PART XXVI

GUEST LECTURE ON TRANSPLANTATION II

Chairmen:  S T Boen
           A Amerio
REJECTION AND NEPHROTOXICITY. DIAGNOSTIC PROBLEMS WITH CYCLOSPORINE IN RENAL TRANSPLANTATION

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Introduction

The new immunosuppressant cyclosporine has been the most important recent innovation in the field of organ transplantation. This new drug differs from all other immunosuppressive substances in biochemical structure, in mode of action and also in the spectrum of side effects. Since it has recently become evident in two multicentre trials [1,2] that it is able to improve transplant survival rates in cadaver kidney transplantation by 15–20 per cent, it is becoming increasingly important to analyse the problems associated with this drug and to further improve its clinical use. Important issues which still have to be resolved are whether cyclosporine should be used alone or in combination with other immunosuppressive drugs, whether it should be given to all patients or whether certain subgroups still would have greater benefit from conventional immunosuppressive treatment; finally information about the long-term effects of cyclosporine treatment is still rather limited. The answer to many of these questions depends on whether it will be possible to develop strategies to reduce or avoid the most serious side effects. Since all known side effects of cyclosporine are dose-dependent an important step in this direction will be the better understanding of cyclosporine pharmacokinetics resulting in improvements of the presently used regimens which are still mostly based on empiricism.

A side effect particularly important in kidney transplantation is the marked nephrotoxicity of cyclosporine. Since the reduction of kidney function is still the most important clinical sign of rejection, nephrotoxicity can cause serious diagnostic problems not seen in conventionally treated patients. Important approaches which could provide at least partial solutions to these problems are (a) improved handling of the drug on the basis of improved knowledge of its pharmacokinetics; (b) attempts to minimise the risk of additional damage to the graft, particularly during organ procurement and in the peri-operative period; and (c) the development of additional procedures for the differentiation between nephrotoxicity and rejection. The purpose of this article is to demonstrate the relevance of these approaches on the basis of our experience with
cyclosporine in kidney and liver transplantation and to review the clinical problems associated with cyclosporine-induced nephrotoxicity.

**Pharmacokinetics and blood monitoring**

Studies of the pharmacokinetics of cyclosporine in humans have shown that after oral administration only 20 to 50 per cent of the drug is absorbed from the intestine [3]. In uraemia [4] and in patients with disturbed intestinal function or disturbed bile secretion [4,5] the absorption rate may be reduced far below this range. In the blood, peak concentrations are measured three to four hours after oral intake [3,6]. The drug has a high affinity to tissues. During steady state after repeated oral administration much higher tissue than blood concentrations were found in rats [7]. The highest amount was found in the liver. The drug is extensively metabolised in the liver and metabolites are mostly excreted with the bile [3,4]. Less than 10 per cent of the metabolites are excreted by the kidney. The elimination half-lives from blood or plasma have been calculated to be 14–17 hours under physiological conditions. They can be markedly prolonged in patients with liver dysfunction [5,6].

With high performance liquid chromatography (HPLC) and the radioimmunoassay (RIA) two methods for monitoring the cyclosporine levels in blood or plasma are available. With HPLC only the parent drug is determined, the RIA detects both the parent drug and several metabolites. The HPLC/RIA ratio can give a rough estimate of the relative proportion of parent drug and metabolites [6].

After oral intake of cyclosporine a characteristic time/concentration curve can be determined in circulation [3,4]. A peak concentration is reached after three to four hours which is followed by a slow decline of the cyclosporine concentration. In steady state, the time/concentration curve reaches a basic value after 8 to 12 hours, which is only slightly decreased at 24 hours. This means that after 12 to 14 hours the blood is in equilibrium with the tissue which can be regarded as the relevant parameter for both the immunosuppressive effect and toxicity. Therefore the trough value has to be regarded as most relevant for the evaluation of the response to treatment.

The blood values referred to in this paper are always trough concentrations determined 12 hours after oral intake. They were determined by RIA in haemolysed whole blood. It should be noted that equivalent plasma values are markedly lower [7].

