of these covariates is often imprecise, thus leaving substantial residual confounding. For example, in the study by Becker *et al.*,[7] the mean estimated glomerular filtration rate was 63 ml per minute and the mean ADPN 6 μmol per liter, compared with 32 ml per minute and 12 μmol per liter in the study by Menon *et al.*[8] The much lower ADPN in the first of the two studies clearly reflects less severe renal insufficiency. Given the close association between ADPN and renal function, the direct relationship between ADPN and mortality in the study by Menon *et al.*[8] may be due to residual confounding attributable to reduced renal function and/or to confounding by processes that accompany chronic renal diseases that are not captured by adjustment for the glomerular filtration rate. Furthermore, differential retention of high-molecular weight forms of ADPN in renal failure,[9] the nutritional and inflammatory status, polymorphisms in the gene encoding ADPN, and the various possibilities of combination of these factors may substantially alter the expected (inverse) relationship between ADPN and clinical outcomes (Figure 1). Causality assessment is a complex process, and epidemiologic associations per se rarely if ever allow definitive conclusions on causality. Biological experiments and randomized experimental studies in animal models and in humans are needed to frame a reliable interpretation of such associations. Yet the study by Kollerits *et al.*[1] is a very intriguing hypothesis-generating exercise, because, in a context where ADPN manifested its insulin-sensitizing and cardiovasculo-protective properties (Becker *et al.*'s analysis in the same database[7]), it also displayed a clear-cut direct association with a faster rate of renal disease progression. This is noteworthy because, in general, cardiovascular and renal damage proceed in parallel in patients with CKD. To explain their counterintuitive findings, Kollerits *et al.*[1] advance the hypothesis that in men with CKD there may be a condition of resistance to ADPN. However, because in this same cohort high ADPN was associated with a lower incident cardiovascular risk,[7] this hypothesis would imply that ADPN resistance in CKD patients is confined to the kidney. Medical research during the past century has been a to-and-fro process, from the bench to the bedside and vice versa. Given the therapeutic potential of increasing ADPN by pharmacologic intervention, the definition of the nature of the relationship between ADPN and progression of renal disease is a worthy scientific question. The precise definition of this association now requires that the research focus be moved to the experimental laboratory.

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Malignancy after kidney transplantation: Still a challenge

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Long-term complications of continuous immunosuppression still remain a serious threat and are currently drawing the attention of transplant physicians. Wimmer *et al.* show that malignancy occurs approximately fourfold more frequently in renal-transplant recipients than in a normal control population. Besides immunosuppression, viruses probably play an important oncogenic role in transplant recipients. The retrospective analysis by Wimmer *et al.* suggests that mTOR inhibitors and interleukin-2 receptor antibodies are promising immunosuppressive drugs to reduce the risk of cancer after transplantation. These preliminary results must be confirmed in large, prospective, randomized, controlled trials, with long follow-up, designed to evaluate the incidence of *de novo* malignancy in transplant recipients.

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Tremendous progress has been made in the field of clinical transplantation since the first kidney transplantation was performed in 1954.[1] Still, transplant physicians are continually coping with the delicate balance between optimizing graft survival and reducing the side effects of immunosuppressive drugs, such as infections, malignancy, nephrotoxicity, and cardiovascular morbidity and mortality (Figure 1).

With the introduction of cyclosporine in the early 1980s, and tacrolimus, mycophenolate, interleukin-2 (IL-2) receptor

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Figure 1 | Immunosuppression: a delicate balance.

blockers, and sirolimus in the 1990s, the rate of acute rejection within the first year could be progressively reduced to almost 10%, and 1-year kidney graft survival improved to more than 90%. These encouraging short-term results urged physicians to focus their attention on long-term complications related to chronic immunosuppression.

Wimmer, Rentsch, and colleagues[2] (this issue) report on the incidence of *de novo* malignancies in 2419 renal-transplant recipients at one institution between 1978 and 2005. This outstanding analysis of a single-center database probably provides more accurate information than registry-based studies, which are often flawed by inherent limitations and incomplete follow-up.

In this retrospective study, renal-transplant recipients had a 4.3 times higher risk of developing any type of cancer, compared with an age- and sex-matched population of the same geographical area.[2] Similar markedly increased risk of cancer after renal transplantation was recently reported in an Australian[3] and a French[4] population, thereby confirming the magnitude of the problem.

Vajdic *et al.*[3] compared the standardized incidence ratios (SIDs) for cancer in patients with end-stage renal disease before renal replacement therapy (SID = 1.16), in dialysis patients (SID = 1.35), and in renal-transplant recipients (SID = 3.27). Their data clearly demonstrate that the risk for cancer is only slightly increased before transplantation but increases almost threefold after transplantation, providing strong evidence that immunosuppression plays an important role in the development of cancer after renal transplantation.

Interestingly, Wimmer *et al.*[2] observed a dramatically increased risk for some specific cancers after kidney transplantation, namely Kaposi's sarcoma, skin cancer, kidney cancer, oropharyngeal cancers, and lymphoproliferative disorders. Many of these cancers are associated with infection by oncogenic viruses, such as human papilloma virus (in the case of skin and cervical cancers), Epstein-Barr virus (in the case of lymphoproliferative disorders), and human herpesvirus 8 (in the case of Kaposi's sarcoma). In contrast, the authors found only a twofold increased incidence in renal-transplant recipients for some of the most common tumors in the general population — colorectal, lung, prostate, and breast cancer. Such data support the hypothesis that immunosuppression is rarely the only culprit for the increased incidence of malignancy after transplantation but rather plays a permissive role in the development of virus-induced tumors. In addition, acquired cystic kidney disease may likely explain the increased incidence of kidney cancer after renal transplantation.

