tressing neurological disorder. In either case, it would seem that this patient's brain stem activity had become set precariously and that the arrival of local anaesthetic caused its temporary breakdown.—We are, etc.,

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REFERENCE

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Carbenicillin and Hypokalaemia

SIR,—Brunner and Frick[1] drew attention to the development of hypokalaemia and metabolic alkalosis with high dose sodium benzylpenicillin therapy. Their patients received 60 g. daily for periods of 10 to 14 days. The standard dose of carbenicillin (α-carboxybenzylpenicillin, Pyopen) for systemic pseudomonas infections is 30 g. per 24 hours. No serious electrolyte disturbances have been recorded to date in patients receiving this antibiotic.[2] However, we have seen recently two patients who developed hypokalaemic alkalosis with carbenicillin therapy and wish to draw attention to this potentially dangerous complication.

An 80-year-old woman fell sustaining an undisplaced pertrochanteric fracture of her left femur which was treated conservatively. Urinary retention occurred, requiring an indwelling catheter. *Pseudomonas pyocyanea* were cultured in pure growth from repeated specimens of urine. She became febrile, had marked anorexia, vomited from time to time, and developed a painful, red, swollen wrist suggestive of bacteraemia although blood cultures proved sterile. Investigations: serum sodium 135, potassium 4·1, bicarbonate 27 mEq/l., urea 29 mg./100 ml. Two days later Carbenicillin 30 g./24 hrs. was given in two litres of normal saline in view of her dehydration. Five days later she had sacral oedema and a raised jugular venous pressure. The infusion volume was halved and bendrofluazide 5 mg. per day given. The patient was afebrile a week later, and felt well, but was hypokalaemic: serum sodium 138, potassium 2·0, bicarbonate >30 mEq/l., urea 30 mg./100 ml. The carbenicillin was stopped and the hypokalaemia rapidly responded to oral potassium chloride.

A 32-year-old woman was involved in a road traffic accident sustaining a compound fracture of her left tibia and fibula with extensive soft tissue damage. An initial exploratory operation revealed injury to the anterior and posterior tibial arteries. The leg became infected and repeated swabs yielded pure cultures of *Pseudomonas pyocyanea*. The patient was febrile with spikes of fever up to 104° F. (40° C.).

On 12 September carbenicillin was started, 5 g. 4-hourly into a dextrose saline infusion. The next day an above knee amputation was performed. Carbenicillin was stopped on 21 September when the patient was complaining of lethargy and weakness and was found to have sluggish tendon reflexes. A day later investigations showed a severe hypokalaemic alkalosis: serum sodium 133, potassium 1·5, bicarbonate 40+ mEq/l., urea 10 mg./100 ml. Again oral potassium chloride in large doses rapidly corrected the electrolyte disorder.

In the first case bendrofluazide and a poor dietary intake may have been partly responsible for the hypokalaemia. In the second case there were no such contributory factors. The mechanism of penicillin-induced hypokalaemia is not certain, but probably depends on penicillin acting as a non-reabsorbable anion thus increasing passive distal tubular potassium excretion down an increased negative transtubular potential difference.[1] Although carbenicillin contains 4·7 mEq/of sodium per gram, an increased distal tubular sodium load is probably not generally an important factor as sodium delivery is only rate limiting for the hypothetical cation exchange mechanism in certain circumstances.[3] However, both the above patients had other factors tending to reduce sodium excretion with probable increased aldosterone production. The first patient developed heart failure, was found to have a serum albumin of only 2·2 g./100 ml. and was on phenylbutazone. The second patient had a general anaesthetic and surgery which are often followed by salt and water retention.[4] Distal tubular sodium reabsorption may thus have been increased in both instances, encouraging tubular excretion of potassium especially in view of the relative deficiency of chloride ion.[5]

The manufacturers recommend that for severe infections probenecid be used to increase blood levels of carbenicillin. Probenecid was not used in the present cases and might well have prevented hypokalaemia by reducing renal tubular levels of carbenicillin. As there is no preparation of probenecid for parenteral administration it is likely that carbenicillin will be used on many occasions by itself. Carbenicillin is a valuable drug in the treatment of pseudomonas infections which were cured in both our patients. However, on occasions it can give rise to dangerously severe hypokalaemia.—We are, etc.,

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Labelled Fibrinogen in Renal Transplantation

SIR,—Mr. J. R. Salaman (30 May, p. 517) has suggested that surface measurements may have particular value in recipients with delayed function of renal transplants in the first few weeks after transplantation, and that a percentage of transplant radioactivity of more than 120% of that of the heart would appear to indicate rejection.

