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*Special Feature*

*Fernando Valderrabano Memorial Lecture*

# Renal transplantation 2004: where do we stand today?

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*On September 6, 2001, Professor Fernando Valderrabano (Hospital Gregorio Marañon, Madrid) died at the age of 59 years. He was a leading figure in Spanish nephrology, a full professor of Medicine/Nephrology at the University Complutense of Madrid, and an outstanding scientist who published more than 300 articles in medical journals. He was a very intelligent and cultured person, and a man of great style who enjoyed a wide range of hobbies and interests in addition to his medical work. All his colleagues and friends mourn his passing.*

**Professor Fernando Valderrabano 29.12.1941–6.9.2001**

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**Abstract**

In spite of considerable progress in immunosuppressive and supportive treatment, numerous problems persist which interfere with the success of renal transplantation. Before transplantation has been performed, factors impacting on outcome include the donor (living *vs* cadaver, age and HLA system) as well as the recipient (age, immunological reactivity, potential sensitization and duration of dialysis). These are the main factors that affect the outcome of the transplant, particularly in the long-term. After transplantation a number of events may put graft function at risk: potential recurrence of the primary renal disease in the allograft; '*de novo*' renal disease triggered by infections, drugs or autoimmunity; and non-specific progression promoters, such as diabetes, hypertension, proteinuria, nephrotoxic agents and/or viral infections. The two most frequent causes of chronic allograft dysfunction are (i) chronic rejection (often triggered by preceding acute rejection, delayed graft function or poor compliance) and (ii) calcineurin-inhibitor nephrotoxicity (more likely to develop in kidneys of older donors or in marginal kidneys). The differential diagnosis between these two entities is generally difficult, but some histological clues (reduplication of glomerular basement membrane, obliterating vasculopathy and C4d deposits) as well as the demonstration of humoral antibodies are pointers suggesting rejection. Treatment of chronic graft dysfunction is difficult, whatever the cause, particularly in cases with advanced renal lesions. Therefore, early diagnosis is of paramount importance. In this regard, graft biopsy can be of great help. In spite of many problems and complications, not only short-term but also long-term results of renal transplantation are improving progressively, as documented by CTS data showing that in Europe for transplants performed between 1982 and 1984 the mean graft half-life was 7 years, while for transplants performed between 1997 and 1999 it was 20 years.

**Keywords:** calcineurin inhibitors; chronic allograft nephropathy; chronic rejection; recurrent disease; renal transplantation

## Introduction

Today, renal transplantation is the treatment of choice for most patients with end-stage renal failure. Yet, in spite of the continuous progress in immunosuppressive and supportive therapy, a number of factors still interfere with the complete success of renal transplantation. Some factors, present at the time of transplantation, concern the donor as well as the recipient, while other complications originate after transplantation. In this review, particular attention will be paid to the main factors and events that impair graft function in the long-term.

## Factors at the time of transplantation

### *The donor*

The *source* of the donor can strongly affect the results of renal transplantation. The renal graft half-life is by far longer for living-donor than for cadaver transplants [1]. This finding cannot be attributed only to a better histocompatibility. In fact, the graft half-life of transplants between spouses who are obviously HLA-mismatched is more than one-third better than that of cadaver donor grafts [2]. The difference may be accounted for by a number of factors. First of all, the quality of the kidney of a living donor can be carefully assessed, while that of a cadaver donor must be evaluated in a hurry and under difficult conditions. Second, brain death causes a hypertensive crisis and also an autonomic storm leading to profound ischaemia and endothelial damage of peripheral organs, even when blood pressure is normal [3]. Third, ischaemia-reperfusion injury is obviously less severe with living donation. Finally, brain death is associated with an upregulation of cytokines and chemokines that favour overexpression of HLA antigens by endothelial and tubular epithelial cells, thus, increasing the risk of acute [4] and chronic rejection [5].

The *age* of the donor is also important. While in the recent past most donors were younger than 50 years, today the age of the donor is increasing progressively. The UNOS registry documented that the higher the age of the donor, the worse the long-term outcome of the graft [1]. Some investigators feel that the poorer results of kidneys of elderly donors are mainly caused by the age-dependent progressive reduction of glomerular filtration rate and renal reserve. To overcome this problem it has been proposed to transplant both kidneys of borderline cadaver donors into one single recipient. Alfrey *et al.* [6] reported good results with dual transplantation in 287 patients, i.e. a 5 year graft survival rate of 69%. Surprisingly, however, in this series the mean age of the donor (58 years) was by no means very advanced and the mean creatinine clearance was borderline, at best (mean: 77 ml/min). It is well justified to ask whether a similar result would not also have been seen by transplanting the two kidneys into two recipients. As a matter of fact, Bunnapradist *et al.* [7] reviewed the data of the US Renal Data System and reported that the 3 year graft survival of kidney grafts coming from donors above age 55 years was 70% for single transplants and 65% for dual transplants. On the other hand, Halloran *et al.* [8] did not find a relation between the initial creatinine clearance of an old donor and subsequent graft survival. He hypothesized that the main problem of old kidneys is replicative senescence rather than decreased renal function. Actually, a strong association has been found between specific markers of replicative senescence and the presence of chronic allograft nephropathy in biopsies of kidney transplants from older donors [9,10]. If so, the best way of utilizing old kidneys could be to transplant them to old recipients. In this regard, the group of La Charité in Berlin reported that in old recipients graft survival was similar for those transplanted with old kidneys and for those who were given kidney grafts based on HLA match, waiting time and cold ischaemia time, irrespective of the age of the donor [11].

