INCREASED DRUG METABOLISM IN CHRONIC RENAL FAILURE

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Introduction

For many years drug metabolism has been considered normal in patients with chronic renal failure. It was, therefore, surprising when Letteri et al (1971) reported increased metabolism of phenytoin in patients with chronic renal failure. Since then there have been further reports, based on plasma half-life studies, suggesting increased metabolism of drugs in chronic renal failure (summarised in Table IV). The reason for increased metabolism of these drugs in chronic uraemia is not clear. As phenytoin and digitoxin are bound to serum albumin, it is possible that the reduced protein binding that occurs with both these drugs in chronic uraemia makes them more rapidly available for oxidation by enzymes of the hepatic endoplasmic reticulum (Reidenberg et al, 1971; Shoeman & Azarnoff, 1972). Alternatively, it is possible that the activity of
TABLE IV. Apparent Increased Metabolism of Drugs in Patients with Chronic Renal Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma half-life</th>
<th>Comments</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D₃</td>
<td>Reduced</td>
<td>Inactive metabolite formation increased</td>
<td>Avioli et al, 1968</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Reduced</td>
<td>Protein binding decreased</td>
<td>Letteri et al, 1971</td>
</tr>
<tr>
<td>Amylobarbitone</td>
<td>Reduced</td>
<td>Normally 61% protein bound</td>
<td>Balasubramaniam et al, 1972</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>Reduced</td>
<td>Protein binding decreased</td>
<td>Rasmussen et al, 1972</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Normal/ occasionally reduced</td>
<td>Given orally. Patients on other drugs.</td>
<td>Lichter et al, 1973</td>
</tr>
<tr>
<td>Pentobarbitone</td>
<td>Reduced</td>
<td>Normally 40–65% protein bound</td>
<td>Reidenberg, 1975</td>
</tr>
</tbody>
</table>

these enzymes is increased in uraemia.

When measuring the plasma half-life of a drug as an index of elimination in uraemia the following factors are important.

1 A specific assay should be used. With uraemic plasma the blank reading may be high and drug metabolites that accumulate in uraemia might interfere with the assay.

2 Patients should not be taking other drugs. Drugs or their metabolites might interfere with the assay or affect the metabolism of the drug being studied by enzyme induction, inhibition or competition.

3 The test drug should be given intravenously. In uraemic patients, aluminium hydroxide therapy, delayed gastric emptying due to nausea and uraemic gastroenteropathy might reduce drug absorption and affect plasma half-life measurements.

4 It is important to measure the drug’s apparent volume of distribution. The plasma half-life of a drug is directly related to its hepatic clearance and apparent volume of distribution. Hepatic clearance is, therefore, a more direct measure of drug metabolism than plasma half-life.

Taking these factors into consideration we have undertaken studies to determine whether there is increased activity of hepatic drug metabolising enzymes in chronic renal failure. This was done in patients by measuring the plasma half-life of antipyrine as an index of drug oxidation and comparing the results with normal controls (Maddocks et al, 1975). Antipyrine is widely used to study drug metabolism as it is extensively oxidised by the liver (Brodie & Axelrod, 1950; Yoshimura et al, 1968), it is only 10% bound to plasma proteins (Soberman et al, 1949), it is distributed throughout the body water and only 5%
of the dose is excreted in the urine in 24 hours (Brodie & Axelrod, 1950). We have also measured hepatic microsomal enzyme activity in vitro in rats with chronic renal failure and sham operated controls (Smithers et al, 1976).

METHODS

Twelve patients with chronic renal failure were studied. Clinical details are shown in Table V. No drugs had been taken by six patients for several months and the other six patients had stopped taking drugs two weeks before the study began; their drug treatment is shown in Table V. None of these drugs are known enzyme inducers. There was no biochemical evidence of liver disease in these patients.

Twenty normal subjects (13 male and 7 female) aged between 16 and 20 (mean 28.2) years served as controls. Their kidney and liver function tests were normal.

Antipyrine 18 mg/kg body weight was given by slow intravenous injection and four heparinised venous blood samples were taken at 3 hourly intervals after the dose. Plasma was separated and stored at −20°C.

The effect of enzyme-inducing agents on the plasma antipyrine half-life was studied by giving oral phenobarbitone or antipyrine for 2 weeks to five uraemics and seven control subjects and repeating the plasma antipyrine half-life determination three days after the course.