**Clinical classification of cyclosporine nephrotoxicity**

The nephrotoxic effect of cyclosporine was obvious in the first patients treated with this drug [8]. It is not confined to transplanted kidneys but has also been observed in patients with liver, heart and bone marrow transplantation, as well as in patients with autoimmune disorders [9]. It has been difficult, however, to demonstrate the nephrotoxic effect in laboratory animals [10]. Rats develop some type of nephrotoxicity if treated with high dosages but are clearly less susceptible than humans; in other animals definite nephrotoxicity can usually
only be demonstrated if cyclosporine treatment is combined with other nephrotoxic insults such as transient ischaemia [11]. The lack of suitable animal models is the cause of the very limited knowledge of the pathophysiology of cyclosporine nephrotoxicity. There is circumstantial evidence that it is mediated by a direct effect on intrarenal prostaglandin production causing profound alterations of renal haemodynamics [10,12,13]. The question whether toxic effects can be recognised morphologically has been controversial. Extensive studies of experimental and human material have led Mihatsch and associates to describe a variety of distinct lesions such as isometric vacuolisation of proximal tubular cells, giant mitochondria and micro-calciﬁcation [13]. Furthermore, a particular type of arteriolar lesion has been deﬁned in humans and in spontaneous hypertensive rats [12,13]. Since pathophysiological and morphological criteria are still insufﬁcient, the various manifestations of cyclosporine nephrotoxicity are best classiﬁed as clinical syndromes. At least three different entities can be differentiated: (a) the dose-dependent reversible nephrotoxic episode; (b) interactive nephrotoxicity; and (c) chronic nephrotoxicity. Although the pathophysiological basis of all three syndromes in all likelihood is closely related, they pose different diagnostic problems and require different therapeutic measures.

Dose-dependent nephrotoxic episodes

This syndrome can best be deﬁned in patients with otherwise uncompromised kidney function, that is in transplants with immediate good function or after recovery from ischaemic injury. It is characterised by a variable increase in the serum creatinine. It can be very slow but frequently develops as rapidly as in acute rejection. Following appropriate reduction in the cyclosporine dose the nephrotoxicity is usually fully reversible [14–16]. Figure 1 depicts the characteristic course of a patient with this complication.

As already suggested by the dose-dependence, the nephrotoxic episode is nearly always a clear sign of overdose. It is usually associated with high blood concentrations. We have analysed the frequency of this type of nephrotoxic episode in 40 consecutive patients during the first three months post-transplantation. Twenty-two episodes occurred in 15 of the 40 patients. Cyclosporine trough blood concentrations in these patients were 1306±310ng/ml at the time of nephrotoxic episode and 662±217ng/ml after appropriate dose reduction and resolution of nephrotoxicity. Patients with values far above 1000ng/ml frequently show other signs of cyclosporine toxicity, such as tremor and in some instances hepatotoxicity. During the first three months after transplantation this type of nephrotoxicity is not seen in patients with blood values below 800ng/ml unless other nephrotoxic insults are also present, such as ischaemic damage or treatment with potentially nephrotoxic antibiotics (vide infra, interactive nephrotoxicity). Therefore we regard a whole blood trough value of 800ng/ml as the upper limit of the therapeutic range in the early post-operative period.

It is obvious that monitoring and adjustment of dose according to blood values will reduce the frequency and severity of acute nephrotoxic episodes. They are particularly difficult to avoid in patients with liver disease, who frequently
Figure 1. Characteristic course of an acute nephrotoxic episode. The elevation of the serum creatinine in the third post-operative week is associated with high blood concentrations and responds quickly to cyclosporine dose reduction.

Develop very high cyclosporine concentrations because of the reduced elimination rate of cyclosporine and the resulting problems with appropriate dose adjustment. If blood values are determined during or immediately after a rejection episode high results can be misleading since high doses of steroids have recently been shown to interact with cyclosporine metabolism [17]. In this instance high values can be secondary to the rejection treatment and thus may not be the cause of the elevated creatinine. A careful analysis of the pattern of blood results is particularly helpful. It has to be stressed, that this diagnostic instrument has its full potential only when performed as a prospective monitoring programme, with frequent blood estimations.

Since the clinical signs of an acute nephrotoxic episode resemble acute rejection closely, the differentiation of the two conditions is a key problem of cyclosporine therapy. In the presence of high blood values the response of the serum creatinine to dose reduction will usually clarify the situation. If the creatinine comes down quickly no further diagnostic procedures are required. In case of an insufficient response to dose reduction or if the creatinine elevation
occurs despite cyclosporine blood concentrations in the therapeutic range, the exclusion of rejection by other means becomes mandatory. If the deterioration of kidney function is rapid, it might even be necessary to start rejection treatment before the definite diagnosis has been obtained. Since the course of acute rejection is ameliorated in cyclosporine treated patients [18,19], however, there is usually sufficient time to wait for the results of further examinations. In the cyclosporine era graft morphology still has remained the most important proof for rejection [13,20,21]. Important supportive procedures are radionucler tests, sonography, and urinary cytology. Recently with the determination of the urinary excretion of neopterin [22] and the measurement of the subcapsular hydrostatic pressure in the kidney graft [23] two new promising methods have been added to the diagnostic armamentarium.

