## Discussion

Gentamicin was isolated by Weinstein *et al.* from two previously undescribed micro-organisms of the genus micromonospora.[11] Early studies showed that it had a nephrotoxic action in animals but only in high doses.[12 13] More recently, however, morphological changes have been shown in the kidneys of rats given low doses of gentamicin.[6 7] Flandre and Damon[13] noted that gentamicin caused more severe damage in rats with surgically-induced renal insufficiency than in rats with normal renal function, which may have some bearing on our findings in patients with renal allografts. Several authors have found little or no evidence of gentamicin nephrotoxicity.[14-17] Leigh[18] and Taguchi and Siddiquuie[19] noted no renal toxicity when gentamicin was used in patients with renal transplants. Nevertheless, evidence of mild renal impairment has been reported in patients treated with gentamicin,[20-25] and some workers have reported more serious disturbances of renal function, sometimes when gentamicin has been given with cephalosporins.[26-31]

The urinary activity of one or more enzymes rose considerably in all patients treated with gentamicin in our study. NAG and GAL are lysosomal enzymes found in abundance in the renal tubules whereas alkaline phosphatase is located mainly on the brush border of the proximal renal tubules. The urinary enzyme increase appeared consistently within three days of the start of treatment and fell towards pre-treatment levels a week after treatment stopped. No such increase in urinary enzyme activity was noted during treatment with any other antimicrobial agent. The size of the increase in urinary enzyme activity in patients given gentamicin and a cephalosporin was similar to that observed when gentamicin alone was given.

The causes of changes in renal function in patients with renal allografts are often difficult to determine; rejection of the graft must always be considered. During 15 out of 20 courses of gentamicin serum creatinine rose, and during 11 out of 17 courses urinary protein excretion increased. Serum creatinine and urinary protein returned towards pre-gentamicin levels during treatment in only a minority of cases. Usually, levels returned to normal the week after stopping treatment. Our evidence suggests that these functional changes were due to gentamicin.

The morphological changes seen in rats[6 7] given gentamicin at doses as low as 1 mg $kg^{-1}$ $day^{-1}$ were also noted in biopsy specimens obtained from patients with renal allografts during gentamicin treatment. Tubular necrosis was not produced in any of our cases, and the observed reduction in urinary enzyme activity after gentamicin treatment implies that the damage was reversible in most cases. Nevertheless, deteriorating renal function during treatment necessitated graft nephrectomy in two patients and haemodialysis in another two. In rats withdrawal of gentamicin results in some tubular regeneration even after high doses of the antibiotic,[6] but caution should be exercised when giving this antibiotic, particularly to patients with renal allografts or renal disease. More specifically, an increase in urinary enzyme activity should not be interpreted as indicating rejection of a renal allograft when the patient is also receiving gentamicin.

We thank Mr. M. Bewick of Guy's Hospital, London, and Dr. B. Hulme of St. Mary's Hospital, London, members of the Southern Transplant Group for permission to study patients under their care. This work has been generously supported by the Endowments Funds of St. Thomas's Hospital.

We also thank Miss Dorcas Sharpe for typing the manuscript.