Plasma antipyrine was measured by the method of Brodie et al (1949). Antipyrine was extracted from alkaline plasma with chloroform. The method was shown to be specific for assay of antipyrine in uraemic plasma by the distribution technique of Brodie and Udenfriend (1945).

Hepatic microsomal enzyme activity was studied in vitro in rats with chronic uraemia and sham operated controls. Eight week-old rats of the Wistar strain were made uraemic by 5/6 nephrectomy (McCance & Morrison, 1956). Twenty eight days after the 5/6 nephrectomy the rats were killed and their livers removed. The livers were homogenised and the microsomal fraction separated by centrifugation.

Microsomal protein was measured by the method of Lowry et al (1951). Drug oxidation by hepatic microsomal enzymes was studied by measuring the rate of oxidation by biphenyl (Burke et al, 1975) and aniline (Kato & Gillette, 1965). Components of the electron transport system involved in drug oxidation, measured, were cytochrome P450 and cytochrome b5 (Omura & Sato, 1964) and NADPH₂− cytochrome c reductase (Phillips & Langdon, 1962).

RESULTS

As shown in Figure 7 the plasma antipyrine half-life of the 12 uraemic patients was 7.3 ± 2.0h (mean ± SD) and that of the 20 normal subjects 13.2 ± 4.3h. The
<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Dialysis</th>
<th>Plasma creatinine mg/100 ml</th>
<th>Haemoglobin g/100 ml</th>
<th>Previous drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>M</td>
<td>No</td>
<td>15.0</td>
<td>7.5</td>
<td>Clonidine, Nitrazepam</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>M</td>
<td>Yes</td>
<td>24.0</td>
<td>7.1</td>
<td>Perphenazine, Propranolol</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>F</td>
<td>Yes</td>
<td>7.0</td>
<td>5.2</td>
<td>Metaclopramide, Ampicillin</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>F</td>
<td>No</td>
<td>26.0</td>
<td>7.6</td>
<td>Metaclopramide, Methyl dopa, Diazepam</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>M</td>
<td>Yes</td>
<td>16.0</td>
<td>7.7</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>F</td>
<td>No</td>
<td>4.9</td>
<td>9.3</td>
<td>Diazepam+, Pethidine+</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>No</td>
<td>11.1</td>
<td>8.7</td>
<td>Nitrazepam</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>M</td>
<td>Yes</td>
<td>12.0/14.0++</td>
<td>7.9</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>M</td>
<td>Yes</td>
<td>17.5/11.5</td>
<td>6.6</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>M</td>
<td>Yes</td>
<td>10.7/17.6</td>
<td>5.1</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>M</td>
<td>Yes</td>
<td>14.5/15.0</td>
<td>7.9</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>F</td>
<td>Yes</td>
<td>13.0/17.0</td>
<td>7.1</td>
<td>None</td>
</tr>
</tbody>
</table>

* Single Dose
++ Values after antipyrine or phenobarbitone administration for two weeks
difference between the two groups was statistically significant \((p < 0.002)\) using Wilcoxon's sum of ranks test.

After phenobarbitone or antipyrine administration for two weeks there was significant shortening of the plasma antipyrine half-life in uraemic patients \((p < 0.005)\) and normal subjects \((p < 0.003)\).

There was no significant difference between the apparent volume of distribution \((VD)\) of antipyrine, calculated from the formula: \(VD (\text{litres}) = \text{Dose (mg)}/\text{Plasma level of zero time (mg/l)}\), of uraemics and controls. Enzyme-inducing drugs did not change the apparent volume of distribution of antipyrine.

The results of the study on rats with chronic uraemia and sham-operated controls are shown in Table VI. Twenty-eight days after the 5/6 nephrectomy the body weight of the uraemic rats was 14\% less than the controls, although there was no significant change in liver weight or the microsomal protein content per gram wet liver weight.
TABLE VI. Hepatic Microsomal Enzyme Activity in Vitro in 28th Day Uraemic Rats and Sham Operated Controls