The role of *HLA* typing with modern immunosuppression has been a matter of controversy. While there is evidence that long-term survival is better for transplants with no antigen mismatch than for mismatched transplants [12], lesser degrees of mismatch are of minor clinical relevance [13]. The analysis of more than 50 000 renal transplant recipients showed that the effect of donor age on patient survival was greater than that of HLA match [14].

### *The recipient*

Not only the age of the donor, but also the *age* of the recipient is increasing in recent years. The UNOS data show that the results are worse for recipients above age 50 years. The main cause of graft failure is death with a functioning graft. As expected, the older the age, the higher the risk of death. On the other hand, the risk of graft failure caused by acute or chronic rejection tends to decrease with age [1]. Since death is due mainly to cardiovascular disease and since malignancy is more frequent at advanced age, intensified cardiovascular investigation and search for malignancies are indicated and appropriate therapeutic measures should be taken before an elderly patient is considered suitable for transplantation. It is also important to assess the patient's nutritional status and rehabilitation, since frail elderly patients are at particular risk of infectious complications. On the other hand, however, since the risk of rejection is less in elderly recipients [1], immunosuppressive therapy can be less aggressive. Particularly, steroid-free

immunosuppression is indicated in elderly recipients to reduce the risk of cardiovascular complications [15], infection and diabetes.

It would be of great utility to know the *immune reactivity* of the recipient in order to adjust immunosuppression accordingly. Unfortunately, we still have no valid pre-transplant markers, but recent data have shed some light on this problem. Susal *et al.* [16] proposed to measure the immunological reactivity of the patient before transplantation by measuring serum CD30, which is expressed on CD4+ and CD8+ T cells that secrete TH2-type cytokines. Patients with CD30 levels <100 U/ml had a significantly better 5 year graft survival than patients with higher serum levels. Rotondi *et al.* [17] measured the serum chemokine CXCL10/IP-10 and found significantly higher pre-transplant blood levels in patients who had graft failure than in patients with good graft function. Uboldi de Capei *et al.* [18] reported that high interleukin (IL)-10 producers mismatched for class I, but matched for class II HLA antigens and low IL-4 producers (independent of HLA match) are protected from chronic rejection. Although it is still too early to tailor immunosuppression according to these parameters, there is hope that in the near future good markers of immune reactivity will permit us to find the immunosuppressive regimen that is most appropriate for the individual patient. In the past, patients who lost their first transplant because of rejection were considered at high immunological risk. More recently, the UNOS data [1] showed that the graft half-life was similar for first (10.6 years) and second transplants (9.4 years). Patients who lost their first graft because of an accelerated rejection may still be considered 'strong responders', however.

Patients who have developed high titres of panel-reactive *anti-HLA antibodies* (PRA) following pregnancies, blood transfusions or transplants are at increased risk of graft failure [19]. Moreover, most patients with very high titre PRA cannot be transplanted because the crossmatch with a potential donor is likely to be positive. In the past, attempts to remove preformed anti-HLA antibodies with immunoadsorption had some success [20]. More recently, Glotz *et al.* [21] reported good results by pre-treating 15 hypersensitized patients with a 3 month course of intravenous high-dose immunoglobulin before transplantation. Thirteen patients were actually desensitized and were transplanted immediately. One patient lost the graft because of thrombosis and another because of rejection. All the other patients were alive with a functioning kidney graft after >1 year. Another potential approach is pre-treatment with the anti-CD20 monoclonal antibody rituximab, which may reduce the PRA titres dose-dependently [22].

*The duration of dialysis treatment* is a problem that has been neglected so far. Strong evidence suggests that the results of pre-emptive transplantation, before dialysis is started, are far better [23,24]. Using a paired donor kidney analysis, Meier-Kriesche and Kaplan [23] demonstrated that the longer the time on dialysis, the worse the long-term outcome of renal transplantation. This was true both for living and cadaver allografts. The authors concluded that the time waiting on dialysis is the strongest modifiable factor influencing transplant outcome.

### *What to do before transplantation?*

From a theoretical point of view, transplantation ideally should be performed between HLA-identical subjects, the kidney should preferably come from a living young donor and the recipient should also be young, have no preformed anti-HLA antibodies and low immunoreactivity and should receive the transplant before starting dialysis treatment. The real world is quite different: only a small minority of patients receive a well-matched kidney; in Europe, as of 2001, only 15% of patients receive a living donor transplant; donor and recipient age increases progressively; and the duration of dialysis treatment while the patient is on the waiting list gets longer and longer. On the other hand, it would be unethical to refuse transplantation to a patient only because of his/her old age, long duration of dialysis or hypersensitization, since even in elderly patients renal transplantation offers higher life expectancy [25] and better quality of life [26] than does dialysis. It is also not advisable to discard marginal donors because of the persistent shortage of kidney grafts.

