found. A diagnosis of pancreatitis was made.

Conservative treatment of fluid replacement, analgesia, and metoclopramide resulted in some improvement. The vomiting and pain subsided by the seventh day though the serum amylase was still raised at 1000 IU/l. She remained in hospital for a fortnight, being slightly jaundiced though fairly well on discharge. The patient's liver function had returned to normal when seen in the clinic three months later and she had had no more vomiting or abdominal pain.

In this case the "pancreatitis" occurred as the liver cellular function was improving (SGPT falling) but also at a time when the alkaline phosphatase and bilirubin were climbing (especially the conjugated form) (see figure). This is in keeping with an oedematous pancreas causing an obstructive picture. The low platelet count at the time of the pancreatitis would suggest a diagnosis of disseminated intravascular coagulation, though no further tests were done to confirm this. DIC is a complication of diabetic ketoacidosis, rather than hyperglycaemia.¹ There is no evidence

that this patient was ketoacidotic, though she had episodes of hyperglycaemia. This case is presumed to be pancreatitis though retroperitoneal haemorrhage is not excluded.

Gilmore and Tourvas's case is of a lady with an alcoholic history. Though alcohol consumption with the paracetamol is not mentioned, she could have had pancreatitis associated with the alcohol.

I am grateful to Dr M S Knapp for permission to report on this patient, who was under his care.

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¹ Timperley, W R, *et al*, *Lancet*, 1974, 1, 952.

Therapeutic test with colchicine in diagnosis of gout

SIR,—It was interesting to read the experience of Dr M L Snaith and Dr E N Coomes in gout with normal serum urate concentrations (12 March, p 685). They emphasise that a definite diagnosis of gout cannot be made unless monosodium urate crystals are seen in the joint aspirate. They conclude by referring to the value of a therapeutic test with colchicine as a diagnostic aid in acute gout (presumably when polarised light microscopy facilities are not available). I wish to point out that the arthritis of sarcoidosis,^{1,2} psoriasis,³ erythema nodosum, and pyrophosphate arthropathy⁴ also responds to colchicine. Although bearing in mind that sarcoidosis and psoriasis can be accompanied by hyperuricaemia, it appears to me that a therapeutic test with colchicine in the diagnosis of acute gout is unreliable and probably should be abandoned.

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¹ Kaplan, H, *New England Journal of Medicine*, 1960, 263, 778.

² Kaplan, H, *New England Journal of Medicine*, 1963, 268, 761.

³ Bunim, J J, *Annals of Internal Medicine*, 1962, 57, 1018.

⁴ Huskisson, E C, *Lancet*, 1972, 2, 271.

Interviewing women applicants

SIR,—At several recent job interviews I have been struck by the proportion of the (brief) time available which is spent discussing the present employment and career prospects of my husband (also a doctor) rather than my own. My husband, on the other hand, has never had his marital status so much as mentioned in a similar situation. I am sure all married women are well aware of the problems of combining marriage and career, but it is sometimes difficult to avoid the conclusion that one is regarded as an appendage to the husband who has no need of a job anyway. I should be interested to know whether any of your readers have similar experiences or feelings on this subject.

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Increased university fees and graduate medical students

SIR,—May we add our voice to that of the graduates at Southampton Medical School