Editorial
Antibiotic Therapy in Renal Failure

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When renal function is impaired, any drug which is normally excreted by the kidneys will be retained in the body. Continued administration of such a drug at normal dosage will result in abnormally high blood levels being reached, and dangerous side-effects may develop. The majority of antibiotics are excreted by the kidney to a variable extent, and it has long been appreciated that some modification of dosage was required in patients with renal failure. Determination of the dose of antibiotic required, however, is fraught with difficulty. Reduction in the amount given may avoid side-effects, but may also fail to achieve serum levels adequate to ensure the destruction of the infecting organism. Varying degrees of renal failure will demand different dose regimes, and in patients on regular dialysis treatment (RDT), the position is further complicated by the effect of dialysis on serum levels of antibiotics. Once therapy has been started other variables may appear, e.g. effective treatment of renal infection may improve renal function, with a subsequent increase in the excretion of the drug and reduction of the serum level below that required for eradication of the infection. Conversely, renal damage may occur after the administration of some antibiotics, and excessive dosage of such a drug even over a short period may establish a vicious circle of increasing renal damage and increasingly toxic serum levels of antibiotic.

Antibiotic therapy is frequently required in patients with renal failure, particularly in those on regular dialysis treatment who are constantly at risk, particularly from staphylococcal shunt infections and from infection with various gram-negative organisms. To prescribe effective antibiotic therapy while avoiding toxicity presents a considerable problem, since few pharmacological studies of antibiotics in man provide rational guide-lines for their use in the presence of renal failure. Kunin and Finland (1959a) reviewed the literature on the restrictions imposed on antibiotic dosage by renal failure, and their work has been the basis of a more logical approach to the problem. Since 1959, many authors have studied various antibiotics and their use in
renal failure, but concise information on the dosage of many of these drugs is still lacking. The problem may be complicated by the presence of fluid and electrolyte upsets in the patient, since overhydration and dehydration will alter the size of the space in which the drug is distributed. Interaction between drugs is a subject about which little is known, and the capacity of the body to detoxicate or excrete drugs is not necessarily constant. This review has been undertaken in an attempt to define rational antibiotic dosage in renal failure where possible, and to indicate where further information is required.

PENICILLINS

Benzylicillin is a remarkably non-toxic drug, and this property is shared by the newer semi-synthetic penicillin derivatives. Eagle and Newman (1947) showed that the renal clearance of penicillin exceeded 500 ml per minute, and the drug undoubtedly accumulates in renal failure. The half life of penicillin given intramuscularly is increased from 1 hour in the normal to about 10 hours in anuric patients (Kunin & Finland, 1959b). Massive doses of penicillin have been said to produce neuromuscular excitability and convulsions; these patients had some degree of renal tubular dysfunction, and the evidence implicating penicillin was not conclusive (New & Wells, 1965). There is no doubt that penicillin accumulates in the body in renal impairment, and that in general this is harmless. One of the few suggestions of toxicity came from Baldwin et al (1968) who reported 7 cases of fever, eosinophilia, allergic features and renal failure occurring in patients receiving large doses of penicillin and methicillin. They reviewed the literature, and found 15 cases of suggested nephropathy after penicillin, but none had convincing evidence incriminating the drug (c.f. methicillin below). Since even very large doses of benzyl penicillin seem safe, the drug can be given in normal dosage to patients with any degree of renal failure, thereby ensuring therapeutic effect without serious risk of side-effects. In patients on regular dialysis treatment, therapeutic blood levels for most sensitive organisms will be achieved by giving 1 million units every 12 hours (Kunin & Finland, 1959a), and again this is quite safe. Since benzyl penicillin is dialysable (Maher & Schreiner, 1969), the dose should be given at the end of dialysis on days when this occurs. If benzyl penicillin is to be used in massive doses (as in sub-acute bacterial endocarditis), then the dose should be monitored by blood levels and the minimum inhibitory concentration (MIC) for the organism known.

Ampicillin is the most widely used of the semi-synthetic penicillins, its spectrum of antimicrobial activity extending into the area of gram-negative bacteria. It is less effective than benzyl penicillin against sensitive gram-positive cocci, and its principal use is against strains of E. coli and some
Proteus strains. Like benzyl penicillin, ampicillin is excreted in the urine, and its half-life is extended from 1.8 hours in normal subjects to 18.2 hours in patients with creatinine clearances of 4 ml/s per minute (Kunin & Finkelberg, 1970). Almost the only adverse effect attributed to ampicillin is a skin rash, which may be severe and become purpuric. This occurs in about 5 per cent of patients without renal damage who receive the drug and is much commoner in the presence of renal damage (Lee & Hill, 1968; McGeown, 1970). Since the rash due to ampicillin may be dose-related, or produced at a certain blood level, it may be advisable to reduce the dosage at creatinine clearances less than 20 ml per minute to 250 mg 6-hourly, and to reduce to 250 mg 12-hourly in the anuric patient. In serious infections, however, it is our policy to give ampicillin in normal dosage (500 mg 6-hourly) to patients with any degree of renal failure, accepting the risk of a skin eruption to ensure good therapeutic effect. Even in anephric patients, resolution of the infection almost always occurs before the rash appears. This view is supported by Kunin and Finkelberg (1970), who also showed that while ampicillin reached good concentration in the urine of patients with moderate degrees of renal failure, the drug would probably be ineffective against urinary tract infection when the creatinine clearance was less than 5 ml per minute.