<table>
<thead>
<tr>
<th></th>
<th>Chronic uraemic n = 7</th>
<th>Sham-operated controls n = 5</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>260 ± 7</td>
<td>301 ± 10</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>8.2 ± 0.3</td>
<td>8.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum urea (mM/L)</td>
<td>15.5 ± 1.4</td>
<td>6.6 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Biphenyl oxidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-hydroxybiphenyl</td>
<td>4.47 ± 0.34</td>
<td>3.03 ± 0.11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>produced μmol/hr/g wet liver weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aniline oxidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-aminophenol</td>
<td>3.13 ± 0.23</td>
<td>2.5 ± 0.17</td>
<td>NS</td>
</tr>
<tr>
<td>produced μmol/hr/g wet liver weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytochrome P-450</td>
<td>30.4 ± 1.9</td>
<td>33.7 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>n mol/g wet liver weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytochrome b5</td>
<td>12.4 ± 1.1</td>
<td>12.6 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>n mol/g wet liver weight</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean ± SEM
Smithers, JL et al (1976) – unpublished

Oxidation of biphenyl was 48% greater in uraemic rats compared with controls (p < 0.01). Although aniline oxidation was increased by 25% in the uraemic group compared with the controls, the difference was not statistically significant (0.1 > p > 0.05).

There was no significant difference in the amount of cytochrome P450 and cytochrome b5 per gram wet liver weight between the two groups of rats. NADPH-cytochrome c reductase activity was 13% greater in uraemic rats compared with controls and the difference was statistically significant (p < 0.01).

**DISCUSSION**

The plasma half-life (T½) of antipyrine is related to its hepatic clearance (C) and its apparent volume of distribution (VD) by the formula: T½ = K / VD; where K is the elimination constant (Dollery, 1972). As there was no significant difference between VD of antipyrine in chronic uraemic and normal subjects, the diminished plasma antipyrine half-life in uraemic patients indicates that the hepatic clearance of antipyrine is increased. With antipyrine the calculated
hepatic clearance of the subjects in this study was low (22–62 ml/min) compared with the normal hepatic blood flow (1500 ml/min) (Sherlock, 1963), so that changes in hepatic blood flow are probably not an important factor affecting its hepatic clearance. It appears, therefore, that the diminished plasma half-life of antipyrine in chronic renal failure is due to increased metabolism of the drug.

Although the plasma half-life of antipyrine is shortened in chronic renal failure, it can be further diminished by administration of phenobarbitone or antipyrine for two weeks. This suggests that hepatic microsomal enzymes can be induced in these patients.

There was 48% increase in the rate of oxidation of biphenyl by hepatic microsomes in vitro from rats with chronic renal failure. In addition, aniline oxidation by hepatic microsomes was greater in the rats with chronic renal failure. Kinetic studies showed that these increases in enzyme activity were due to enzyme induction. Recently, Mezey et al (1975) reported a marked increase in the alcohol dehydrogenase activity in the liver of uraemic rats. In contrast, Leber et al (1972) found a decrease in drug oxidation in vitro by hepatic microsomal enzymes of uraemic rats. However, their rats were much more uraemic than the ones in the present study and they were sacrificed six days after subtotal nephrectomy. The degree and duration of uraemia could well be important in determining hepatic microsomal enzyme activity.

References

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Open Discussion

KERR Many of the patients in whom we want to calculate drug dosage arrive in hospital with an unknown GFR and with a serum creatinine which is changing rapidly because of the intercurrent illness for which the drug is required. How does Professor Dettli's system work in these circumstances?

DETTLI An equation has been described from which you can calculate GFR from changes in the serum creatinine concentration, with corrections for age, sex and so forth (Jelliffe & Jelliffe (1971) Lancet, ii, 710). I have checked this equation and it works not too badly but it is a rather complicated differential equation. There is another system requiring a computer programme (Chiou & Hsu (1975) Chemical Pathology and Pharmacology, 10, 315).

KERR So it is fine if you have your pocket computer with you?

RAWLINS Could Professor Dettli be persuaded to use clearances instead of elimination rate constants? The whole system would work just as well with clearances and I suspect that it would be more accurate.

DETTLI Yes, it would be better, much better. I have looked at the data of Ohnhaus on beta-blocking agents. If you analyse these data all the differences are caused by differences in distribution volume. If you use clearance of the drug then the whole distribution is linear. However clearances are difficult to use clinically; they are too complicated. The important question is: "Is the difference made by using clearance sufficient to invalidate the system I have described?" I do not think it is.
McGEOWN (Belfast) Have the members of the panel any information on the metabolism and rate of elimination of diazepam and related drugs, as these are widely used for relief of anxiety and night sedation in patients with chronic renal failure?