We have performed similar studies in nine patients here,[1] and have found that late transplant rejection is accompanied by surface accumulation of fibrinogen radioactivity. However, it was observed that during the early phase after transplantation it was the wound healing rather than rejection of the transplant that accounted for the increased radioactivity. Thus, the patient shown in Fig. 1 had a marked increase of radioactivity over the transplant although there was no evidence of rejection, and there was a similar increase in radioactivity over the nephrectomy wound of the other side. Although in the patient shown in Fig. 2 the control side, where the nephrectomy had been performed two years before transplantation, showed no increase of radioactivity, the increase over the transplanted side was most probably due to the process of wound healing, since there was no evidence of rejection. The bladder was emptied before each measurement and no haematomas were present. It may be noted (right half of both

Figure 1

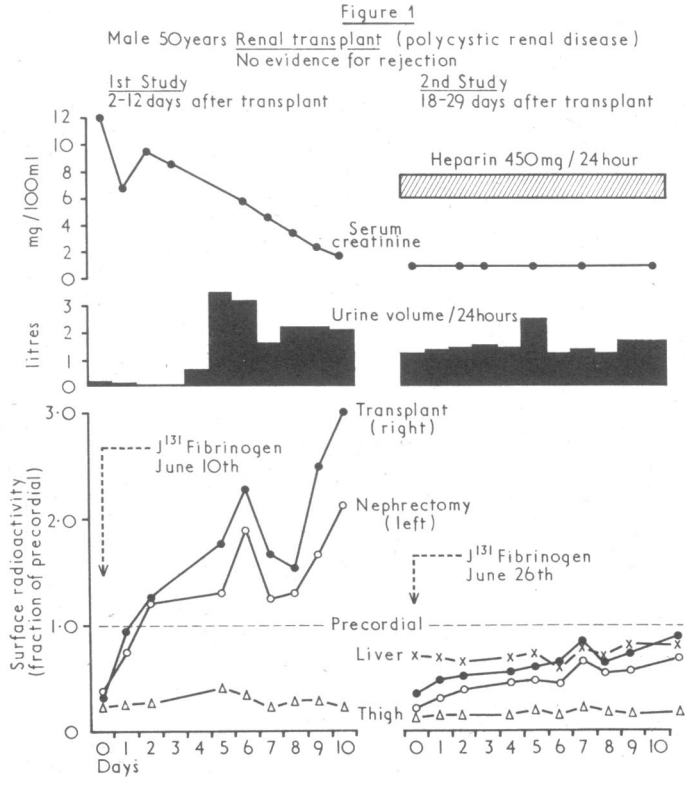
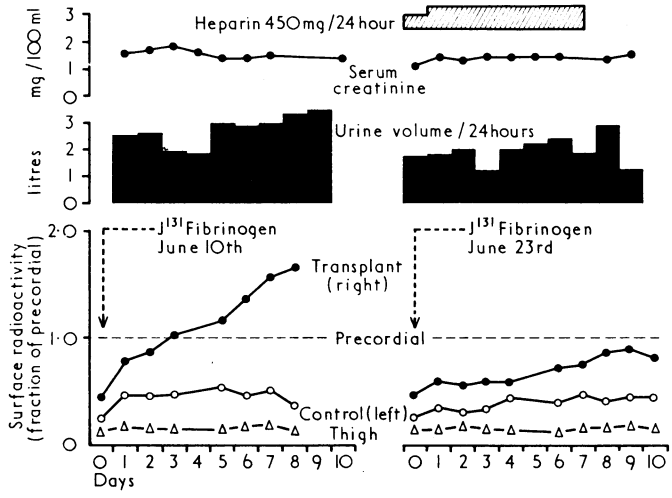


Figure 2



figures) that radioactivity increase was absent on a subsequent study, due either to the heparin therapy or to the disappearance of the effect of wound healing. A similar increase of surface radioactivity was observed in the operative field after surgical operations other than transplantation.

It may be concluded from the foregoing that surface measurements following injection of labelled fibrinogen may become a useful diagnostic tool for the detection of late renal transplant rejection, but unfortunately will probably not be of value in non-functioning transplants during the first few weeks after transplantation.—I am, etc.,

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REFERENCE

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Beta-blockers in Hypertension

SIR,—Dr. A. W. D. Leishman and others (7 November, p. 342) state in the introduction to their paper on practolol and oxprenolol in hypertension that both drugs are relatively cardio-selective. By this they mean that the two drugs show "much less activity than propranolol in blocking other beta-receptors." No reference is given to support this statement.