Carbenicillin is one of the newest of the semi-synthetic penicillins, and is also effective against gram-negative organisms. Levels above 12 μg/ml are bactericidal for 90 per cent of Proteus organisms and at such low serum levels carbenicillin is probably without toxic effect. Its use has also been advocated for treatment of Pseudomonas infections but in this instance serum levels of carbenicillin around 100 μg/ml are required. In the presence of normal renal function, such levels can be maintained only by giving 1 g of carbenicillin intravenously each hour, together with probenecid to block tubular excretion of the drug. Johnson et al (1969) suggested that carbenicillin was still virtually non-toxic at such high serum levels, but it has recently been suggested that when given in doses of 24 g per day to patients with renal impairment a severe and persistent haemorrhagic diathesis may develop (Lurie et al 1970). The mechanism appears to be an interference with the conversion of fibrinogen to fibrin.

Carbenicillin is retained in the body in renal failure and is fairly rapidly removed by haemodialysis (Maher & Schreiner, 1969). In the treatment of infection with sensitive organisms, with an MIC of 12 μg/ml or less, 1 g of carbenicillin 12-hourly will suffice in patients with creatinine clearances between 20 and 5 ml per minute. Patients on RDT should have 1 g of carbenicillin daily, the dose on dialysis days being given at the end of the procedure (Linton et al 1968). The high serum carbenicillin levels required to eradicate Pseudomonas infections can be achieved in patients with renal failure with relative ease. Eastwood and Curtis (1968) suggest that patients with
creatine clearances of less than 5 ml per minute should have 2 g of carbeni-
cillin every 8 to 12 hours to maintain serum levels around 100 µg/ml, and
that this should be increased to 2 g every 4 hours while dialysis is being
carried out. Even at these blood levels, however, some strains of Pseudo-
omonas will not be destroyed and carbenicillin is probably not the drug of
first choice in infections of this nature.

Methicillin and cloxacillin are two of the penicillins which are resistant
to cleavage by penicillinase, and their use should be confined to infections
with penicillinase-producing staphylococci, which are frequently responsible
for shunt infections and chest infections. There is some evidence to suggest
that methicillin may be more liable than other penicillins to produce renal
damage associated with allergic phenomena. Baldwin et al (1968) described
4 cases in which this type of renal damage followed the use of methicillin and
they suggested that the effect was dose-related. Braminger and Remington
(1968) reported the same syndrome associated with methicillin therapy, and
suggested that it was a hypersensitivity response which might occur at any
serum level. Although such hypersensitivity reactions are reversible, they
should probably be avoided, and some modification of methicillin dosage may
be advisable. Like the other penicillins, both methicillin and cloxacillin are
retained in the body in renal failure, but to a lesser degree, and the serum
levels are relatively little effected by dialysis (McCloskey & Hayes, 1967;
Linton et al 1968). There is as yet no available information about the degree
of reduction in dosage of these drugs required at the earlier stages of chronic
renal failure. Linton et al (1968) showed that in patients on RDT, 1 g of
cloxacillin given daily would maintain serum levels over 5 µg/ml for 24 hours,
the dose being given after the procedure on dialysis days. This serum level
should be sufficient to eradicate 100 per cent of penicillinase-producing
staphylococci (MIC < 3 µg/ml).

STREPTOMYCIN

Although most commonly used in the treatment of tuberculosis, streptomycin
is also effective against many gram-negative organisms. Very little strepto-
mycin is absorbed from the alimentary tract, but after intramuscular
injection, the majority of the drug is excreted in the urine. Kunin and
Finland (1959b) showed that considerable retention of streptomycin occurs in
uraemia, the half-life being extended from 2.4 hours in the normal to over
50 hours in the anuric patient. Streptomycin is cleared mainly by glomerular
filtration, and is readily removed by haemodialysis (Edwards & Whyte, 1959).
Toxic effects of streptomycin include vestibular damage, nerve deafness,
agranulocytosis and renal damage (Goodman & Gilman, 1965). These toxic
effects are related to the magnitude and duration of therapy, and seldom
occur if the blood streptomycin level can be kept below 25 µg/ml.

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The areas of therapeutic use of streptomycin have become constricted with the development of other drugs with broader and more potent antibacterial activity. However, streptomycin is still widely used in treating tuberculosis, which not infrequently complicates chronic renal failure. For patients who retain some renal function (creatinine clearance below 20 ml per minute and above 5 ml per minute), streptomycin dosage must be reduced. No safe schedule of administration can be given because of the relatively narrow range of serum levels which are both safe and therapeutically effective; the blood streptomycin levels should be kept between 8 and 25 µg/ml (90 per cent of M. tuberculosis sensitive at 8 µg/ml). Kunin and Finland (1959a) suggest a loading dose of 1 g of streptomycin followed by 0.5 g every 2 or 3 days. The dose must then be adjusted by frequent measurements of the blood level of the drug, since variation in renal function may occur.