In order not to penalize patients at risk and not to compromise the success of transplantation, it is advisable to take some practical measures. Hypersensitized patients should be treated with intravenous immunoglobulins or rituximab and should be transplanted immediately after their PRA titres have decreased substantially. Patients with high immunological reactivity and those who lost a previous graft because of an early rejection should receive aggressive immunosuppression. In contrast, frail patients, such as older recipients, those with long exposure to dialysis as well as HCV- and HBV-positive patients should receive less-aggressive immunosuppression, possibly altogether avoiding the use of corticosteroids. Finally, in patients who receive a kidney from elderly or marginal donors the use of calcineurin inhibitors should be avoided or at least minimized, since these kidneys are particularly vulnerable to the nephrotoxic effects of these agents.

## Post-transplant events

### *Specific diseases*

*Recurrence of primary disease* may lead to graft failure, particularly in the long-term. It is difficult to assess the risk of recurrence for the individual renal diseases, because duration of follow-up and indication for biopsy are so heterogeneous in the available reports. If one reviews the most recent large series [27–32], it appears that some diseases, such as immuno-

**Table 1.** Risk of recurrence and relative risk of graft failure of primary renal disease

| Disease | Recurrence | Relative risk |
|---|---|---|
| IgA GN | 30% | 1.2 |
| MN | 6–30% | 1.2 |
| SLE | 3–30% | 1.1 |
| FSGS | 20–40% | 2.3 |
| MPGN | 3–48% | 2.5 |
| HS purpura | 20–40% | 2.6 |
| HUS | 6–56% | 5.6 |

IgA GN, immunoglobulin-A glomerulonephritis; MN, membranous nephropathy; SLE, systemic lupus erythematosis; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; HS purpura, Henoch–Schoenlein purpura; HUS, haemolytic uraemic syndrome.

globulin-A nephritis, membranous nephropathy and lupus nephritis, do not affect the 10 year graft survival even when they have recurred in the graft (Table 1), although over even longer periods recurrence of these renal diseases may eventually contribute to graft failure. More dangerous is the recurrence of focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, Henoch–Schoenlein purpura and, particularly, haemolytic uraemic syndrome (Figure 1). In many cases the recurrence of these diseases leads to the loss of graft, although sporadic cases of response to plasmapheresis or immunoadsorption have been reported [33–35].

'*De novo*' *thrombotic microangiopathy* may occur in patients on cyclosporin, tacrolimus, anti-mTOR agents or OKT3. Only half of cases show the typical picture of haemolytic uraemic syndrome. In the remaining patients, systemic signs and symptoms may be absent and there is only a progressive decline of graft function [36]. In these patients, renal biopsy is indispensable for early diagnosis of thrombotic microangiopathy. Prompt withdrawal of the offending drug leads to recovery in some patients. Plasmapheresis may also be helpful. In a large series [37], graft function recovered in 23 of 29 patients with post-transplant thrombotic microangiopathy. In all patients, calcineurin inhibitors were stopped and plasmapheresis was administered for a mean of 8.5 days.

Aggressive immunosuppression may reactivate *polyoma BK virus*, which is usually latent in the urinary tract. As a consequence, ~5–6% of transplant patients develop interstitial nephritis, which causes graft failure in about half the cases. There are not specific symptoms or signs. The diagnosis should be suspected in any patient with progressive graft dysfunction, particularly if treated with a combination of tacrolimus and mycophenolate mofetil [38]. Cells in the urine with viral inclusions, so-called 'decoy cells', may be used to monitor the patient, although the presence of decoy cells is sensitive but not very specific. Detection of virus DNA in plasma by polymerase chain reaction is more specific, but expensive. Once again, renal biopsy is of paramount importance. It shows interstitial nephritis with cytopathic changes and inclusion bodies (Figure 2). Staining with monoclonal antibodies against the simian virus can confirm the diagnosis. Reduction of immunosuppression or replacement of tacrolimus and mycophenolate mofetil with leflunomide, an immunomodulator agent