Interactive nephrotoxicity

An interactive effect between cyclosporine nephrotoxicity and kidney damage by a variety of other agents has now been well established [11,12,24]. It is a characteristic feature of this type of nephrotoxicity that it can become manifest with much lower dosages and with blood concentrations regarded to be in the therapeutic range. Failure to differentiate this cumulative type of cyclosporine nephrotoxicity from the dose dependent acute nephrotoxicity described above is the most likely cause for the bad correlation between nephrotoxic effects of cyclosporine and blood concentrations described by others [25]. The interactions occurring between cyclosporine and additional nephrotoxic insults are probably manifold and depend on the nature of the additional insult. The interaction can be thought of as an increased susceptibility of a pre-damaged kidney for the nephrotoxic cyclosporine effect or vice versa depending on the sequence in which these insults become effective.

Relevant additional insults for the transplanted kidney are ischaemic damage [2,11,26], treatment with other potentially nephrotoxic drugs [24,27–29] and acute or chronic allograft rejection. In the early post-operative period a cumulative effect of a variety of harmful factors has to be considered. During organ procurement and implantation the length of the cold and warm ischaemic periods and of prolonged machine perfusion have been found to influence strongly the nephrotoxic effect of cyclosporine [2]. In the recipient the state of hydration and the use of other potentially nephrotoxic drugs can lead to cumulative organ damage. Low cyclosporine blood values do not exclude this type of nephrotoxicity: high blood values, however, will clearly increase this effect. In anuric patients and in patients with severely impaired kidney function quick dose adjustments according to blood concentrations are mandatory. Another obvious consequence of these considerations is the reduction of all other potentially harmful factors to a minimum. Under these conditions residual cyclosporine nephrotoxicity and the effect of other injuring factors may not become clinically manifest.

The crucial clinical relevance of interactive nephrotoxicity in the early post-operative course results from the fact that, if it reaches the state of initial non-function, the graft survival rate becomes reduced [2,26]. The detrimental
effect of initial non-function on graft survival has frequently been shown under conventional immunosuppression and is even more relevant during cyclosporine treatment. Figure 2 compares the graft and patient survival rates for patients with and without initial graft function in our institution. It clearly demonstrates the increased risk to the graft if initial non-function occurs. The reasons for this increased rate of graft loss are complex. A major factor is that a superimposed rejection is difficult to detect and thus may be treated too late or inadequately. It has to be considered that a graft which is damaged by ischaemia and toxic effects has a reduced capability to recover from severe rejection. Since the postoperative management of anuric patients is more difficult, the more frequent use of other potentially nephrotoxic drugs will also contribute to the increased complication rate in these patients. Table I lists some of the drugs which have to be considered in this context. It includes drugs with a direct effect on the kidney [24,27–29], but also substances interfering with cyclosporine metabolism and thereby increasing the risk of nephrotoxic complications [15,30].

On the basis of these considerations the initial non-function rate can be kept low only by a multifactorial approach. Greatest attention to any avoidable injury during the harvesting process, during preservation and during the recipient operation is essential. As a result of this approach we have been able in our institution to reduce the frequency of initial non-function from 53 per cent in 1982 to 40 per cent in 1983 and 32 per cent in patients receiving a first cadaver kidney graft during the first six months of 1984. Table II demonstrates the dependence of the cold ischaemic time on the incidence of initial non-function for the whole patient population. The data suggest that a cold ischaemic time below 30 hours can reduce the frequency of initial non-function. This
TABLE I. Enhancement of cyclosporine nephrotoxicity by other drugs

I. Drugs with direct effect on kidney
(without effect on cyclosporine blood concentrations)
   a) tubulotoxic drugs
      aminoglycosides
      cephalosporines
      other potential nephrotoxic antibiotics
      frusemide?
   b) inhibitors of prostaglandin synthesis
      indomethacin
      other potentially nephrotoxic analgesics

II. Drugs interfering with cyclosporine metabolism
(high blood values, nephrotoxic effect mediated by toxic cyclosporine
   tissue values)
   Ketoconazole
   H₂-receptor blockers (cimetidine, ranitidine)
   steroids?