In patients on RDT, safe and effective levels of streptomycin can be maintained by giving 10 mg of the drug per kg of body weight at the end of each dialysis (Linton et al 1968). Ogg et al (1968) described the treatment of tuberculosis in a patient on RDT. Similar doses of streptomycin were used, but mild vestibular damage appeared after 11 g of streptomycin had been given in 5 weeks. Serial assays of the serum level of streptomycin are therefore also required in this situation. These authors also recommend the administration of Isoniazid in a daily dose of 3 mg/kg body weight. Pyridoxine was also given in a daily dose of 20 mg to combat the clinical evidence of pyridoxine deficiency which may occur when Isoniazid is used (Robson & Sullivan, 1963). Para-aminosalicylic acid (PAS) was begun at a dose of 6 g per day and reduced to 3 g after each dialysis (dialysed thrice weekly). These dosage regimes provide some guide to satisfactory therapy, but it is probable that long term treatment of a chronic infection like tuberculosis cannot safely be maintained without serial measurements of antibiotic levels. Recently rifampicin has been found to be useful as a second line drug in the treatment of patients with tuberculosis. However as it is excreted almost entirely in the bile and can be given to patients in renal failure without modification of dosage (McGeachie et al 1970) there is a strong case for using it in the primary treatment of tuberculous patients with renal failure.

KANAMYCIN

Kanamycin is an extremely effective drug in the treatment of gram-negative infections. Fekety et al (1962) showed that 90 per cent of strains of E. coli were sensitive to serum kanamycin levels of 5 µg/ml and 80 per cent of Proteus spp to 8 µg/ml. The use of kanamycin in renal failure has been restricted because of the well documented ototoxicity and nephrotoxicity of the drug (Kunin & Finland 1959a).

Kanamycin is very stable in the body and the kidney is virtually the sole
route of excretion with recovery in the urine of over 90 per cent of the parenteral dose. Excretion is by glomerular filtration and kanamycin clearance is about 76 per cent of inulin clearance. There is a linear prolongation of the half-life of kanamycin as creatinine clearance falls (Sørensen et al 1967). Toxic effects usually occur when the serum level of kanamycin exceeds 25 µg/ml, but there have been reports of ototoxicity at lower blood levels (Toma & Main, 1967). Since the therapeutic index of kanamycin is relatively low (e.g. for Proteus infections the serum level of kanamycin should be kept above 10 µg/ml for effect and below 25 µg/ml to avoid toxicity), modification of dosage has to be undertaken with almost any degree of renal impairment. Sørensen et al (1967) suggested a complex dose regime based on the serum creatinine level, but the validity of this is questioned by work done by Orme and Cutler (1969). These authors measured simultaneous renal clearances of creatinine, inulin, PAH and kanamycin in 34 patients, confirming that the clearance of kanamycin approaches that of inulin, and suggesting that kanamycin is distributed in the inulin space, (i.e. the extracellular water). They also showed that changes in extracellular fluid volume made significant differences to the half-life of kanamycin. Reduction in extracellular fluid volume reduced the half-life of kanamycin considerably when compared with the half-life in an overhydrated patient with the same GFR. They suggest that the half-life of kanamycin be determined from the following formula:--

\[ T_{1/2} \text{ (Hours)} = \frac{3.6 \times \text{body wt (kg)}}{C_{\text{creatinine (ml/min)}}} \]

and that the dosage of kanamycin be 7 mg/kg body weight, given at intervals of three times the half-life of kanamycin. Even this regime should be modified if gross overhydration or dehydration exists. Although this work perhaps represents the most scientific approach to determination of kanamycin dosage, for patients with renal impairment who have not yet reached the stage of RDT it is still advisable to check the efficacy and safety of the dose given by serial estimations of serum kanamycin levels.

Dosage of kanamycin in the patient whose renal function is negligible is perhaps easier than in those with some degree of residual function. Ory et al (1966) and Linton et al (1968) showed in patients on RDT that 0.5 g of kanamycin given at the beginning of each dialysis avoided dangerously high serum levels, yet achieved therapeutic concentrations around 10 µg/ml, maintained for up to 80 hours. The same dose of kanamycin repeated at the beginning of each twice-weekly dialysis achieves continuous therapeutic levels for as long as is necessary.

GENTAMICIN

Gentamicin is a broad-spectrum antibiotic belonging to the amino-glycoside group which includes streptomycin and kanamycin. It is effective against a
wide range of gram-positive and gram-negative bacteria, including Pseudomonas aeruginosa, Proteus and various staphylococci. Serum gentamicin levels of 4.5 \( \mu g/ml \) are bactericidal for all these organisms (Weinstein, 1967). Like kanamycin, gentamicin produces vestibular damage if excessive blood levels are reached (Jao & Jackson, 1964), and the manufacturers advise that a serum level of 10 \( \mu g/ml \) should not be exceeded (Curtis et al 1969).

