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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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.

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

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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