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TABLE II. Correlation between initial non-function (INF) and cold ischaemia time (CIT)

<table>
<thead>
<tr>
<th>CIT (hours)</th>
<th>INF/total</th>
<th>% INF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>3/21</td>
<td>14</td>
</tr>
<tr>
<td>20–30</td>
<td>27/63</td>
<td>43</td>
</tr>
<tr>
<td>30–40</td>
<td>27/44</td>
<td>61</td>
</tr>
<tr>
<td>&gt;40</td>
<td>19/36</td>
<td>53</td>
</tr>
</tbody>
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time limit is still compatible with periods required for organ exchange between
different centres even long distances apart.

The rather high frequency of initial non-function in Table II even with cold
ischaemia times of 20 to 30 hours points to the fact that this is not the only and
even not the most important factor for the frequency of initial non-function. As
already discussed, warm ischaemia time, the hydration state of the recipient,
the treatment with other potentially nephrotoxic drugs and the loading dose of
cyclosporine may be important. We presently still use a standardised loading
dose of 14mg/kg three to six hours before transplantation, followed by 14mg/kg
during the first 10 post-operative days. This dosage is then reduced by 2mg every
other week until a maintenance dose of 2 to 7mg/kg is reached. For about 30
per cent of the patients this regimen is still too high and quicker dose reductions
are necessary on the basis of blood monitoring. In particular in these patients
lower loading doses would probably be helpful. We are currently studying the
question of how these patients can be identified before excess values are found.
Another approach to reduce the risk of this type of nephrotoxicity are immunosuppressive regimens which combine cyclosporine in a reduced dosage with azathioprine and/or antilymphocyte globulin in addition to low dose steroids. It is not clear yet whether this approach is more effective than cyclosporine therapy in strictly blood concentration adjusted protocols either with or without steroids.

Since it occurs with cyclosporine concentrations in the therapeutic range, the interactive type of nephrotoxicity raises particularly difficult diagnostic problems. In patients with a functioning kidney the coincidence of functional deterioration with the addition of another drug to the regimen is an important clue. In anuria this information is not available. In this situation we have found the serial determination of the subcapsular hydrostatic pressure very helpful: it is below 40cm H$_2$O in kidneys suffering from ischaemic damage or toxicity but increases to over 40cm H$_2$O during rejection [23]. These results have recently been confirmed by Salaman et al [31]. Furthermore, repeated graft biopsies appear to be indicated in order to detect rejection at a time when it is still reversible. The fine needle aspiration biopsy has the advantage that it can be performed very frequently with no or very limited risk [21].

**Chronic nephrotoxicity**

Chronic cyclosporine nephrotoxicity is a badly defined entity but nevertheless one of the most serious therapeutic problems. It can be characterised as a state of poor long-term function which can be either stable or progressively deteriorating. Histology shows marked fibrosis and frequently also signs of chronic vascular injury, such as intimal thickening. The histological signs are not characteristic. The diagnosis is made by exclusion. The most important differential diagnosis is chronic rejection. Other conditions which have to be excluded are arterial stenosis, ureteric problems and recurrent disease.

The frequency of chronic nephrotoxicity depends on the maintenance dose of cyclosporine and on the blood values [15]. There is no doubt that during the maintenance therapy reduced blood values are sufficient to control allograft rejection [15]. On the other hand tubular cells appear to develop an increased susceptibility to cyclosporine. This leads to a high incidence of creatinine elevations in patients maintained above 600ng/ml during long-term treatment. This type of chronic nephrotoxicity usually responds very well to a reduction in the cyclosporine dose. In order to achieve blood levels between 150 and 600ng/ml cyclosporine maintenance doses between 2 and 6mg/kg bodyweight are required in most patients. Occasionally, however, nephrotoxic syndromes do not resolve even after adequate reduction. It is not yet clear whether this represents a particularly high susceptibility to cyclosporine or an interaction with pre-existing damage resulting from chronic rejection or other nephrotoxic insults. That the deterioration in kidney function is indeed caused by cyclosporine can be demonstrated in the individual patient by conversion to conventional immunosuppression. Figure 3 demonstrates the course of a patient with a living related kidney, who showed the characteristic signs of chronic nephrotoxicity three months after transplantation in face of adequate blood cyclosporine.
Figure 3. Effect of conversion of cyclosporine to conventional immunosuppression in a patient with chronic nephrotoxicity four months after transplantation

Concentrations. Conversion, leading to a marked reduction in the serum creatinine. The patient has now maintained stable kidney function over an observation period of 18 months.

