clinical studies of acute myocardial infarction have shown an association between mortality or the incidence of ventricular fibrillation and the use of oral hypoglycaemic agents.[9] We have been impressed by the acceptability to the patient of the relatively intensive dietary management adopted in our study, and if present trends continue a much smaller proportion of our maturity onset diabetic patients will be considered for treatment with oral hypoglycaemic agents. After the six-month assessment only six of our patients were admitted to the second stage of this study and started on an oral hypoglycaemic agent. We do not intend here to analyse this group in detail, but the criterion for advising oral hypoglycaemic treatment was a fasting plasma glucose consistently above 11 mmol/l (200 mg/100 ml).

Fasting plasma glucose, which is a relatively unimportant factor in predicting risk of a subsequent cardiovascular event,[10] showed as good an improvement in the good dieters as in those who co-operated less well. Thus, if plasma glucose alone was used as an index of diabetic control all of these patients might be classified as making a satisfactory response. The significant hyperinsulinaemia and hypertriglyceridaemia in the poor dieters shows that factors other than fasting glucose must be considered in assessing diabetic control in a long-term study. In this initial report these factors have not been affected by any therapeutic regimen other than diet and one foresees the complicated effects of random allocation on the basis of plasma glucose alone of some of these patients to treatment groups with one or other type of oral hypoglycaemic treatment or insulin. Furthermore, the simple fact of real carbohydrate intake as a prime cause of hypertriglyceridaemia in this subgroup of diabetic patients may not always have been rigidly assessed in studies of lipoprotein levels in patients attending a routine diabetic clinic.[11 12]

Another aspect of our study is the demonstration that the fall in fasting blood glucose which occurs in the first month of dietary treatment is much greater than in any subsequent month, though weight loss proceeds steadily throughout the first six months (except where interrupted by the 200-g carbohydrate intake before the second G.T.T., which itself indicates the overall degree of dietary restriction attained for the rest of the time). This is in keeping with the concept that carbohydrate restriction rather than weight loss is the determining factor in the control of the diabetic state.[13]

Dr. E. Trimble was in receipt of a Royal Victoria Hospital Fellowship. The plasma insulin assays were supported by a grant from the British Diabetic Association.

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# Evidence of Gentamicin Nephrotoxicity in Patients with Renal Allografts

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*British Medical Journal*, 1975, **3**, 278-281


## Summary

**Renal damage was assessed by measuring urinary enzyme excretion in 180 patients with renal allografts. Thirty-six of these patients were studied during 53 courses of treatment with antimicrobial agents which had begun when renal function was stable. Gentamicin was the only antimicrobial agent which was associated with an increase in urinary enzyme activity. There was usually also evidence of reduced renal function. Renal morphological changes similar to those produced by gentamicin in rats were observed in human allograft biopsy specimens obtained during gentamicin treatment.**



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## Introduction

The activity of certain urinary β-glycosidases is a sensitive indicator of renal cell damage. Increased urinary activity of *N*-acetyl β-D-glucosaminidase (NAG) and β-galactosidase (GAL) have been found in patients with renal disease.[1-3] Some workers have noted an increase in urinary NAG activity during rejection of renal allografts.[4 5] Increased urinary activity of these enzymes indicates renal injury but not the cause of injury. During a 15-month study of 180 patients with renal allografts the administration of gentamicin was always followed by a rise in urinary enzyme activity within three days of the start of treatment. The effect of gentamicin on the excretion of urinary enzymes and renal morphology in rats was therefore studied. At doses of 5 mg $Kg^{-1}$ $day^{-1}$ increased excretion of urinary enzymes and renal morphological changes were found.[6] Kosek *et al.*[7] noted renal morphological changes in rats given doses as low as 1 mg $kg^{-1}$ $day^{-1}$. We describe here the effects of gentamicin treatment on patients with renal allografts.

## Patients and Methods

Enzyme assays were performed on fresh mid-stream specimens of urine within six hours of collection. It was unnecessary to dialyse or centrifuge the urine before enzyme assay.[4] Fluorimetric methods were used to determine the activity of NAG,[8] GAL,[9] and alkaline phosphatase,[10] using urine samples diluted twenty fold and the appropriate 4-methylumbelliferyl substrates. Enzyme activity was expressed per mg of urinary creatinine to account for the effect of varying rates of urine flow at the time of collection.[3] Creatinine concentration was measured by the alkaline picrate method modified for autoanalyser (Technicon).

During a 15-month study of 180 patients with renal allografts urinary enzyme activity was measured during and either before or after 171 courses of treatment with antimicrobial agents in 63 patients. At the time of administration of many of these agents, however, there were other possible causes for changes in renal function and increased enzyme excretion, such as septicaemia, hypotension, allograft rejection, or urinary fistulae. Such cases were therefore excluded and we studied the effects of treatment in 36 patients receiving 53 courses of antimicrobial agents when there was no other recognized factor which could have caused an increase in urinary enzyme activity (table I). The reasons for the administration of these drugs are shown in table II.