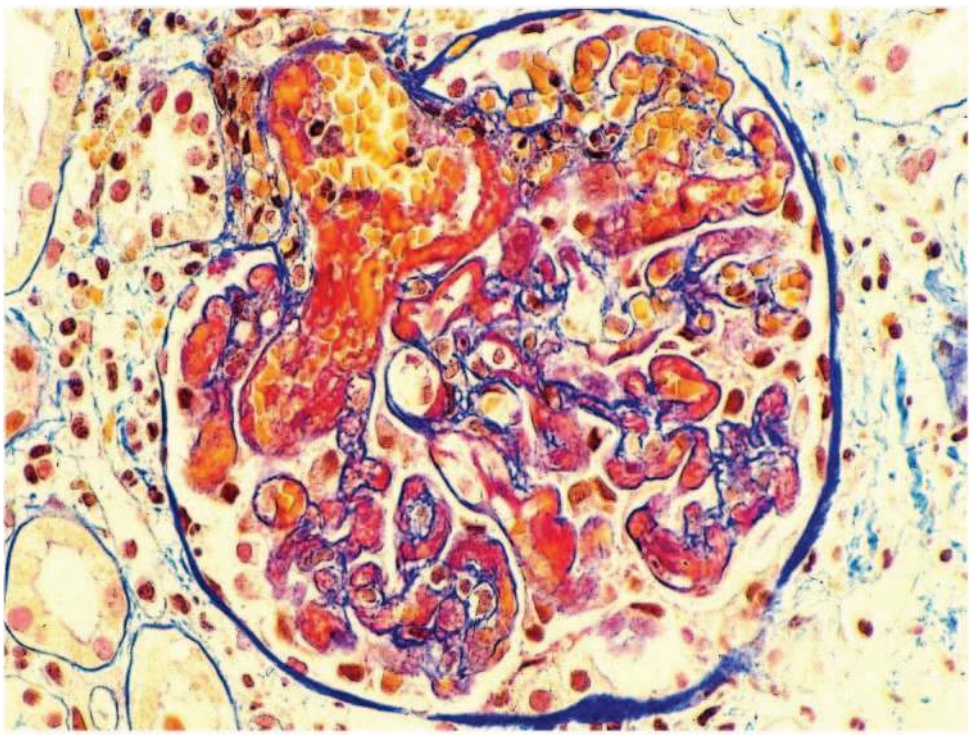

**Fig. 1.** Recurrence of haemolytic uraemic syndrome and severe thrombotic microangiopathy. (Courtesy of Dr G. Banfi, Nephrology, IRCCS Ospedale Maggiore, Milan, Italy.)

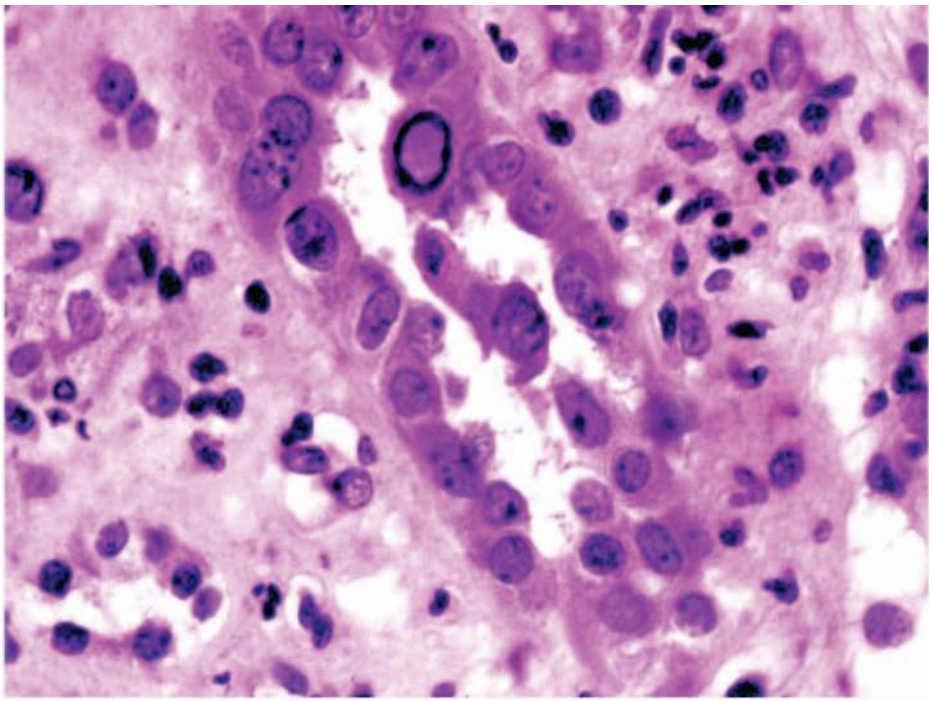

**Fig. 2.** Polyoma BK virus nephritis. Interstitial nephritis with severe tubular damage. The nuclei of epithelial cells are enlarged with chromatin irregularly distributed and vesicular changes (decoy cells). Note in a tubular cell the large nucleus with chromatin circumferentially distributed around a central halo (howl eye). (Courtesy of Dr G. Banfi, Nephrology, IRCCS Ospedale Maggiore, Milan, Italy.)

with antiviral properties, may rescue the kidney in a number of cases. Cidofovir has also been used with success in anecdotic observations [38].

Besides BK virus, cytomegalovirus (CMV), herpes viruses 1 and 2 and adenovirus may cause *interstitial nephritis* as well. Moreover, a number of drugs that are often used in renal transplant recipients, such as antibiotics, sulphonamides, allopurinol, diuretics and non-steroidal anti-inflammatory drugs, may also cause interstitial nephritis. The diagnosis is difficult, since eosinophilia, fever and rash are generally absent because of the administration of corticosteroids and immunosuppressive drugs. The diagnosis rests on renal biopsy.

The transplanted kidney may also develop *'de novo' glomerulonephritis*. The most frequent forms are membranous nephropathy usually related to HBV infection [39] and membranoproliferative glomerulonephritis in HCV carriers [40]. However, cases of '*de novo*' idiopathic membranous nephropathy [41], acute glomerulonephritis [42], collapsing focal glomerulosclerosis [43] and minimal change nephropathy [44] have been described as well. Although the pathogenesis of these cases is still obscure, one may speculate that the proinflammatory alloimmune response in a transplanted subject modifies anti-inflammatory mechanisms that protect from autoimmunity. Consequently, the immune responses to autoantigens may be subverted by alloimmunity, resulting in an autoimmune response.