## References

1 Price, R. G., *et al.*, *Clinica Chimica Acta*, 1970, **27**, 65.
2 Dance, N., *et al.*, *Clinica Chimica Acta*, 1970, **27**, 87.
3 Wellwood, J. M., *et al.*, *British Medical Journal*, in press.
4 Wellwood, J. M., *et al.*, *British Medical Journal*, 1973, **2**, 261.
5 Sandman, R., Margules, R. M., and Kountz, S. L., *Clinica Chimica Acta*, 1973, **45**, 349.
6 Wellwood, J. M., *et al.*, *Journal of Pathology*, in press.
7 Kosek, J. C., Mazze, R. I., and Cousins, M. J., *Laboratory Investigation*, 1974, **30**, 48.
8 Leaback, D. H., and Walker, P. G., *Biochemical Journal*, 1961, **78**, 151.
9 Robinson, D., Price, R. G., and Dance, N., *Biochemical Journal*, 1967, **102**, 525.
10 Fernley, H. N., and Walker, P. G., *Biochemical Journal*, 1965, **97**, 95.
11 Weinstein, M. J., *et al.*, *Journal of Medicinal Chemistry*, 1963, **6**, 463.
12 Black, J., *et al.*, *Antimicrobial Agents and Chemotherapy*, 1963, **3**, 138.
13 Flandre, O., and Damon, M., in *Gentamicin: First International Symposium*, p. 47. Lucerne, Essex Chemie Ag., 1967.
14 Jackson, G. G., in *Gentamicin: First International Symposium*, p. 62. Lucerne, Essex Chemie Ag., 1967.
15 Gingell, J. C., and Waterworth, P. M., *British Medical Journal*, 1968, **2**, 19.
16 Jackson, G. G., *Practitioner*, 1969, **198**, 855.
17 Cox, C. E., *Journal of Infectious Diseases*, 1969, **119**, 486.
18 Leigh, D. A., *Postgraduate Medical Journal*, 1969, **45**, 254.
19 Taguchi, Y., and Siddiquuie, N., *Journal of Urology*, 1972, **107**, 911.
20 Shimizu, K., in *Gentamicin: First International Symposium*, p. 84. Lucerne, Essex Chemie Ag., 1967.
21 Lemercier, M., and Poilleux, F., in *Gentamicin: First International Symposium*, p. 101. Lucerne, Essex Chemie Ag., 1967.
22 Mariani, B., and Velluti, G., *Giornale Italiano Di Chemoterapia*, 1969, **16**, 1.
23 Arcieri, G. M., *et al.*, *Medical Journal of Australia*, 1970, **1**, 30.
24 Wilfert, J., *et al.*, *Journal of Infectious Diseases*, 1971, **124**, 148.
25 Hewitt, W. L., *Postgraduate Medical Journal*, 1975, **50**, Suppl., 55.
26 Brogard, J. M., *et al.*, *Therapeutique*, 1970, **46**, 627.
27 Schultze, R. G., Winters, R. E., and Kaussman, H., *Journal of Infectious Diseases*, 1971, **124**, Suppl., 145.
28 Opitz, A., *et al.*, *Medizinische Welt*, 1971, **22**, 434.
29 Kahn, T., and Stein, R. M., *Lancet*, 1972, **1**, 498.
30 Kleinknecht, D., Geneval, D., and Droz, D., *Lancet*, 1973, **1**, 1129.
31 Sillastre, J. P., *et al.*, *British Medical Journal*, 1973, **2**, 396.

# SHORT REPORTS

## Removal of Paraquat from Blood by Haemoperfusion over Sorbent Materials

Human ingestion of the herbicide paraquat (N,N'-dimethyl 4,4'-bipirydilium) can be fatal, mainly because of paraquat's effects on the lung.[1] Recent studies in animals[2] have shown that death and progressive lung fibrosis are preventable by minimizing absorption of paraquat from the gastrointestinal tract using repeated doses of oral sorbent agents.

We examine here the effect of haemoperfusion over activated charcoal or cation exchange resin, on plasma paraquat concentrations, since the toxic effects of paraquat seemingly result from selective accumulation of paraquat from blood into lung.[2]

### Methods and Results

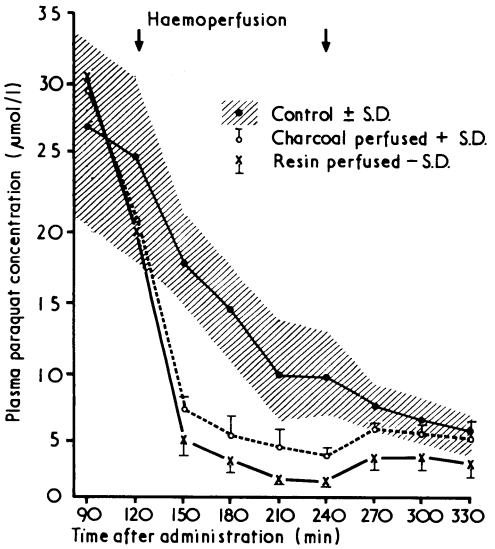
Initial screening of sorbents for their ability to remove paraquat from plasma (R.M. unpublished) suggested that uncoated extruded activated charcoal (Norit Clydesdale Limited, Scotland) and a cation exchange resin, Zerolit 225 SRC 21 (Permutit Company Ltd., London) were most suitable for haemoperfusion.