TABLE I—*Courses of Antimicrobial Agents Given while Urinary Enzyme Activities were being Measured*

| | No. of Courses | No. of Courses in which Effect on Urinary Enzyme Activity could be Assessed |
|---|---|---|
| Gentamicin alone | 19 | 11 |
| Gentamicin and another antibiotic | 20 | 8 |
| Penicillins | 63 | 17 |
| Cephalosporins | 32 | 6 |
| Sulphonamides | 8 | 4 |
| Nalidixic acid | 4 | 1 |
| Nitrofurantoin | 2 | 1 |
| Tetracyclines | 2 | 1 |
| Others | 11 | 4 |
| Total | 171 | 53 |

TABLE II—*Reasons for Administration of Courses of Gentamicin and Other Antimicrobial Agents whose Effect on Urinary Enzyme Activities could be Assessed. Results are Numbers of Courses*

| | Gentamicin | Other Agents |
|---|---|---|
| Asymptomatic urinary infections | 2 | 20 |
| Respiratory infections | 4 | 8 |
| Pyrexia of uncertain origin | 8 | 3 |
| Prophylaxis and miscellaneous | 5 | 3 |
| | 19 | 34 |

## Results

### URINARY ENZYME ACTIVITY

The effect of administration of 34 courses of antimicrobial agents other than gentamicin on urinary NAG activity is shown in table III. Mean NAG activity did not rise by more than 10% during the administration of any of these drugs. Urinary NAG activity was assayed daily during 19 courses of gentamicin and also in the week before and the week after 12 of these courses. Gentamicin was the only antibiotic given in five of the 12 courses assessed but was given with cephalexin in four of the courses and with cloxacillin in three other courses. Table IV shows the changes in urinary NAG activity before, during, and after gentamicin treatment. Urinary enzyme activity rose in all cases during gentamicin treatment, the daily ratios from the start of treatment varying from 1·1 to 10·7. The lower ratios reflected the 24- or 48-hour lag after the start of gentamicin before a sizeable increase in urinary NAG activity occurred. Urinary NAG activity fell after stopping treatment and one week later had usually almost reached pre-gentamicin levels. The ratios of the daily NAG activity during and after treatment ranged from 0·8 to 0·2. The higher ratios reflected the two or three days after completion of treatment, when urinary enzyme activity was still greatly raised. Urinary NAG measurements made during the other seven courses of gentamicin (gentamicin alone (six); gentamicin and clindamycin (one)) could be compared only with the enzyme activity in the week before (six) or the week after (one) gentamicin. The ratio of the mean NAG activity during to the mean NAG activity before gentamicin in the six courses varied from 1·5 to 5·6. In the week after the seventh course of gentamicin the mean urinary NAG activity was half the value during treatment.

TABLE III—*Changes in Urinary NAG Activity (nmol $h^{-1}$ $mg^{-1}$ urinary Creatinine) before, during, and after 34 Courses of Antimicrobial Drugs other than Gentamicin. Results are Ranges (and Means)*

| Antimicrobial Agent | No. of Courses | Ratio of Mean NAG Activity during Therapy: Mean NAG Activity before Therapy | Ratio of Mean NAG Activity after Therapy: Mean NAG Activity during Therapy |
|---|---|---|---|
| Ampicillin | 12 | 0·6-1·1 (0·8) | 0·6-1·4 (0·9) |
| Ampicillin and cloxacillin | 5 | 0·9-1·1 (1·0) | 0·6-1·2 (0·9) |
| Cephalexin | 6 | 0·7-1·1 (0·8) | 0·7-1·4 (1·0) |
| Sulphonamides | 4 | 0·6-0·9 (0·8) | 0·8-1·8 (1·3) |
| Nalidixic acid | 1 | 0·6 | 1·0 |
| Nitrofurantoin | 1 | 1·1 | 1·0 |
| Tetracycline | 1 | 0·7 | 0·8 |
| Combinations | 4 | 0·8-1·1 (1·0) | 0·8-1·2 (1·0) |

TABLE IV—*Changes in Urinary NAG Activity (nmol $h^{-1}$ $mg^{-1}$ Urinary Creatinine) before, during, and after 12 Courses of Gentamicin. Results are Ranges (and Means)*

| | Ratio of Daily NAG Activity during Gentamicin: Mean NAG Activity before Gentamicin | Ratio of Daily NAG Activity after Gentamicin: Mean NAG Activity during Gentamicin |
|---|---|---|
| Gentamicin alone (5 courses) | 1·4-9·3 (4·1) | 0·8-0·2 (0·4) |
| Gentamicin and cephalothin or cephalexin (4 courses) | 1·9-10·7 (4·7) | 0·7-0·3 (0·5) |
| Gentamicin and Cloxacillin (3 courses) | 1·1-6·6 (2·8) | 0·8-0·2 (0·6) |