The potential development of chronic graft dysfunction from *calcineurin-inhibitor toxicity* is well known. These drugs may cause persistent vasoconstriction and endothelial lesions (Figure 3) that eventually lead to interstitial fibrosis and tubular atrophy. Important contributors are activation of the renin–angiotensin system, increased synthesis of osteopontin and chemokines as well as diminished production of nitric oxide. All these factors may trigger excessive production of profibrogenic transforming growth factor-β1) and/or directly cause tubulointerstitial damage [45]. Factors increasing the risk of severe nephrotoxicity are the dose of the calcineurin inhibitor, the age of the patient and his or her renal function. 'Marginal' kidneys are more vulnerable to the nephrotoxicity of calcineurin inhibitors. To prevent the development of severe renal toxicity, the blood levels of cyclosporin and tacrolimus should be monitored regularly; the doses should be adjusted accordingly; particularly, the possibility of pharmacokinetic interferences should be taken into account between calcineurin inhibitors and drugs that increase (macrolides, triazolic antifungal, calcium-channel blockers, etc.) or decrease (antiepileptic agents, rifampin and derivates, etc.) the bioavailability of calcineurin inhibitors; and the simultaneous use of nephrotoxic agents should be avoided whenever possible. In patients with graft dysfunction, a renal biopsy should be performed to exclude or confirm a diagnosis of nephrotoxicity. It should be kept in mind that the lesions caused by calcineurin inhibitors can be halted or even improved by reducing or stopping the drug in the due time [46].

In summary, specific diseases represent a frequent cause of graft failure. In a number of cases, an early

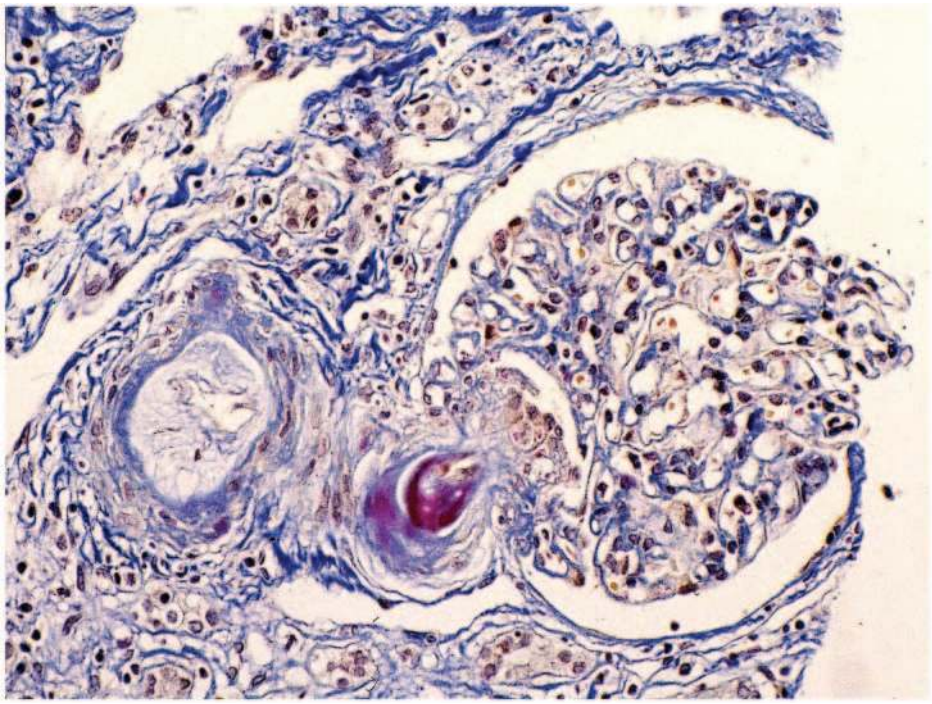

**Fig. 3.** Cyclosporin-related arteriolopathy. Mucinoid thickening of the intima with intraluminal thrombosis. (Courtesy of Dr G. Banfi, Nephrology, IRCCS Ospedale Maggiore, Milan, Italy.)

diagnosis and an appropriate treatment may allow the reversal of graft dysfunction. The diagnosis is often difficult. Renal biopsy is the most important tool to establish the diagnosis and should be performed in any case of graft deterioration of uncertain origin.

### *Non-specific causes of graft dysfunction*

Up to 20–25% of renal transplant recipients develop overt *'de novo' diabetes* [47,48]. These patients have an increased risk of cardiac, cerebrovascular and peripheral vascular disease [49]. Moreover, patients with post-transplant diabetes may develop a diabetic nephropathy and graft dysfunction in the long-term [47,50].

*Arterial hypertension* is frequent in renal transplant patients. Opelz *et al*. [51] showed a strong association between the values of blood pressure and the risk of chronic graft dysfunction.

The inappropriate use of *nephrotoxic agents* may also expose to progressive graft dysfunction. Aminoglycosides, fluoroquinolones, cidofovir, foscarnet, sulphonamides, non-steroidal anti-inflammatory drugs, analgesics, contrast media, etc. may cause renal toxicity, which is usually dose-dependent. Patients showing an increase in serum creatinine should be always asked about the use of potentially nephrotoxic drugs.