Gentamicin is excreted almost entirely by glomerular filtration (Black et al 1963), and there is a good inverse correlation between serum half-life and GFR (Kunin, 1968; Gingell & Waterworth, 1968). It should be remembered, however, that the peak serum level after a single intramuscular dose of gentamicin is related to body weight, and not to GFR, reflecting presumably the size of the space in which the antibiotic is diluted (Gingell et al 1969). In patients with varying degrees of renal failure, the dosage of gentamicin must be adjusted in relation to renal function. The recommended dose of gentamicin in normal patients is 0.8 mg/kg every 8 hours for systemic infections, but only 0.4 mg/kg for urinary infections; the latter dose produces average peak serum levels of 2.6 \( \mu g/ml \), inadequate for some organisms, particularly Pseudomonas. Gingell et al (1969) found that single doses of 1 mg/kg body weight produced peak serum levels all higher than 4 \( \mu g/ml \) but lower than 10 \( \mu g/ml \). They suggest that after the full loading dose, modification of the dosage for varying degrees of renal failure should be achieved by altering only the interval between doses:

<table>
<thead>
<tr>
<th>Dose and Frequency</th>
<th>GFR (ml/min)</th>
<th>Serum Creatinine (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg 8-hrly</td>
<td>70</td>
<td>1.2</td>
</tr>
<tr>
<td>1 mg/kg 12-hrly</td>
<td>30 - 50</td>
<td>1.2 - 2</td>
</tr>
<tr>
<td>0.5 mg/kg 24-hrly</td>
<td>10 - 30</td>
<td>2 - 5</td>
</tr>
<tr>
<td>0.5 mg/kg 36-hrly</td>
<td>5 - 10</td>
<td>5 - 10</td>
</tr>
<tr>
<td>0.5 mg/kg 48-hrly</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Initial dose in all cases 1 mg/kg (Gingell, 1970).

As for kanamycin, it may be that variations in extracellular water influence the half-life of gentamicin, and estimation of serum levels would still be advisable, at least until further clinical experience of this dose schedule has been obtained.

In patients on RDT, satisfactory levels of gentamicin can be maintained by giving a dose of 1 mg/kg towards the end of each twice-weekly dialysis (Curtis et al 1969). These authors also recommend the administration of antibiotics by the intravenous route, in order to avoid haematomatformation.

**COLISTIN**

Colistin, which has been shown to be identical to polymyxin E, is active
primarily against gram-negative bacteria, and is used principally against Pseudomonas aeruginosa. The antibiotic is bactericidal for this organism at serum levels which are fairly readily obtainable in man. Approximately 90 per cent of Pseudomonas strains are killed by colistin serum levels of 5 μg/ml, and in subjects with normal renal function the recommended dose is 5 mg/kg body weight daily for adults with systemic infections (Goodman & Gilman, 1965).

A large proportion of injected colistin is excreted in the urine, and it would be expected that the serum half-life of this drug would be prolonged in renal failure; this has been shown to be so by Goodwin and Friedman (1968). Despite this, few recommendations as to dosage at various levels of renal function have been made, although many authors acknowledge the need for modification of dose. The following regime was suggested by MacKay and Kaye (1964):

<table>
<thead>
<tr>
<th>C_{creatinine} (ml/min)</th>
<th>Dose (mg/kg body wt)</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>2.5</td>
<td>12 hrs</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>1.5</td>
<td>12 hrs</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>1.5</td>
<td>18 - 36 hrs</td>
</tr>
<tr>
<td>0</td>
<td>2.0</td>
<td>given once only</td>
</tr>
</tbody>
</table>

It would be relatively simple to improve on this schedule by repeating for colistin the studies described on kanamycin and gentamicin. However, evidence is accumulating to suggest that colistin is nephrotoxic, and its use in patients with impaired renal function may not be advisable. Brumfitt et al (1966) showed that even in normal subjects, a single dose of colistin produced a significant fall in creatinine clearance, and that this did not return to normal for up to 4 weeks. This reversible effect might be acceptable in patients with good renal function, but might be catastrophic in those with pre-existing renal damage. This curios effect of colistin has been confirmed by Price and Graham (1970), who observed a rapid and profound fall in creatinine clearance and rise in blood urea in patients given high dose colistin. Some of these patients died from the underlying infection and 5 were found to have pathological evidence of acute tubular necrosis. In those who survived, renal function returned to baseline levels in a few weeks. These observations might seem to exclude colistin from use in renal impairment, but it is of interest to note that Caldwell et al (1969) claim to have produced a transient fall in creatinine clearance in normal subjects not only with a single injection of colistin, but also with single injections of ampicillin, and of sterile saline.

In patients on RDT with no significant residual renal function, Curtis and Eastwood (1968) considered the possible nephrotoxicity of colistin to be irrelevant, and emphasise the value of colistin in treating Pseudomonas...
infections. They suggest that a single dose of 2-3 mg/kg body weight given intravenously at the end of each twice weekly dialysis will maintain satisfactory blood levels in patients on RDT. This regime does, however, produce transient very high serum levels of colistin, and there have been reports of convulsions, coma and respiratory arrest when colistin has been given in high dosage to uraemic patients (Greenberg & Sanford, 1967).

CEPHALOSPORINS

Several cephalosporin antibiotics have come into general use since their initial discovery by Brotzu in 1948. In the United Kingdom cephaloridine has been the most widely used drug, with cephalothin and cephalaxin becoming available more recently. These drugs all have a wide antibacterial spectrum, being bactericidal to many gram-positive and gram-negative organisms. Their main clinical use is against penicillinase-producing staphylococci, but they are also effective against Clostridia, streptococci and a variety of gram-negative organisms, including E. coli (Muggleton & O'Callaghan, 1967). Cephaloridine and cephalothin must be given by the parenteral route but cephalaxin can be administered orally.