Urinary GAL activity was measured before, during, and after three courses of gentamicin combined with cephalothin (one), cephalexin (one), and cloxacillin (one). Urinary alkaline phosphatase activity was measured before, during, and after three courses of gentamicin alone and one course of gentamicin and cephalexin. Urinary GAL activity increased on each occasion during treatment—sometimes fivefold—and decreased on completion of treatment. Urinary alkaline phosphatase also rose during each of four courses of gentamicin; on one occasion the activity reached 37 times the value before treatment. Urinary alkaline phosphatase activity fell towards pre-gentamicin levels the week after stopping the drug.

The dose of gentamicin varied from 25 to 90 mg three times a day, but there was no obvious relation between the administered dose and the size of the rise in urinary enzyme activity. Evidence of excessive retention of gentamicin was not detected, but records of serum levels were incomplete in some patients.

### CHANGES IN RENAL FUNCTION

Fig. 1 illustrates changes in serum creatinine, urinary protein excretion, and urinary NAG activity during two courses of gentamicin given to a patient with a renal allograft. Gentamicin was given prophylactically before two operations. On the first occasion bilateral nephrectomy was performed and on the second teeth were extracted under local anaesthetic. Serum creatinine, urinary protein, and urinary NAG activity rose during both courses of the drug. Gentamicin was discontinued and the patient was treated for rejection. Serum creatinine and urinary protein levels then fell, and the urinary NAG activity returned towards the pre-treatment level. Allograft biopsy was not performed on either occasion.

Serum creatinine and urinary protein were measured during 20 courses of gentamicin and changes in one or other of these values occurred in most courses. There seemed to be no reason why renal function should deteriorate during these 20 courses other than gentamicin treatment or possibly rejection. Serum creatinine and urinary protein were measured for the seven days before and during gentamicin treatment. Increases in serum creatinine of 26·5 μmol/l (0·3 mg/100 ml) or less were not regarded as evidence of a change in renal function, and single isolated increases in serum creatinine of

greater than 26·5 μmol/l were similarly disregarded. Urinary protein estimates were not sufficient to enable assessment before three of the courses of gentamicin. In the remaining 17 courses urinary protein excretion was less than 1 g/24 hours during the week before treatment. Table V shows the changes in serum creatinine and urinary protein which occurred when gentamicin was given. Serum creatinine rose during 15 of the 20 courses of gentamicin and urinary protein in 11 of the 17 courses. Table VI indicates the time of the return of raised serum creatinine and urinary protein levels towards pre-gentamicin values.

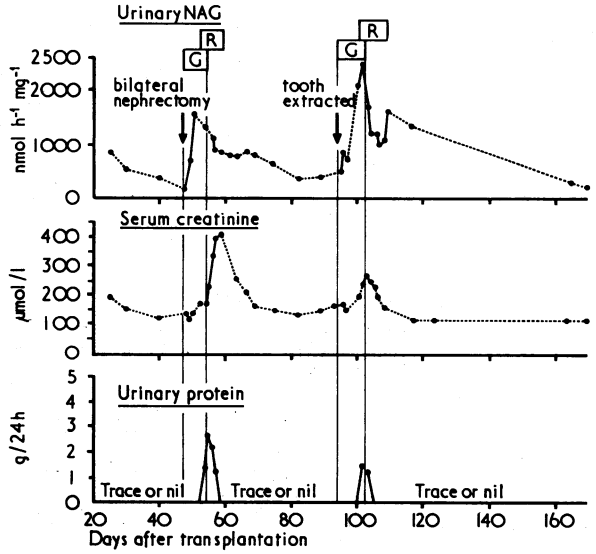


FIG. 1—Changes in urinary NAG activity, serum creatinine, and urinary protein excretion during two courses of gentamicin (G) given to patient with renal allograft as prophylactic measure before surgical operations. As result of changes patient was treated for rejection (R) both times.

TABLE V—*Changes in Serum Creatinine and Urinary Protein Excretion in Relation to Gentamicin Administration. Results are Numbers of Courses.*

| | Serum Creatinine | | | Urinary Protein | |
|---|---|---|---|---|---|
| | Rising | Stable | Falling | ≤1g/24h | >1g/24h |
| Before gentamicin .. | 0 | 8 | 12 | 17 | 0 |
| During gentamicin .. | 15 (mean rise 256 μmol/l; range 35-681) | 2 | 3 | 6 | 11 (mean peak 2·0g/24 h; range 1·1-3·4) |

TABLE VI—*Time when Raised Serum Creatinine and Urinary Protein Levels Returned to Normal before Gentamicin Treatment*

| | No. of Increases Related to Treatment | During Gentamicin Treatment | Within 7 Days of End of Treatment | No return within Week of End of Treatment | Unassessable* |
|---|---|---|---|---|---|
| Serum creatinine .. | 15 | 4 | 6 | 1 | 4 |
| 24-Hour urinary protein excretion .. | 11 | 3 | 7 | 0 | 1 |

*Deteriorating renal function after onset of gentamicin necessitated removal of two grafts, and two other patients required heamodialysis.