The role of *proteinuria* in the progression of renal disease has been the subject of numerous experimental and clinical studies. Roodnat *et al*. [52] showed that both patient survival and graft survival (censored by death) were significantly lower in renal transplant recipients with proteinuria than in non-proteinuric patients.

*CMV infection* is a frequent complication in renal transplantation. More than 50% of seronegative [53] and ~10% of seropositive transplant patients [54] may develop symptomatic CMV disease. Apart from the well-known consequences of CMV disease, the infection can increase the risk of acute [55] and chronic rejection [56] through overproduction of mediators, cytokines, chemokines and growth factors.

To prevent the deleterious impact of these factors on progression, fasting and postprandial glucose should be checked frequently and glucose intolerance should be treated as early as possible; arterial hypertension should be treated aggressively, trying to keep blood pressure levels within the normal range; nephrotoxic agents should not be used unless strictly necessary; angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers should be considered in patients with proteinuria; and CMV infection should be prevented or treated with specific antiviral agents.

### *Transplant glomerulopathy*

This still mysterious entity is characterized clinically by proteinuria and progressive graft dysfunction. Graft biopsy shows enlarged glomeruli, mesangiolysis and glomerular capillary enlargement with microaneurysm formation. In advanced stages, reduplication of glomerular basement membranes is seen. Electron microscopy shows widening of the subendothelial

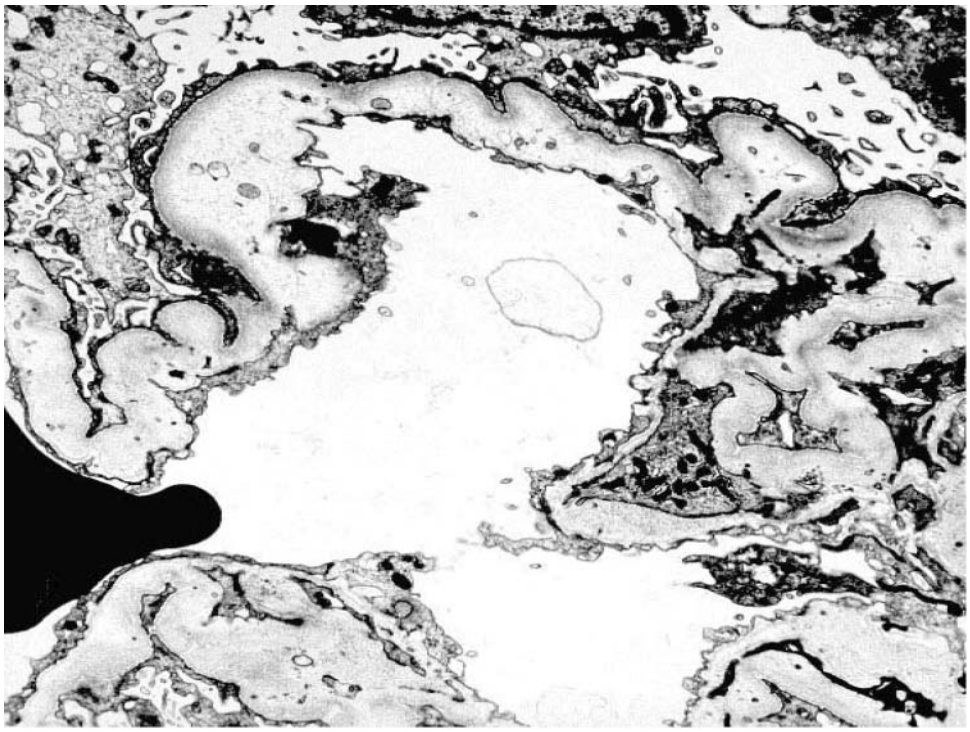

**Fig. 4.** Transplant glomerulopathy. Reduplication of glomerular basement membrane with large subendothelial space (electron microscopy). (Courtesy of Prof. M.J. Mihatsch, University of Basel, Switzerland.)

space (Figure 4). Transplant glomerulopathy is often classified as an expression of chronic rejection, but other investigators prefer to consider it as a separate entity. The prognosis is poor [57]. However, a few patients may maintain some degree of renal function even for years. There is no effective therapy.

### *Post-transplant predictors of chronic rejection*

There is evidence that *acute rejection* can influence the long-term outcome of renal transplantation. Graft half-life is longer in patients who never experienced acute rejection [58]. However, the long-term impact of rejection on graft function is related more to its characteristics than to its occurrence. Long-term graft survival is better in patients who had only a single episode than in patients with two or more episodes of rejection [59,60]. Opelz [61] showed that when rejection is completely reversible, it does not affect 5 year graft survival. Sijpkens *et al.* [62] pointed out that the prognosis is worse for patients who had late rejection than for those who had early rejection: 10 year graft survival censored by death was 86% for patients who developed rejection by the third post-transplant month and 45% for patients who had rejection after the third month. Long-term graft survival is usually excellent in patients with borderline or grade I rejection, according to the Banff '97 classification [63], while the prognosis is worse for patients with grade II and very poor for patients with grade III rejection [64,65]. More recently, the Banff classification has been revised by adding the category 'humoral rejection', defined by either the presence of deposits of C4d (a split product of the C4 component of complement) in peritubular capillaries and/or the presence of circulating donor-specific antibodies [66]. The histological equivalents are the presence of neutrophils in the peritubular capillaries and glomeruli and fibrinoid necrosis of arteries. Thus, the impact of an acute rejection on the long-term outcome depends on the number of rejections, on the reversibility (complete or partial), on the time of onset (early or late), on the histological outlook according to the Banff criteria and on the development of humoral antibodies.