Cephaloridine

Within 6 hours of an intramuscular injection, 75 per cent of cephaloridine is excreted in the urine, and this excretion is unaffected by the coincidental administration of probenecid (Naumann, 1967). Most of a single intramuscular dose is excreted within 24 hours by glomerular filtration. The half-life of cephaloridine in the serum of normal subjects is 94 minutes and this is prolonged to 3-4 hours when the creatinine clearance falls below 40 ml per minute. With a creatinine clearance of 5 ml per minute the serum half-life of cephaloridine is 20-24 hours. Urine concentrations of cephaloridine fall from over 1000 µg/ml at creatinine clearances of 70 ml per minute to under 80 µg/ml at creatinine clearances of less than 10 ml per minute (Pryor et al 1967). These authors also observed a progressive decline in the half-life of this drug in the serum of an anephric patient from an initial level of 21.5 hours to a level of 8.2 hours after a period of several months regular dialysis treatment. This observation was confirmed by Curtis and Marshall (1970) who noted an inverse relationship between the serum half-life and the duration of regular dialysis therapy. The reason for these observations is not clear, but it is possible that the increase in the rate of break-down of cephaloridine is due to an enzyme induction effect of barbiturates or heparin which are regularly given to these patients.

Cephaloridine resembles penicillin and methicillin with respect to its retention in the body in chronic renal failure, since a significant proportion of it may be inactivated by non-renal mechanisms (Kunin & Atuk, 1966). For patients on RDT Curtis and Marshall recommend a dose of 1 g cephaloridine

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intravenously daily, increased to 6-hourly during dialysis, if the drug is being given for staphylococcal infections. In the treatment of gram-negative infections in patients on RDT, they recommend a dose of 1 g 12-hourly intravenously increased to 1 g intravenously every 4 hours during dialysis. They suggest that the drug be given slowly, dissolved in 20 ml of saline.

While the use of cephaloridine in patients with no significant residual renal function is probably safe, there is some evidence to suggest that its use in patients with renal impairment not yet requiring dialysis is potentially dangerous. Perkins et al (1968) showed that the drug was nephrotoxic in rabbits and monkeys when given in high dosage. Foord (1969) summarising the evidence for nephrotoxicity of cephaloridine in animals and humans, concluded that serum levels over 100 µg/ml should be avoided. He noted also that in the 36 cases of acute renal failure in which cephaloridine was a suspected cause, two-thirds of the patients were known to have had impaired renal function prior to beginning treatment. Finally, he observed that in several of these patients, cephaloridine had been given coincidentally with diuretics, particularly frusemide; he postulated that these substances might enhance the nephrotoxicity of cephaloridine. It is possible that retention of cephaloridine in patients with pre-existing renal disease produced toxic serum levels (above 100 µg/ml). However, the studies of Lawson et al (1970a) have suggested that in the presence of minor degrees of renal damage, cephaloridine may produce severe acute tubular necrosis at serum cephaloridine levels which were well below the suggested nephrotoxic level. This side-effect of cephaloridine was enhanced by the coincidental administration of frusemide, and until further information is available, it may be advisable to avoid the use of cephaloridine in patients with renal impairment.

Cephalothin
Cephalothin is normally excreted rapidly in the urine but in chronic renal failure is metabolised in the liver, so that the normal half-life in the serum of 0.85 hours is extended only to 2.9 hours in the anuric patient (Kunin & Atuk, 1966). Dose modification is therefore probably not required in patients with renal failure. There is at present no definite evidence that cephalothin is nephrotoxic in man, and Perkins et al (1968) failed to demonstrate a nephrotoxic effect in rabbits and monkeys. It would appear, therefore, that cephalothin is preferable to cephaloridine in patients with chronic renal failure although its spectrum of antibacterial activity is not quite so wide as that of cephaloridine.

Cephalexin
Cephalexin, the orally administered cephalosporin, has an antibacterial spectrum similar to cephaloridine and is likely to be effective against most organisms found in the urinary tract, except Pseudomonas. The antibiotic is
rapidly cleared from the body by glomerular filtration and 95 per cent of an oral dose can be recovered from the urine in normal patients within 6 hours. The cephalexin half-life in the serum is prolonged from 1 hour in normal subjects to approximately 20 hours in the anephric patient (Kabin et al 1970). Serum levels achieved after a single oral dose become slightly higher as the creatinine clearance decreases, but at all levels of renal function the minimum level of cephalexin in the urine exceeded 32 µg/ml between 4 and 18 hours after the oral dose. At lower levels of creatinine clearance, only approximately 60 per cent of the ingested dose was recoverable in the urine, suggesting extra-renal disposal. The serum half-life of cephalexin is reduced to 4.6 hours during dialysis (Bailey et al 1970). Neither these authors nor Gower and Dash (1969) noted any evidence of deterioration in renal function during cephalexin therapy, but Galbraith and Pilsworth (1969) reported a fall in creatinine clearance in 5 out of 14 patients given this drug.

