Tolerance of Rifampicin

SIR,—One of the virtues of rifampicin is said to be a good patient tolerance which, as you have noted (30 August, 1969, p. 487), should be particularly valuable in treatment of tuberculosis where tolerance is poor.

To demonstrate objectively whether this good tolerance extends to domiciliary ambulant therapy we have used a simple urine test for rifampicin on patients attending the Dagenham Chest Clinic, consecutively during June, July, August, and September last year (Table). During the same period we examined urines of all patients on P.A.S., using Phenistix.[1]

	No. of patients	Positive	Negative
Rifampicin (Butanol)	23	23	Nil
P.A.S. (Phenistix)	68	57	11

Butanol test for rifampicin.—This is derived from the biochemical method for estimation of rifampicin in urine, given in *Lepetit Handbook*.[2] The depth of colour, which varies from salmon pink to dark orange, is a guide to urinary concentration of rifampicin.

If rifampicin 10 mg./kg. of body weight has been ingested on an empty stomach two to eight hours previously, it is likely that the supernatant layer will be light orange or darker. The salmon pink colour may be found at 12 hours or even 24. A light orange corresponds to about 25 μg./ml. rifampicin; salmon pink to 2·5 μg./ml. We base this statement on 240 urine samples taken from 11 patients over a period of three to five days, at two-hourly intervals from 7.30 a.m. to 7.30 p.m. False positives may occur in the presence of excess urinary bile pigments.

Pines *et al.*[3] suggested that rifampicin is obvious in untreated urine, but the colour is, in our experience, more orange than brown. However, simple inspection proved misleading to seven nurses in 82 out of 189 observations on eight "positive" and 19 control urines. Using the butanol test on these same urines reduced the error to 12 out of 189 observations.

Although we agree that patient tolerance of rifampicin appears so far to be good, we suggest it may be wise to check from time to time that the drug is being taken. The above simple butanol test may help in this connexion.—We are, etc.,

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Digoxin-Phenytoin Interaction

SIR,—We would like to draw attention to what appears to be a toxic interaction of digoxin with phenytoin. Cardiac glycosides inhibit the Na,K-ATPase which is closely related to the metabolic "sodium pump". The inhibiting effects of ouabain and phenytoin on the Na,K-ATPase enzyme system are additive.[1] Phenytoin causes bradycardia[2] as well as digoxin.

A man with Down's syndrome, aged 53, began to get *grand mal* seizures once per month. Because he also had mitral insufficiency 0·25 mg. of digoxin and 200 mg. of phenytoin were administered daily. After having this medication two months he again had a seizure. At that time his serum phenytoin level was 11·0 μg./ml. only and thus the dosage of the drug was increased to 300 mg. daily. Within two weeks the patient became lethargic and rigid, his cardiac rate fell to 34/min. and the E.C.G. showed a complete heart block. At first this was suspected to be due to digoxin, which was discontinued. The dosage of phenytoin was also reduced to 200 mg. daily. Two days later the patient was comatose with Cheyne-Stokes respiration; cardiac rate 40/min.

In the next few days he began to improve, and a week after the dosage of phenytoin had been decreased from 300 to 200 mg. the serum phenytoin level was 20·2 μg./ml. and the cardiac rate 34/min. The dosage of phenytoin was further decreased to 100 mg. daily. Ten days later the cardiac rate was still 34/min. and phenytoin was discontinued. Within one month without phenytoin, the cardiac rate returned to 60-70/min., and the E.C.G. showed a normal sinus rhythm again. However, the patient is still unable to walk and has ataxia, slight nystagmus, and rigidity suggesting permanent cerebellar damage.

This case, with a nearly fatal outcome, suggests that the combination of digoxin with phenytoin or the treatment of digitalis-induced cardiac dysrhythmias with phenytoin may be hazardous. It is conceivable that the toxicity of phenytoin is due to the inhibition of Na,K-ATPase and the physiological sodium transport, which are impaired further by digoxin. However, cardiac glycosides increase, and phenytoin decreases, the intracellular sodium concentration.—We are, etc.,

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Childhood Urinary Tract Infection

SIR,—Dr. N. C. Mond and his colleagues (7 March, p. 602), in their study of childhood urinary tract infection in general practice, successfully emphasize that pyuria and proteinuria do not prove useful in the prediction of asymptomatic bacteriuria. The findings do, however, illuminate the doubtful value of the present emphasis on bacteriuria itself as a guide to the presence of preclinical urinary tract infection. In their findings approximately ten times as many children displayed pyuria as were found to have bacteriuria. As most of the children may be assumed to have been prepubertal, and the specimens themselves were collected after effective local cleansing had taken place, is it not reasonable to assume that the source of the pus cells was the urinary tract?

In my experience as an obsessive urine microscopist in general practice, the continued presence of pyuria during follow-up of cases of treated overt urinary infection is an indication that an exacerbation will occur sooner or later, despite the finding of sterile urine over the same period.

In studying the early history of urinary tract infection is there not perhaps some justification for emphasizing pyuria rather than bacteriuria in the search for preclinical infection?—I am, etc.,

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Entrapment Neuropathies

SIR,—In your leading article on entrapment neuropathies (14 March, p. 645), the list of diagnostic criteria is headed by pins and needles. But it is well to realize that paraesthesia is absent in many cases of pressure on the external aspect of a nerve—for example, with pressure on the lower trunk of the brachial plexus from a cervical rib the only complaint may be wasting of the thenar eminence without any sensory change. In sciatica, where the nerve root is trapped at the intervertebral foramen, or in meralgia paraesthetica pins and needles are often absent.

The criteria that were originally put forward for a diagnosis of "perineuritis" (as I called it in 1942[1]) were simply: pain referred to a region obviously corresponding to the cutaneous area of supply of a peripheral nerve, without loss of conduction, in a case where no pain could be elicited on testing the non-nervous tissues. No particular attention was paid to my "medium perineuritis" until the classic paper of Brain, Wright, and Wilkinson,[2] which certainly should figure in the otherwise extensive bibliography of your leading article.—I am, etc.,

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Pulmonary Sensitivity to Nitrofurantoin

SIR,—Your leading article (20 December 1969, p. 704) mentions confusing this condition with pulmonary oedema or pneumonia. The following case demonstrates another differential diagnosis—pulmonary embolus.

A woman aged 24 years was given nitrofurantoin 100 mg. q.d.s. for a urinary infection. Three weeks later she developed pretibial erythema and pruritus, aching pains in calves and thighs, and general malaise. She had tightness in the chest and a non-productive cough. She vomited once and later that day fainted while waiting for a bus. On recovering consciousness the difficulty in breathing was more severe.

On admission that evening her temperature was 102°F. (39°C.), pulse rate 124. She was not breathless nor cyanosed. There was a pink papulo-urticarial rash over both shins. Both calves were tender but Homan's sign was negative. Chest examination and *x* ray were normal. She had been taking a contraceptive pill, Lyndiol, for 18 months. This fact, together with calf tenderness, respiratory distress, and the collapse, suggested the possibility of pulmonary