The occurrence of *delayed graft function* (DGF) may require dialysis, may prolong hospitalization and may expose to an increased risk of infection. Whether DGF *per se* affects long-term graft survival is still controversial. However, there is agreement that the combination of DGF with rejection has a deleterious effect on graft survival [67,68]. As a matter of fact, it is very difficult to identify acute rejection in an oliguric patient. Moreover, the endothelial damage caused by reperfusion injury and by acute rejection may eventually result in the development of a chronic obliterative vasculopathy (Figure 5). Thus, efforts should be made to prevent or attenuate the damage caused by ischaemia-reperfusion injury. Reduction of the cold ischaemia time has been advocated by some investigators. However, two large studies [69,70] showed that, at least up to 30–36 h, cold ischaemia time does not significantly affect graft survival. Intracellular perfusion solutions are now extensively used after it has been demonstrated that they reduce the risk of DGF. Antioxidant and antiapoptotic agents proved to be effective in experi-

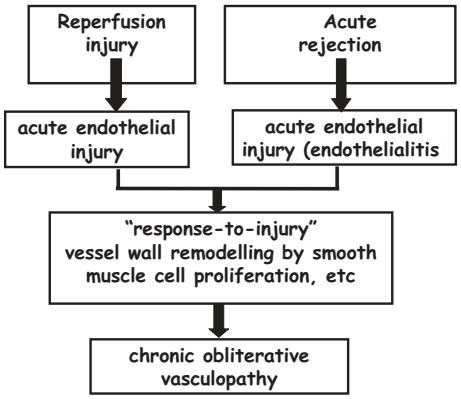


**Fig. 5.** The combination rejection–delayed graft function can lead to chronic obliterative vasculopathy.

mental models, but they are still not used widely in clinical practice. As the problem of ischaemia-reperfusion injury is becoming more and more important with the more frequent use of marginal donors, further studies are needed to overcome this potential consequence.

An important cause of late graft failure is poor patient *compliance*. Its frequency is poorly known, as many patients are reluctant to admit non-adherence to therapy. A recent paper [71] reviewed the studies devoted to the problem of compliance. Cross-sectional studies based on a self-report questionnaire suggested poor compliance in 22% of transplant recipients. Cohort studies indicated that 36% of the cases of graft loss were preceded by episodes of non-adherence. Meta-analysis of these studies showed that the odds of graft failure increased seven-fold in non-adherent patients. Poor compliance is often related to the complexity of and disfiguration from treatment as well as to the social isolation of the patient. To improve the compliance of the patient, the treatment should be simplified; the patient should be informed about the effects of the drugs and the consequences of a poor adherence; and the clinician should have a firm partnership with the patient and should pay attention to their problems, by modifying therapy in case of disturbing side effects. Significant improvements in graft survival might be obtained by improving the compliance of our patients.

## Chronic allograft nephropathy

This term encompasses most causes of late dysfunction and has been adopted to indicate a progressive and irreversible histological and functional deterioration of the transplanted kidney. However, for the clinician it is of great importance to know the main cause of chronic allograft nephropathy (CAN). In this regard there is much confusion, because in many cases a late renal biopsy shows non-specific features rendering a correct diagnosis almost impossible. The transplant community seems to be divided into two parties: those (including this writer) who feel that the main cause of late graft failure is chronic rejection and those who feel that it is the chronic toxicity of calcineurin inhibitors.

The term *chronic rejection* should be applied only to cases of CAN caused by a cellular or humoral alloimmune response. Unfortunately, it is not easy to recognize whether a CAN is caused by rejection or by non-immunological causes, as in both cases the graft biopsy shows interstitial fibrosis, tubular atrophy and glomerular sclerosis. Some cases of late rejection, characterized by major infiltration by mononuclear cells, are probably sustained by T-cell activation, favoured by inadequate immunosuppression or poor compliance. If promptly recognized, unfortunately unusual, such late rejections may benefit from standard anti-rejection therapy plus reinforcement of maintenance therapy. However, most cases of chronic rejection are caused by humoral antibodies, either directed against HLA or minor antigens [72]. Besides the presence of *de novo* humoral antibodies, some histological features are considered to be specific for chronic humoral rejection, such as multilayering lamination of the basement membrane of peritubular capillaries on electron microscopy [73], arterial intimal fibrosis with intimal mononuclear cells (Figure 6) and a bright linear staining of CD4 along over half of peritubular capillaries [66]. Theoretically, plasmapher-