However, the crucial question that needs to be addressed in the field of transplantation remains: Can we reduce the incidence of malignancy in transplant recipients, while still maintaining adequate immunosuppression? In their retrospective analysis, Wimmer *et al.*[2] attempted to address this issue. The authors investigated the impact of the initial immunosuppressive regimen (around 3 weeks after transplantation, at the time of discharge) on the subsequent development of malignancy. However, this approach has important limitations, as it does not take into account the subsequent changes in immunosuppressive regimen, which may have influenced the occurrence of *de novo* malignancies. In addition, in this study, the group of patients, treated with mammalian target of rapamycin (mTOR) and IL-2 receptor antagonists, was small and had a short period of follow-up. The results of this statistical analysis therefore need to be interpreted cautiously and should encourage transplant physicians to undertake long-term prospective, randomized and controlled clinical trials addressing this issue.

Despite these limitations, the data provided by Wimmer *et al.*[2] strongly suggest that two classes of immunosuppressive drugs may have the potential to reduce malignancy after transplantation. According to their study, mTOR inhibitor-based therapies show a clear trend toward a lower tumor risk (both overall and skin cancer) as compared with all other immunosuppressive regimens. Several clinical trials in renal-transplant recipients have confirmed the significantly reduced risk of developing any malignancy under treatment with mTOR inhibitors.[5–7] In these studies, with median follow-up between 963 days and 5 years, mTOR inhibitors not only reduced the relative risk of any *de novo* cancer by almost 60% but also delayed the first presentation of these tumors. In addition, Stallone, Schena, and colleagues[8] observed in 15 kidney transplant recipients that sirolimus induces remission of dermal Kaposi's sarcoma within 6 months, while providing adequate immunosuppression.

Wimmer *et al.*[2] also observed that IL-2 receptor antibodies significantly reduce the incidence of post-transplant lymphoproliferative disease, as compared with depleting antibodies, such as ATG, ALG, or OKT3. Similar conclusions were reached by Cherikh *et al.*,[9] who compared the actual incidence of post-transplant lymphoproliferative disease in 38 519 primary kidney transplant recipients according to the induction therapy (monoclonal, polyclonal, or IL-2 receptor antibodies or no induction

therapy). In this study, the actual incidence of post-transplant lymphoproliferative disease was similar in patients treated with IL-2 receptor antibodies versus patients who received no induction therapy but was significantly lower in these groups than in patients who received depleting antibodies as induction treatment.

Whether mycophenolate mofetil (MMF) may reduce the risk of cancer is currently unclear. Although the analysis by Wimmer *et al.*[2] suggests that MMF may even enhance the risk of cancer, when combined with calcineurin inhibitors, this conclusion could be biased by the retrospective design of their study and the preferential assignment of MMF to older recipients. Robson *et al.*[10] prospectively examined the risk of lymphoma and other malignancies in 6751 *de novo* renal-transplant recipients treated with MMF and observed a similar risk at 3 years in comparison with an equal number of matched controls receiving non-MMF-based immunosuppression.

Obviously, malignancy is still a challenging complication of long-term immunosuppression. Immunosuppressive drugs, such as mTOR inhibitors and IL-2 receptor antibodies, probably reduce the risk for all or some specific malignancies and are currently tested in clinical trials designed to reduce the incidence of some specific cancers in kidney transplant recipients.

Achieving tolerance, the Holy Grail for transplant physicians, would undoubtedly obviate the need for lifelong immunosuppression and its associated complications. Pilot clinical trials are currently running to explore the biology of tolerance in humans and will hopefully shed more light on the feasibility of this goal in the future.

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Diabetic nephropathy and proximal tubule ROS: Challenging our glomerulocentricity

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Diabetic nephropathy is currently viewed as a predominantly glomerular process with glomerular injury driving secondary tubular loss. Brezniceanu and colleagues apply transgenic methods to support a prominent role for reactive oxygen species as mediators and for the proximal tubule as a major site of early disease activity in diabetes. Results support evidence for early tubular apoptosis and atrophy in human diabetic nephropathy.

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Diabetic nephropathy has long been considered virtually synonymous with glomerulosclerosis, the latter viewed as the cardinal manifestation and primary lesion of this functionally devastating disease. Recent gentle challenges to our collective dogmatism on this topic have emerged, but the paper by Brezniceanu and colleagues[1] (this issue) takes a giant step toward shifting the glomerulo-tubular balance in the field. These authors have made elegant use of transgenic technology to achieve selective overexpression of catalase in the renal proximal tubular epithelial cell (RPTC). Catalase, an enzyme that breaks down H_2O_2 to inactive components, is used as a tool to reduce generation of reactive oxygen species (ROS) and thereby probe their function. Using the RPTC-specific, androgen-regulated KAP promoter to drive transgenic catalase expression, Brezniceanu and colleagues[1] found that adult males exhibited spontaneous overexpression of catalase protein and activity in RPTCs, without the addition of exogenous androgen. The investigators accordingly used the wild-type and transgenic adult male mice to examine the role of ROS in early streptozotocin (STZ)-induced diabetic nephropathy, specifically asking whether limiting ROS generation attenuates selected diabetes-induced abnormalities in the proximal tubule: increased angiotensinogen (Agt), plasminogen activator inhibitor-1, apoptosis, and histologic injury following 2 weeks of diabetes.

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