Until further experience has been gained with cephalexin, it is probable that the dose should be reduced as GFR falls. The dose schedule suggested by Bailey et al (1970) is as follows:

<table>
<thead>
<tr>
<th>C_{creatinine} (ml/min)</th>
<th>Dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>500 every 8 hrs</td>
</tr>
<tr>
<td>20 - 50</td>
<td>500 every 12 hrs</td>
</tr>
<tr>
<td>20</td>
<td>500 per day</td>
</tr>
<tr>
<td>RDT</td>
<td>500 per day + 500 at the end of each dialysis</td>
</tr>
</tbody>
</table>

These doses of cephalexin will be adequate for most urinary tract infections, but should be approximately doubled for systemic infections.

**CHLORAMPHENICOL**

Chloramphenicol is a bacteriostatic antibiotic which is effective against many gram-negative organisms and in higher concentrations, against some streptococci and staphylococci. It also has a place in the treatment of rickettsial infections and in infections with mycoplasma (Goodman & Gilman, 1965). The drug is rapidly absorbed orally, is approximately 60 per cent protein bound and is excreted in the urine largely by glomerular filtration. The urine concentration is approximately 20 times that of the plasma in normal individuals. In renal failure, the concentration of active drug is little altered by falling creatinine clearance, but the accumulation of inactive metabolites is inversely proportional to the glomerular filtration rate (Lindberg et al 1966). These inactive metabolites are predominantly aryl amine derivatives which are removed by dialysis with an efficiency of approximately half that of removal of creatinine, (Kunin et al 1959a). These substances may be responsible for some of the side-effects of chloramphenicol which
have largely dictated its withdrawal from routine use. The most important side-effect is that on the bone marrow, usually manifested as aplastic anaemia.

Although some centres still use chloramphenicol in patients with chronic renal failure, particularly when the infecting organism is unknown, the evidence above suggests that other broad spectrum antibiotics might be preferable. Since there is little accumulation of active drug as the creatinine clearance falls, reduction in dosage is contra-indicated, but this in turn means that there will be accumulation of potentially toxic metabolites.

**ERYTHROMYCIN**

Erythromycin is predominantly bactericidal to many gram-positive organisms, and is effective when given orally. Many organisms develop resistance to erythromycin very rapidly. Only some 15 per cent of the drug can be recovered in the urine after administration, and approximately 30 per cent is excreted in the bile. The half-life of erythromycin in the serum of anuric patients is prolonged to 4 to 8 hours, compared with the normal value of 1.4 hours (Kunin et al 1959b). The drug is relatively non-toxic, providing that the lauryl sulphate salt of the propionic acid ester of erythromycin is avoided, since this derivative may cause an allergic cholestatic hepatitis (Goodman & Gilman, 1965). With erythromycin stearate or lactobionate little reduction in normal dosage is required for patients with renal failure, although data on the clearance of erythromycin is limited.

**NALIDIXIC ACID**

Nalidixic acid is an antibacterial substance which is excreted in the urine in sufficient concentration to be active against many gram-negative organisms, including E. coli, Klebsiella and Proteus spp. but not Pseudomonas. The concentration attained in other body fluids is insufficient for any antibacterial effect (Goodman & Gilman, 1965). Nalidixic acid is given orally and is generally free of toxic reactions. Data concerning its use in chronic renal failure is scanty, but Sachs et al (1968) reported its use in 17 patients with creatinine clearances ranging from 8 to 121 ml per minute. In a dose of 1 g 6-hourly, they found high urine concentrations, even in patients with very low glomerular filtration rates. No toxic effects attributable to the treatment were observed, and it would seem that nalidixic acid is a useful antibacterial substance for the treatment of urinary tract infection in patients with reduced renal function.

**NITROFURANTOIN**

Like nalidixic acid, nitrofurantoin is a urinary antiseptic, effective against many gram-negative and gram-positive organisms. Approximately 40 per
cent of an orally administered dose can be recovered in the urine in normal patients (Paul et al 1959), but in uraemic subjects the recovery of nitrofurantoin from the urine is proportional to the creatinine clearance (Sachs et al 1968). Goff et al (1968) reported that blood levels of nitrofurantoin remained low after a dose of 100 mg every 6 hours until the creatinine clearance fell below 14 ml per minute, when accumulation occurred in the serum. They noted an inverse relationship between creatinine clearance and urinary excretion in 14 patients. Maher and Schreiner (1969) have shown that the dialysance of nitrofurantoin is 70 ml per minute at a flow rate of 200 ml per minute.

The side-effects of nitrofurantoin therapy include haemolysis, hypersensitivity reactions and alimentary upset as well as a severe polyneuropathy which occurs particularly in patients with renal impairment (Martin et al 1962). It is probable that any degree of renal impairment should be regarded as a contra-indication to nitrofurantoin therapy, partly because of the likelihood that inadequate levels will be attained in the urine, but more importantly, because of the risk of polyneuropathy.

**FUCIDIC ACID**

Fucidic acid is a new steroid antibiotic chemically akin to cephalosporin P. It is bactericidal to most strains of staphylococci and is unaffected by penicillinase. The combination of fucidic acid with penicillin, methicillin or tetracycline, is particularly effective against gram-positive organisms, but fucidic acid is ineffective against gram-negative bacteria, fungi and yeasts (Godtfredsen et al 1962; Goodman & Gilman, 1965). The drug is excreted almost entirely by the liver and does not appear to have any nephrotoxic effects. It is 97 per cent protein bound and is unaffected by peritoneal or haemodialysis (Beeley et al 1970). No modification of dosage is required in patients with chronic renal failure or in those undergoing dialysis, although Beeley et al (1970) have suggested that gastro-intestinal side-effects may limit its oral use in patients with renal disease.