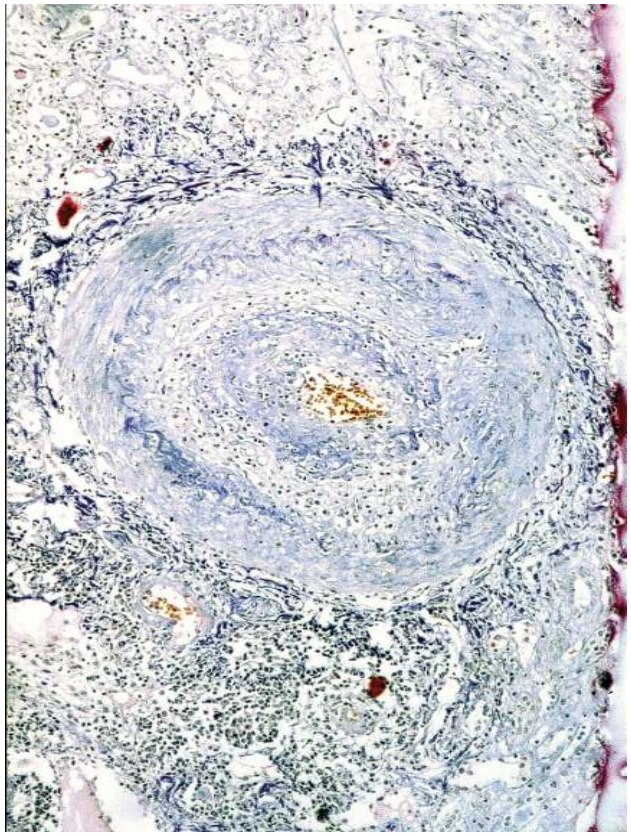

**Fig. 6.** Severe obliterative transplant arteriopathy in an interlobular artery. (Courtesy of Dr G. Banfi, Nephrology, IRCCS Ospedale Maggiore, Milan, Italy.)

esis, intravenous immunoglobulins and/or rituximab might obtain some reduction of circulating antibodies, but it remains unclear whether these measures may actually benefit the clinical outcome in patients with chronic humoral rejection. The problem is further complicated by the fact that the nephron loss, caused by T cell-mediated or humoral rejection, can trigger a vicious circle perpetuating the progression through non-immunological factors, such as glomerular hyperfiltration, hypertension, proteinuria, hyperlipidaemia and atherosclerosis. Moreover, anti-graft antibodies can stimulate cell proliferation that may result ultimately in the development of transplant arteriosclerosis [74]. Finally, release of novel self-antigens caused by rejection might trigger an indirect recognition of alloantigens by antigen-presenting cells of the recipient as demonstrated in lung transplantation [75]. This synergistic interplay of immunological and non-immunological events might explain why it is so difficult to manage chronic rejection.

Also, in cases of CAN caused by *calcineurin-inhibitor toxicity* or by *accelerated senescence*, graft injury can trigger non-specific accelerating factors that contribute to progressive graft dysfunction. In a number of patients, some improvement of renal function has been achieved by replacing calcineurin inhibitors with mycophenolate mofetil [76,77] or with sirolimus [78]. However, even with graft biopsy, it is not easy to exclude immunological activation in these cases of CAN. A number of patients are, therefore, exposed to the risk of late irreversible rejection after stopping the calcineurin inhibitor. It is also possible to speculate that the overexpression of chemokines and cytokines and a release of antigens from the damaged kidney can favour an indirect recognition and T-cell sensitization that may trigger a late rejection even in cases of CAN originally triggered by non-immunological factors.

## Conclusions

Many factors and events can complicate the outcome of renal transplantation and can eventually lead to progressive renal dysfunction and graft failure. Some of these factors are unmodifiable a priori and for some other complications we do not have any effective therapy. A recent review of the American data concluded that, in spite of a marked decrease in acute rejection, there is a lack of improvement in long-term graft survival [79]. Should we conclude that progress in renal transplantation is limited, i.e. that we have achieved better graft survival in the short-term without having achieved any significant impact in the long-term? This is not the impression of this writer. In Milan we reviewed our own results in patients treated with kidney transplantation. The review included patients transplanted between 1983 and 2000. Consequently, a number of patients were treated with too high doses of cyclosporin and others could not profit from the use of newer immunosuppressive and supportive therapy. In spite of these drawbacks, the cumulative graft half-life was 20 years. If the data were censored by death, the pure graft half-life would have been 31 years [80]. At any rate, not only single-centre results, but also the cumulative European data clearly show that there has been a progressive improvement of the graft half-life in spite of the older age of donors and recipients. The data of CTS reported a graft half-life of 7 years for cadaver grafts transplanted between 1982 and 1984 *vs* a graft half-life of 19.5 years for graft transplanted between 1997 and 1998 [81].

In summary, many different factors and events may lead to chronic graft dysfunction. In the case of specific renal diseases or drug-related nephrotoxicity, prompt recognition and treatment of the underlying cause may slow progression. Thus, an early diagnosis is of paramount importance and the use of renal biopsy in doubtful cases should be encouraged. Whatever the cause of graft dysfunction, non-specific accelerating factors, such as hypertension, CMV infection, glucose intolerance, proteinuria etc., should be treated early and aggressively. The differential diagnosis between chronic rejection and chronic drug toxicity is difficult, but some clues may help to identify the immunological nature of a CAN. In many cases an early biopsy is helpful, while a late biopsy is generally of no use. Today, although many unresolved problems persist, long-term graft survival is possible for many transplant recipients, if they are monitored regularly by experienced clinicians. It is likely that in the near future the results will even be improved further by the introduction of newer immunosuppressive agents with a better therapeutic index.

*Conflict of interest statement*. The author is an external consultant of Novartis, Italy.

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