RAWLINS The diazepam and clonazepam group are all metabolised extensively in the liver. Diazepam, chlor Diazepoxide and medazepam are all metabolised to an active metabolite, nordiazepam, which undergoes oxidation to become oxazepam; all of these compounds are readily marketable. There is undoubtedly some retention of metabolites in renal failure. Alexanderson in Sweden (personal communication, 1973) has shown that the levels of oxazepam glucuronide are elevated nearly 1000-fold in patients with end stage renal disease. This poses an interesting problem: although we say that a metabolite is ‘inactive’ because it has only 1% of the pharmacological activity of the parent drug, our statement may be relevant to patients with normal renal function but totally irrelevant when we consider patients with abnormal renal function.

LEBER It has been shown in patients with normal renal function that these drugs actively induce drug metabolism. If you give them for several days, drug metabolism is faster than before. I do not know whether this is also true for patients with renal failure.

MADDOCKS There has been another study in England showing that there was no interaction between these drugs and anticoagulants. They are recommended sedatives for all patients taking anticoagulants (Orme et al 1972 BMJ, 3, 611).

LEBER Another study in Marburg on a large group of psychiatric patients showed that these drugs undoubtedly altered the half-life of antipyrine and phenylbutazone. The study did not include anticoagulants. This illustrates a problem in interpreting studies of drug metabolism. Each laboratory investigating this problem looks at the metabolism of one or two drugs; the results may be quite different from those in another laboratory using different test drugs. Unfortunately there is no single ideal drug that can be used as a measure of drug metabolism.

MADDOCKS Recently there has been a study of the protein binding of diazepam and its methylated metabolite. There is a marked decrease in protein binding, and a consequent increase in the free drug level. So it is quite possible that patients in renal failure may be more sensitive to these drugs than normal subjects.

KERR I think I can summarise the opinion of the panel by saying that diazepam and its chemical relatives produce some problems in renal failure but they are less troublesome than barbiturates and are probably the best sedatives to give to uraemic patients, with the risks of accelerating bone disease and upsetting anticoagulant therapy in mind.

DANDONA (London) Would the members of the panel comment on any alterations of end organ sensitivity to drugs in renal failure?

MADDOCKS We have carried out some work with rats in chronic renal failure to investigate the blood-brain barrier (Smithers et al 1976 Clinical Nephrology, 5, 114). We used a drug called phenglutaramide which has
never been marketed. It acts like atropine and was introduced to treat patients with Parkinson’s disease but was abandoned because it did not get into the brain. It is therefore a useful drug to study the blood-brain barrier. It is not protein-bound, it is not metabolised in the liver and is eliminated in the urine unchanged. We gave this drug to uraemic rats and controls. The renal pedicles were ligated in both groups so there was no difference in rate of elimination. Much more of the drug entered the brain in the chronic uraemic rats than in the controls. The blood-brain barrier is therefore one end-organ that is altered in chronic renal failure.

KERR So there is one explanation of apparently altered end organ sensitivity — a change in the distribution of a drug in the end organ or of its concentration there. There are others. The reduced reactivity to angiotensin in some patients with renal failure is probably a reflection of the high concentration in circulating blood which has already elicited a nearly maximal response. The unresponsiveness of bone to parathormone infusion may be another example of ‘flogging a tired horse’.

DANDONA We have described another example: the altered sensitivity of the pituitary gland to thyrotrophin-releasing hormone (Proceedings of the European Dialysis and Transplant Association 12 (1975) 268). There was a fall in plasma thyroxine levels with regular haemodialysis, especially in patients who had been dialysed more than three years, and the baseline serum TSH concentrations were high, as one would expect in this situation. However there was no stimulatory effect of TRH. I believe Professor Kerr’s group showed the same, last year?

KERR That is correct (Gomez-Pan et al (1975) Clinical Science, 49, 23p). We should also mention the relative unresponsiveness of the bone marrow to erythropoietin in chronic renal failure (Wallner et al (1976) Blood, 47, 561) which is probably due to a circulating inhibitor(s).