**AMPHOTERICIN B**

Amphotericin is an anti-fungal antibiotic, effective against most of the organisms which infect man, including histoplasma, coccidioides, candida spp., and cryptococcus. Although these organisms have been relatively rare causes of infection up to the present, opportunistic fungal infections are an increasingly important complication in patients on immunosuppressive therapy after renal transplantation.

Given intravenously in doses of 0.5 mg/kg body weight per day after a loading dose of 1 mg/kg body weight, serum levels of amphotericin considerably in excess of those required to kill sensitive fungi are maintained
in the normal individual. Only about 5 per cent of the administered drug is excreted in the urine (Goodman & Gilman, 1965).

Amphotericin is known to be associated with many side-effects, including hypersensitivity reactions, acute hepatocellular dysfunction and red cell aplasia; these complications have been well reviewed by Utz et al (1964). When given to normal individuals amphotericin demonstrates nephrotoxic effects producing a wide variety of histological appearances ranging from glomerular proliferative changes to tubular degeneration. Hypokalaemia and renal tubular acidosis have been described (Douglas & Healy, 1969). However, the occurrence of renal toxicity does not appear to have been related to serum levels of the drug. Bindschadler and Bennett (1969) reported the use of amphotericin in 3 patients with impaired renal function. The dose used was 0.5 mg/kg body weight per day and the drug was given intravenously. They failed to show a correlation between renal function and peak serum levels, and observed that there was no evidence of poor urinary excretion of the drug, nor of further impairment of renal function. Despite the very considerable toxicity of amphotericin it may often be necessary to use it in patients receiving immunosuppressive drugs; the evidence available at present suggests that the risk of toxicity is not increased by giving the normal dosage to patients with renal impairment.

TETRACYCLINES

The tetracyclines are a group of broad spectrum bacteriostatic antibiotics which show marked antagonism to concurrently administered penicillin. They may be given orally or intravenously, show a variable degree of protein binding and are excreted both in the bile and by glomerular filtration. The renal clearance of chlortetracycline is 35 per cent of the creatinine clearance, while that of oxytetracycline is 85 per cent of creatinine clearance. Nausea and diarrhoea are the principal toxic effects of the tetracyclines. Photosensitivity has been recorded following the administration of demethylchlortetracycline, as has persistent high fever and eosinophilia. Large doses of tetracycline, particularly if given parenterally, may lead to hepatic damage. Negative nitrogen balance and a rise in blood urea, together with an increased excretion of riboflavin in the urine also occur during tetracycline therapy (Kunin et al 1959b). These authors also demonstrated that the serum half-life of chlortetracycline is normal in renal impairment and that the drug is not cleared by dialysis. Following a single intravenous dose of tetracycline, however, they demonstrated a correlation between the creatinine clearance and the serum half-life of the antibiotic, this value being approximately 10 times the normal of 4.8 hours in the anuric patient. These observations suggest that if tetracyclines are to be used in patients with renal disease, chlortetracycline is the analogue to choose and this should be given in normal
dosage. Evidence is still accumulating, however, to suggest that tetracyclines given to patients with renal damage may produce acute deterioration in renal function (Eastwood et al 1970).

**SULPHONAMIDES**

The sulphonamides are bacteriostatic agents, effective against many gram-positive and gram-negative organisms. In recent years they have been used principally in the treatment of urinary tract infection. Their antibacterial action is inhibited by the presence of blood, pus and tissue breakdown products. The most commonly used sulphonamides are sulphadimidine and the sulphonamide-trimethoprim combination. A wide range of toxic effects has been reported with the sulphonamides (Goodman & Gilman, 1965), and in particular, 2 types of nephropathy have been described. With the earlier and less soluble sulphonamides, desposition of crystals occurred in the urinary tract, producing haematuria and urinary obstruction. This type of nephropathy is rare with sulphadimidine. The second type of nephropathy apparently consists of a hypersensitivity reaction, resulting in tubular necrosis or necrotising angiitis (Abramowicz & Edelmann, 1968).