An important issue is whether the chronic progressive form of nephrotoxicity has to be ascribed only to cyclosporine or to an interaction of cyclosporine with chronic rejection and furthermore how frequent this clinical syndrome occurs. Figure 4 demonstrates the distribution of serum creatinine values in 32 patients who were followed over a period of 24 months post-transplantation. It clearly demonstrates that in the vast majority of patients a stable creatinine could be maintained over the whole observation period. In accordance with the results of others [15,18,32] the average creatinine in these patients, however, is undoubtedly higher than in historical controls under conventional immunosuppression. Evaluation of this fact has to take into consideration that the cyclosporine treated population includes patients who would have lost their graft under conventional immunosuppression. In contrast to the majority of patients who maintained a slightly impaired but stable kidney function, five patients showed progressive deterioration. We would assume that most of these patients would benefit from conversion to conventional immnosuppression similar to the patients depicted in Figure 3. This might even be true in patients suffering from chronic rejection, since the relief of the graft from the additional toxic effect of cyclosporine in all likelihood leads to functional improvement. There are virtually no data available demonstrating a superiority or inferiority of cyclosporine in the treatment of chronic rejection. The answer to this question will require the long-term follow-up of this particular patient population.
Conclusions

Nephrotoxicity is the most important side effect of the new immunosuppressant cyclosporine. On the basis of clinical experience and the limited experimental results available, a clinical classification has been suggested. The purpose of this classification is to permit the development of diagnostic and therapeutic guidelines.

Dose-dependent acute nephrotoxicity in well functioning grafts is the first type which has been discussed. It is usually associated with a high blood concentration and responds quickly to dose reduction. In patients with an otherwise impaired kidney function it can mostly be avoided if the cyclosporine dose is adjusted by blood monitoring. The second type, interactive nephrotoxicity occurring with blood values in the therapeutic range is a more difficult problem. The most serious manifestation of this form is the early post-operative nephrotoxicity caused by the additive effects of ischaemia and cyclosporine treatment. This condition is associated with an increased rate of graft loss. Important
approaches to reduce the occurrence of this complication are to reduce the risk of additional damage of the graft during organ procurement and during the peri-operative period. Cumulative nephrotoxicity resulting from the interaction of other potentially nephrotoxic drugs with cyclosporine is best treated by the avoidance of the interacting drug whenever possible. In order to limit the toxic component of cyclosporine as far as possible, frequent blood monitoring is even more important in patients with impaired kidney function than in patients with well functioning grafts.

Particularly difficult to evaluate is the chronic form of nephrotoxicity. It is a badly defined entity which probably includes a variety of different states. There is certainly some type of basic nephrotoxicity leading to elevated creatinine concentrations in most patients when compared to conventionally treated controls. In contrast to others we feel that this type of nephrotoxicity is progressive only in a minority of patients who should be converted to other forms of immunosuppression. In the majority of patients the development of a chronic cyclosporine nephropathy can be avoided by dose reductions in order to maintain blood values in the range of 150 to 600 ng/ml in whole blood. Finally, it can be expected that a better understanding of the pathophysiology of cyclosporine nephrotoxicity will open the way to more refined procedures to avoid this side effect or for protecting the kidney against it. Since recently a related compound with no nephrotoxic effect in animal models has been found, there is also some hope that it finally will be possible to separate the immunosuppressive and the nephrotoxic effect by chemical modification of the cyclosporine molecule [16, 33].

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Open Discussion

BOEN (Chairman) Thank you Dr Pichlmayr. I think that since Professor Calne gave his lecture at the EDTA meeting in Amsterdam on the early experience with cyclosporine and transplantation, we have learned quite a lot, especially of the dosage. I have read some alarming observations about chronic tubular-interstitial damage which led to chronic renal disease in patients following heart transplantation. I wonder whether in transplanted kidney patients some of the other centres have seen this. Do you know about this complication Dr Pichlmayr?

PICHLMAYR I think the figures that have been presented from the Stanford group are, of course, alarming. The findings are similar to those described by the Basle group in the very early experience of clinical renal grafting with excessively high doses of cyclosporine. We would avoid these today and we rarely see these histological changes since we have used cyclosporine in a much lower dose. It has to be added that the patients in the Stanford group are the patients which primarily have been treated with a high dose of cyclosporine, and their serum levels are, I think, too high. Particularly in heart patients who have injured kidneys before grafting, the addition of a nephrotoxic substance in too high a dose produces a typical combination effect which may be very harmful to kidneys.