MADDOCKS The poor response to erythropoietin may be partly explained by some work on the metabolism of erythropoietin in rats with chronic renal failure; the half-life is shortened. It can be prolonged by giving substances which interfere with drug oxidation. This problem was looked at because of the observation that uraemic patients who developed hepatitis had a rise in haemoglobin, which raised the possibility that hepatitis decreased the degradation of erythropoietin.

KERR (sotto voce) .... or diminished the enthusiasm of doctors for blood-letting!

KNAPP (Nottingham) Some drugs contain materials which are not clearly identified to the prescriber. An obvious example, which I reported some years ago, is the inclusion of electrolytes, e.g. sodium, potassium and bicarbonate in Sandocal, with possible ill-effects for the uraemic patient. Are other substances being included by manufacturers which might be toxic to patients in renal failure, though well tested and non-toxic in the normal subject?

KERR The hypercalciuria of spironolactone therapy was traced to its calcium sulphate excipient and several other tablets were found to contain a lot of calcium (Prati et al (1972) Journal of Laboratory and Clinical Medicine, 80, 224). I suppose this ‘inert’ excipient could cause hypercalcaemia in the right clinical setting.
There are, of course, other examples. Carboxymethylcellulose is an excipient which is used in intravenous preparations of many penicillins and other drugs; one can develop antibodies and allergy to the carboxymethyl-cellulose rather than to the penicillin molecule itself. A lot of drugs are given as their sodium salts because it dramatically improves the absorption. Phenotylic acid is very incompletely absorbed from the gastrointestinal tract so it is administered as sodium phenytoin which is completely absorbed. The amount of sodium you take in phenytoin may not be important but the quantity is much greater when you consume drugs like PAS.

KERR Fortunately the sodium-containing drugs that make a big difference to blood pressure control in chronic renal failure are few. The worst offenders are indigestion mixtures like Mist Mag Trisol NF which contribute 20–30 mmol of sodium per day.

WRIGHT (Rhyll) Could the panel comment on my experience that the use of nomograms can result in suboptimal blood levels of drugs?

DETTLE This is a complex problem. Gentamicin is a mixture of three substances; each has a specific activity and probably the relation between renal function and speed of elimination is different for each. So it is no wonder that an article has appeared on “The unpredictability of serum concentrations of gentamicin” (Kaye et al 1974 Journal of Infectious Diseases, 130, 150), but the concentration is not easily predictable even in patients with normal renal function. Since 98% of the drug is usually eliminated through the kidney, in the anuric subject you are trying to estimate 2% of the usual dose. No wonder that even the best estimating procedure has a very wide scatter. In a very uraemic patient there is no other way than to measure the drug level. Even this measurement has its problems. You should not measure serum gentamicin by microbiological methods because most such methods are influenced by uraemic serum. So you have to use an enzymatic method, which is not so simple. So there are problems with the aminoglycosides, and you must choose carefully your nomogram or method of dosage modification. In my opinion there cannot exist one dosage rule for the whole range of renal insufficiency. If you use the Cutler and Orme method you are bound to end up with an absurdly long dosage interval — 20 days or so — in severe renal failure. For at least a week of those 20 days the serum gentamicin will be below therapeutic levels. So you have to divide up renal failure into moderate CRF, when you use the Cutler and Orme method, and severe CRF when you should use a formula originally described by Kunin.

EISINGER (Carshalton) What antituberculous drugs would the panel recommend for renal failure?

DETTLE Isoniazid is shown on the nomograph I gave you. You have to differentiate between fast and slow inactivators but the effect of renal disease is not very great. I would not change the normal dosage except that I would avoid very high doses; I would not go above 5 mg/kg/day. The metabolism of ethambutol is still too poorly investigated to allow any predictions. Streptomycin, like the other aminoglycosides, is dangerous in renal failure; only 2–3% of the dose is eliminated by non-renal pathways. You should not alter the normal dose of rifampicin because about 95% of it is removed by metabolism and other non-renal pathways.
It is not certain whether enzyme induction plays a role in the kinetics of rifampicin.

KERR  I suppose few people use PAS now?

DETTLE With PAS you would expect a marked effect on dose from renal function, but you would not choose this drug in an uraemic patient.

LEBER There was a report (I think by Dumas) which suggested that the dose of ethambutol should be reduced to about 18mg/kg/day (compared with 25mg/kg/day in normal renal function) in patients with chronic renal failure. Rifampicin is a very strong enzyme-inducer in subjects with normal renal function so it may be necessary to increase the dose after some days of treatment, even in renal failure.