*In-vitro Experiments.*—One litre of heparinized bovine blood containing 7·8 μmol/l (2 mg/l) total paraquat (pure paraquat dichloride admixed with methyl $^{14}C$—paraquat) was continously recirculated at 200 ml/min from a reservoir at 37°C through a 250-ml polypropylene column containing either activated charcoal (three experiments) or cation exchange resin (three experiments). Paraquat concentrations were determined from radioactivity measurements. Both sorbents were totally effective within one hour.

*In-vivo Experiments.*—Nine male beagles (mean weight (±S.D.) 11·41±1·27 kg) were anaesthetized and injected intravenously with 29 μmol/kg (7·5 mg/kg) total paraquat (pure paraquat dichloride with 250 μCi methyl $^{14}C$-paraquat, specific activity 30 Ci/mol). After two hours three animals were haemoperfused with activated charcoal and three with cation exchange

resin while three remained untreated. Anticoagulation was achieved with heparin and blood flow maintained at 200 ml/min throughout haemoperfusion (two hours).

Both forms of haemoperfusion significantly reduced plasma paraquat levels ($P<0.05$) compared with control values (see fig.), cation exchange resin being more effective than activated charcoal ($P<0.05$). Plasma paraquat clearances remained consistently high using cation exchange but were lower and more variable with activated charcoal. After haemoperfusion plasma paraquat concentrations increased in both treated groups. Paraquat concentrations approached control values 30 minutes after charcoal haemoperfusion but took 90 minutes after cation exchange haemoperfusion.




Plasma paraquat concentrations in untreated dogs (control), those treated with uncoated activated extruded charcoal, and those treated with cation exchange resin. All points represent mean of three experiments.

*Conversion: SI to Traditional Units*—Paraquat: 1 μmol/l ≈ 0·26 mg/l.

Activated charcoal reduced blood platelet concentrations by 40% and cation exchange resin reduced them by 50%. The cation exchange resin was equilibrated before haemoperfusion with electrolyte solutions, and subsequently plasma calcium, magnesium, sodium, and potassium remained normal.

### Discussion

Progressive lung fibrosis leading to respiratory failure remains the most important lethal complication of paraquat poisoning in man, though renal failure is also common. Early reports suggested that paraquat exerts its toxic effect in a "hit and run" fashion.[3] Recently, however, paraquat has been shown in vivo to accumulate selectively in rat lung[2] and in vitro in rat and human lung by similar mechanisms.

After oral dosage of paraquat to rats sustained plasma paraquat concentrations of about 3·9 μmol/l (1 mg/l) resulted in paraquat accumulating in the lung and in death.[2] Repeated oral doses of sorbents (bentonite, Fuller's earth) effectively reduce gastrointestinal absorption of paraquat resulting in reduced plasma paraquat concentrations and preventing lung damage and death.[2]

In man paraquat removal has been attempted using forced diuresis,[1] peritoneal dialysis,[4] and haemodialysis.[5] The treatment we propose for rapid and efficient reduction of paraquat concentrations combines the haemoperfusion methods described here with forced diuresis and repeated administration of oral sorbents. The platelet falls we saw are acceptable.

The rebound in plasma paraquat concentration after haemoperfusion may be partly due to the method of paraquat administration, but may indicate the necessity for prolonged haemoperfusion, especially when renal excretion is impaired by concomitant acute renal failure.