## MORPHOLOGICAL CHANGES IN RENAL ALLOGRAFTS DURING GENTAMICIN TREATMENT

Renal biopsy specimens obtained from three patients with renal allografts during treatment with gentamicin were fixed in 4% methanol-free formaldehyde and then divided for light and electron microscopy. Tissue for light microscopy was processed through paraffin wax but for electron microscopy the tissue was post-fixed in osmium tetroxide and processed through Epon 812. There was tubular dilatation and interstitial fibrosis, but none of the biopsy specimens showed the light microscopic changes of tubular necrosis or of acute rejection.

Thin sections from the Epon-embedded tissue were stained with 1% toluidene blue before preparation of the blocks for ultra-thin sectioning. These thin sections showed occasional dark granules in the cytoplasm of proximal tubular epithelium similar to those seen in the epithelium of rats treated with gentamicin. Electron microscopy showed that these dark granules corresponded with dense laminated bodies found throughout the cytoplasm of the proximal tubular cells (fig. 2). Similar laminated bodies were also found in the tubular lumen.

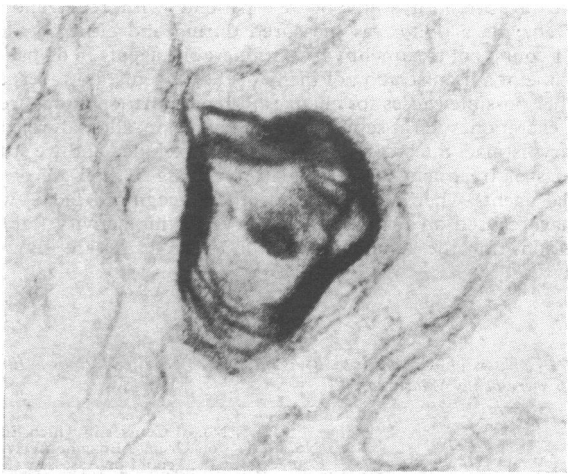

FIG. 2—Laminated dense body in basal portion of proximal tubule epithelial cell shown by electron microscopy. (× 60 000.)

There were also other features of degeneration in the proximal tubular epithelium, notably swelling and vacuolation of mitochondria, formation of coarse multivesicular bodies, and increased prominence of apical dense tubules and vesicles (fig. 3). Cell necrosis was not apparent. These changes resembled very closely the degenerative changes in the proximal tubular epithelium of rat kidneys during low-dose gentamicin treatment.[3]

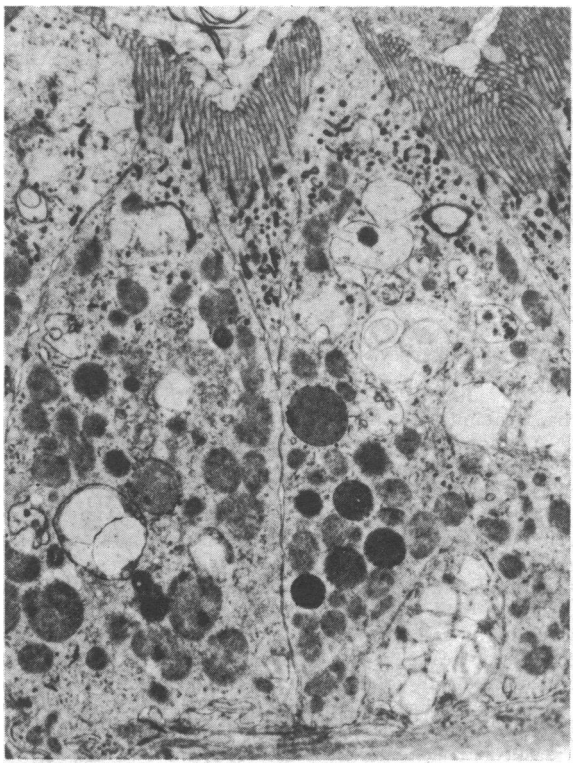

FIG. 3—Proximal tubular epithelium showing swelling of mitochondria and increased prominence of subapical tubules and vesicles. Laminated bodies are seen some of which are present in tubular lumen (top). (×8 500.)

## 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.

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# 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