DETTLE Rifampicin has a complex behaviour. During the first two days of treatment the half-life increases, then it falls. It could be that this pattern is accentuated in renal failure.

MADDOCKS There is one other point about rifampicin. It is actively eliminated by the liver. The active transport mechanism is blocked by probenecid and it has been found that uraemic plasma contains substances which are capable of inhibiting the transport of organic acids. So it would be worthwhile checking the half-life of rifampicin in renal failure before making the assumption that it is normal.

DETTLE It is because of this process that CIBA advocate using only two or even one dose of rifampicin a day. The dissociation constant of this transport affinity is so high that you already have saturation phenomena. So if you give one dose a day you need less drug — and rifampicin is expensive.

KERR With regard to ethambutol; the standard practice in the United Kingdom is to reduce the dose from 25 to 15mg/kg after two months to avoid visual damage. This is especially important in renal failure. We have recently had a patient with renal tuberculosis — and only minimally elevated serum creatinine — go blind on 25mg/kg/day of ethambutol, fortunately with complete recovery after a very worrying month. It is essential to warn the patient to report the very first visual impairment as it is reversible at an early stage but not at a late stage.

KNAPP We have had an apparently irreversible case of ocular toxicity as a result of delayed reaction to the first symptoms. The patient was not in renal failure but it is pertinent to report that the visual impairment may become permanent since this is not generally known. There were no other cases of which the company were aware when we reported ours. There is virtually no recovery of vision after one year.

DRUKKER (Jerusalem) Does age affect renal elimination in renal failure, particularly in the paediatric and geriatric age groups?

RAWLINS There is uncertainty about the effect of ageing on drug metabolism in the absence of renal failure. The original story was that drug metabolism slowed down as you grew older but this is becoming less and less easy to support, and the position is not clear. What happens to the elderly in renal failure is even more difficult to predict. One of the striking things about the elderly is that they have low plasma protein concentrations and therefore reduced drug binding. This is one of the things that has made all the studies very complicated.
MARSH (London) We have been concerned about the effect of drugs on renal transplant patients with varying degrees of renal function and fungal or parasitic infections. We thought that we had caused renal impairment with pentamidine in one patient but there seems to be some difference of opinion as to whether pentamidine is nephrotoxic or simply causes extra-renal uraemia. What do the panel think about pentamidine and should amphotericin dosage be modified during the course, as renal function becomes impaired, to prevent a circular effect on renal function?

MADDOCKS The effects of amphotericin B on renal function are thought to be largely reversible. One effect is constriction of the renal artery and another is an effect on the tubule; it can produce a type of renal tubular acidosis. It looks as if the drop in GFR is related to its effect on the renal artery, reducing renal blood flow, so it does not necessarily indicate renal damage. We have found that when we have stopped the drug there has been an improvement in renal function, but it is a very difficult drug to use. We have had a number of renal transplant patients with fungal infections in whom we have used it and we have not been certain whether it has caused renal trouble or not because renal function changes in these patients with rejection episodes.

KERR Presumably, whatever the cause of the drop in GFR, even if it is a reversible one, you have to modify the dose of amphotericin while it lasts.

McGEOWN Can the panel comment on the use of beta-blockers in chronic renal failure? We have had several episodes of severe congestive failure associated with bradycardia in patients receiving beta-blockers who had very low GFR.

LEBER Ohnhaus has reported on pindolol and according to him conversion of the original drug proceeds normally in renal failure, but nobody knows about the metabolites at the moment. Propranolol was investigated by Thompson and his group and they found an accelerated or normal conversion, but, as was pointed out this morning, some of the metabolites are still active. I think this is one drug which should be measured, or dosed with regard to the clinical response, not according to a schedule.

DETTLI Practolol was the simplest drug to use in renal failure but unfortunately you can no longer get it.

DALMAV (Palma) Colchicine is useful in the crises of familial mediterranean fever. How should the dose be modified when the patient has amyloidosis and requires haemodialysis?

MADDOCKS So far as I know it has not been studied. The dose is very low and there is no assay procedure which has the sensitivity to detect it in plasma. We have given colchicine to patients in renal failure and they have had no adverse effects. It is easy to titrate the dose because the gastrointestinal toxic effects are closely related to the dose.