Williams et al (1968) studied the renal clearance of sodium sulphadimidine in normal and uraemic subjects. Sulphadimidine is a weak organic acid excreted by glomerular filtration, proximal tubular secretion, tubular re-absorption and passive pH dependent non-ionic back diffusion. The sulphadimidine clearance was found to be higher in patients with chronic renal failure than in normals, the mean clearances being 11.4 ml per minute in patients with renal impairment and 6.3 ml per minute in normal subjects. There was no correlation between glomerular filtration rate and sulphadimidine clearance. No significant difference was found between the mean sulphadimidine urinary excretion rates in normals and patients with chronic renal failure; the increased sulphadimidine clearance in the uraemic patients was due to the lower serum levels obtained. In normal patients the sulphadimidine clearance was related to urine pH but not in patients with chronic renal failure. These authors concluded that sodium sulphadimidine was not retained in chronic renal failure and the urine levels achieved were adequate for the eradication of sulphonamide sensitive organisms. With sulphamethizole on the other hand, Goff et al (1968) showed that following the administration of 1 g of this drug the serum half-life was considerably prolonged in patients with low glomerular filtration rates. This was associated with increased urinary sulphamethizole concentration and this reached bactericidal levels after 2 to 3 days. The available evidence suggests that sulphadimidine can be given in normal dosage to patients with any degree of renal impairment and may, in fact, be one of the most satisfactory drugs for the treatment of urinary tract infection with sulphonamide sensitive organisms.
Little information is available concerning the recently introduced sulphonamide-trimethoprim mixture. The concentration ratio of the 2 drugs in the urine varies with GFR and with urine pH, but how this affects the efficacy of the treatment is unknown. McGeown (1970) has reported a high incidence of troublesome gastro-intestinal side-effects when the sulphonamide-trimethoprim mixture was given to patients with renal impairment; these effects may limit the usefulness of this preparation, but further information is required.

DISCUSSION

This review of the subject of antibiotic therapy in renal disease was undertaken in an endeavour to provide guidance on the choice of antibiotic and to indicate dosages which would be safe yet effective at various levels of renal function. Analysis of the published work has proved difficult because few studies are directly comparable in methods used. The classical work of Kunin and his colleagues (1959) remains a good model, and more recently the studies of Gingell and Waterworth (1968), of Bailey et al (1970) and of Eastwood and Curtis (1968) illustrate how the pharmacology of any new antibiotic should be investigated in relation to degree of renal impairment and to the effect of haemodialysis.

The pattern of absorption, metabolism and excretion of the drug should be defined in the normal, and studies on patients with reduced renal function should include serum and urine antibiotic levels, peak serum levels obtained, serum half-life and the effect of dialysis. Side-effects, particularly any affecting renal or hepatic function, must be correlated with all these factors before conclusions can be drawn. It is equally obvious that all serum and urine levels of antibiotics should now be determined by one of the modifications of the cup plate technique, since tube dilution methods are too inaccurate.

Comparison of various suggested dosage schedules has also proved difficult, since some authors advocate reduced dosage at the usual time intervals, while others favour prolongation of the time between doses. The system suggested by Gingell and Waterworth (1968) for gentamicin has much to commend it, and variation of the time intervals between doses may be the best solution, provided that the peak serum level achieved is not dangerous. In the same context, clinical and investigative results would be better if all antibiotic doses were prescribed in terms of mg/kg body weight of the patient.

Little can be said about choice of antibiotic, since a questionnaire sent to all renal units in Great Britain and Ireland revealed that many units had favourite antibiotics with which they had gained experience and achieved favourable results. With increased knowledge about dosage, there seems to
be an increasing willingness to use effective but potentially toxic antibiotics such as kanamycin, while chloramphenicol and the tetracyclines seem to be used much less because of their dubious efficiency and considerable toxicity. In the treatment of urinary tract infections when severe renal impairment exists, sulphonamides, with or without trimethoprim might be underestimated. Against this, Chisholm et al (1968) advocate the use of antibiotics which achieve high tissue levels for the treatment of infection in the renal parenchyma.

Despite the volume of work carried out on this subject, many unsolved problems remain, and suggest that a very complex field of drug metabolism and action is just being touched upon. It may be that the complex mathematical studies of Dettili (1970) will provide a guide to dosages of many drugs given to patients with impaired renal function. These calculations, however, depend upon the assumption that the body's ability to handle any given drug does not vary from time to time, and that detoxication mechanisms do not change. There is already evidence that these assumptions cannot be made; Pryor et al (1967) showed that the serum half-life of cephaloridine became shorter the longer patients were on RDT, without any change in residual renal function.

Until recently, it has been assumed that most side-effects of antibiotics arise either because of hypersensitivity of the patient to the drug, or because abnormally high serum levels of the antibiotic had been attained. It was thought also that the high incidence of untoward effects of antibiotics in patients with renal impairment was usually due to retention of the drug producing higher serum antibiotic levels. This is probably true in most cases, but the work of Lawson et al (1970a, b) suggests that in the presence of minor degrees of acute renal damage, antibiotics such as cephaloridine and colistin may exacerbate the renal damage at serum antibiotic levels within the therapeutic range. This effect is potentiated by the coincident administration of frusemide, and it may be that stimulation of renin by trauma, dehydration, antibiotics and diuretics leads to the development of acute renal failure (Brown et al 1970). It is increasingly obvious that the interaction of drugs is an area in which much further work is required.

The demonstration by Orme and Cutler (1969) that the half-life of kanamycin is significantly altered by the state of hydration of the patient introduces yet another variable into calculation of dose schedules, and one which may alter very rapidly from day to day. The whole question of the effect of protein binding of antibiotics remains unsolved, and it probably influences the distribution of drugs in tissues. Changes in the handling of drugs over a period on RDT (Pryor et al 1967) may occur in other situations, perhaps related for example to hepatic perfusion or other metabolic changes; much further work is required here.

This review has probably raised more problems than it has solved. For
many of the common antibiotics, sensible dose schedules can now be prescribed over short periods, but the need remains for readily available estimations of serum levels to control antibiotic therapy in renal impairment.

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