This work is part of a continuing joint research programme for the development of artificial organs directed by Professor A. C. Kennedy, Department of Medicine, University of Glasgow, and Professor R. M. Kenedi, Bioengineering Unit, University of Strathclyde, and receives support from the Scottish Home and Health Department which is gratefully acknowledged. We thank Dr. J. M. Mackay and Mrs. E. Blakeley for invaluable help during this study. This work was carried out in close collaboration with Dr. M. S. Rose and Mr. L. L. Smith of Central Toxicology Laboratory, Imperial Chemical Industries, and the advice and help received is warmly appreciated. R. M. acknowledges receipt of a Science Research Council grant.

[1] Matthew, H., *et al.*, *British Medical Journal*, 1968, **3**, 759.
[2] Smith, L. L., *et al.*, *British Medical Journal*, 1974, **4**, 569.
[3] Barnes, J. M., *New Scientist*, 1968, **38**, 619.
[4] Oreopoulos, D. G., *et al.*, *British Medical Journal*, 1968, **1**, 749.
[5] Eliahou, H. E., *et al.*, *Israel Journal of Medical Sciences*, 1973, **9**, 459.

**Bioengineering Unit, University of Strathclyde, Glasgow G4 0NW**
R. MAINI, B.SC., Research Student

**University Department of Medicine, Royal Infirmary, Glasgow G4 0SF**
J. F. WINCHESTER, M.B., M.R.C.P., Senior Medical Registrar

# Gastric Fistula after Proximal Gastric Vagotomy

Though proximal gastric vagotomy is generally regarded as a safe operation[1] occasional complications have occurred.[2 3] Of particular importance is necrosis of the lesser curve of the stomach which may be accompanied by fatal peritonitis. We describe a patient who underwent routine proximal gastric vagotomy and developed a gastric fistula—a previously unrecorded complication of this procedure.

### Case Report

A previously fit 41-year-old man was admitted for elective surgery for a chronic duodenal ulcer. He had a 15-year history of recurrent dyspepsia. Barium meal examination had shown a chronic duodenal ulcer on two occasions. Apart from old healed inactive tuberculous lesions shown on chest *x*-ray films no abnormalities were found. Duodenal ulceration was confirmed endoscopically and a routine proximal gastric vagotomy carried out by a surgeon (R.W.H.) familiar with the method developed by Mr. H. Burge.

Three days later the patient developed fever, which began to swing and reached a peak of 39·2°C. Initial clinical examination and investigations showed no abnormality. Blood cultures were taken. The wound became indurated on the fifth day after operation and the pyrexia continued. Seven days after surgery *Klebsiella* spp. and *Pseudomonas* spp. were isolated from the blood cultures and gentamicin treatment began. The next day there was a profuse purulent discharge from the upper end of the abdominal wound. The patient had remained uncomplaining but on the 10th day he remarked that he was a little worried because his morning tea had discharged through the wound. Our suspicions of a gastric fistula were confirmed by giving an oral dose of methylene blue, which appeared on the wound dressing after a short interval. The pH of the discharge from the fistula was acid.

Subsequently the discharge decreased and when a Gastrografin swallow and fistulogram were carried out on the 14th and 15th days no gastric fistula could be shown. The patient left hospital three weeks after surgery feeling well and with no further discharge from the wound.

### Discussion

Sloughing of the lesser curve of the stomach is a rare but well-recognized complication of proximal gastric vagotomy.[4] We believe that our patient developed necrosis of the lesser curve which remained localized and subsequently discharged through the wound, thus creating a gastric fistula.

The stomach is a difficult organ to devascularize. The creation of an avascular strip along the lesser curvature of the stomach after proximal gastric vagotomy may be related to excessive use of diathermy, division of the ascending branch of the left gastric artery, damage to the stomach wall by a closely applied ligature, or intramural haematoma. Accidental perforations at operation are usually detected and oversewn. Sloughing usually occurs four to six days after operation[5] whereas a "missed" operative perforation often presents earlier as localized or diffuse peritonitis. Of six "operative" perforations after selective vagotomy reported from Copenhagen[3] at least two seem to have been due to necrosis of the lesser curve.