Though beta-receptors are widely distributed throughout the body,[1] the clinically important beta-receptors are found in the heart and bronchial smooth muscle, blockade of the former reducing cardiac activity and of the latter preventing beta-stimulated bronchial relaxation. When a beta-blocking drug is said to be cardio-selective, this implies that the dose of drug which blocks the cardiac beta-receptors has little or no effect in blocking bronchial and peripheral vascular beta-receptors.[2] The effects of oxprenolol, propranolol, and practolol on cardiac, bronchial, and peripheral vascular beta-receptors in animals have been reported. The dose of propranolol that blocks the cardiac response to a standard dose of isoprenaline (0·2 μg./kg i.v.) also blocks the peripheral vascular beta-receptors.[3,4] In contrast, practolol in doses which completely block cardiac beta-receptors has no effect on the peripheral vascular receptors.[4] We have compared also the effects of oxprenolol on cardiac and vascular receptors. The results, comparing the three drugs are given (A), which show that oxprenolol resembles propranolol in being non-selective.

This lack of selectivity of oxprenolol on cardiac versus peripheral vascular beta-receptors is confirmed by the studies reported from the laboratories of the manufacturers of oxprenolol.[6] They compared oxprenolol and propranolol and showed that it had identical effects on both cardiac and peripheral vascular beta-receptors at the same dose in the cat. Turning to the bronchial beta-receptors, the same authors[6] showed that oxprenolol was extremely active in blocking the bronchial beta-receptors, in that 1-3γ/kg i.v. of oxprenolol antagonized by 50% the actions of isoprenaline on bronchospasm induced by pilocarpine in the cat. This potent activity on bronchial beta-receptors is confirmed by Marmo *et al.*[7] We have compared the three compounds for their effects on bronchial smooth muscle in vivo in the guinea-pig.[5] The results of such studies (B above) show that the dose of propranolol and oxprenolol causing 50% of guinea-pig death is between 0·1 and 0·18 mg./kg., while that of practolol is 15 mg./kg. In other words, 150 times as much practolol must be given to achieve the same effects on bronchial beta-receptors as propranolol or oxprenolol.

The conclusion that may be drawn from these studies, and those from Switzerland and Italy, is that there is no evidence from pharmacological studies in animals to suggest that oxprenolol differs from propranolol in being cardio-selective, though there is ample evidence[5] to show that practolol is.

Dr. Leishman and colleagues mention the quinidine-like properties of propranolol but omit to mention that oxprenolol has similar properties.[7] They also omit to state that while Barrett *et al.* showed that practolol is 40% as active as propranolol in antagonizing the action of isoprenaline on the heart,[8] it is equally active in blocking endogenously released noradrenaline in the cat.[9] It is appreciated that brevity is the essence in writing a report, but it should not be such that it may be misleading.—I am, etc.,

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TABLE.—*Comparison of the effects of propranolol, oxprenolol, and practolol on heart, peripheral blood vessel and bronchial smooth muscle.*

Drug	A		B
	*ED_{50}(μg./kg./min)	% blockade of depressor response	50% mortality in G.P. bronchospasm test (mg./kg.)
Propranolol	62·0 ±5·0	†64%	0·1
Oxprenolol	30·25 ±5·0	61%	0·18
Practolol	162 ±4·0	0%	15·0

*ED_{50} is the dose of drug giving a 50% blockade of isoprenaline induced rise in heart rate in the cat.
†A figure higher than 50% indicates a greater activity on peripheral vessels than on the heart.

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Serum Trypsin Inhibitor and Paraquat

SIR,—Recently, we had the opportunity of estimating serum antitrypsin levels in three patients suffering from paraquat poisoning. In all three we found depressed levels. One patient, who subsequently died, had a serum antitrypsin level of 0·77 μmoles trypsin inhibited/min./l. Our normal value is 2·16 by the method of Dietz.[1] Two patients who subsequently recovered had levels of 0·99 and 1·10. The latter patient's level increased to 1·64 at a time when his lung function was returning to normal.

We were prompted to examine the serum trypsin inhibitor level following a report of abnormally low levels in certain patients with respiratory distress syndrome.[2] Paraquat poisoning has been suggested as an experimental model for the respiratory distress syndrome. Emphysema is another lung condition where there is a depressed