AMERICO (Bari) What is the incidence of lymphoma in your experience and are these related to nephrotoxicity?

PICHLMAYR The incidence of lymphoma in our material is zero but we have to remember that the incidence of lymphoma in heart recipients from the Stanford experience is very high. As you know the first experience by Professor Calne had a high incidence of lymphoma but this is most likely due to the effect of high dose combined with other immunosuppressive drugs. I think that those centres using blood-level guided cyclosporine dose have not seen lymphoma in kidney recipients. There is one in a liver graft patient by Dr Starzl. I think that Dr Wiskott would be able to clarify the situation if I may ask him to do so.

WISKOTT (Basle) We have now analysed almost 10,000 patients and the overall incidence is 0.3 per cent. This compares rather well with the experience in azathioprine and conventionally treated patients where this incidence has been
reported by Kinlon in 1979 before the use of cyclosporine. In conventional treatment the incidence is 0.5 per cent and it is his experience in the heart transplant recipient that this figure is 3.3 per cent in about 400 transplanted patients with cyclosporine to date, compared to about six per cent before the use of cyclosporine, which has been published by Anderson in 1982.

HANSEN (Aarhus) I think one of the problems with chronic nephrotoxicity perhaps is that it is a little bit difficult to find out what dosage you have to continue with after the first half year of cyclosporine treatment. Perhaps it might be possible, at least in some patients who exhibit nephrotoxic symptoms, to reduce the dose below 4 to 8mg/kg/day to around 2 to 3mg/kg/day. In some cases when we have had patients with constantly elevated serum creatinine above 200μmol/L. We have seen a decrease in serum creatinine in some patients following a reduction in cyclosporine doses.

PICHLMAYR I think this is a problem in the individual patient. If we have normal ranges of blood or serum concentrations and we have some nephrotoxic state should we reduce even more the cyclosporine or should we switch to other therapy? I am convinced many of our patients, in spite of the fact that they have whole blood levels of about 500, these levels are too high and so we could reduce them, but of course one is afraid of rejection.

BRODERSEN (Germany) I think it was Professor Toussaint who showed us figures about acute renal failure after heart transplantation and I would like to hear of the episodes of acute renal failure under the conventional regimes after heart transplantation, or let us say deterioration of renal function with conventional immunosuppressive regimes.

PICHLMAYR At the moment we are giving loading doses of cyclosporine to most heart and kidney transplant recipients and it might be better to postpone the administration of the drug.

TOUSSAINT (Brussels) Using conventional therapy there was no case of acute renal failure after heart transplantation necessitating haemodialysis: this is very common at the present time.

MEES (Utrecht) You mentioned the differentiation between the acute rejection and cyclosporine toxicity utilising measurement of the subcapsular pressure. Do you measure that regularly and how do you do that?

PICHLMAYR With a very fine needle which is inserted subcapsularly, and we do this for about two to three weeks. There is a little fluid injected and the drift of this fluid is measured. It is a little bit more complicated than that, but that is how we do it.

DOSSETOR (Alberta) I would like to report that it is possible to have normal blood levels when giving a high dose of cyclosporine if the assay is interfered
with. One instance of this is the association between cyclosporine dosage and anti-platelet drugs such as Sulphapyrazone or Antusan, and under such circumstances, despite the maintenance of normal blood levels, we have observed a lymphoproliferative disorder. I would like to ask whether the incidence of post-cardiac transplant complications could be associated with an increased use of a drug such as Sulphapyrazone?

PICHLMAYR I think that is a good idea, but I have no answer. I would guess that it might act in such a way.

TOUSSAINT The cardiac transplant I talked about earlier did not receive anti-aggregating drugs.

PICHLMAYR Nevertheless, we have to think very carefully about any interactions of the drug.

PAPADIMITRIOU (Thessaloniki) I think one way to approach the problem of acute nephrotoxicity is to see which part of the nephron is affected. Do you have any experimental studies? We know what aminoglycoside toxicity is doing and what happens in the ischaemic model, but is there any evidence on which part of the nephron is first affected by a high dose of cyclosporine?

PICHLMAYR Sorry to say not, but I think I have an explanation of this because all animal models for nephrotoxicity are very difficult. In the rat nephrotoxicity can be shown, but with extremely high doses we do not know if it is the same. The dog is very resistant to nephrotoxicity of cyclosporine which explains why one did not know about it before using it in the human situation. We have no good models at the moment.