50 years ago, on Dec 23, 1954, the first kidney was successfully transplanted, with an identical twin brother as donor. The graft functioned well without immunosuppressive drugs for 9 years until relapse of disease. Kidney transplantations between non-identical twins or non-twins were less successful, implicating the importance of close relationship. In the 1950s people were not aware of HLA matching or panel reactive antibodies as a cause of graft failure. However, in the past 50 years, renal transplantation has become increasingly successful with rates of graft survival now over 90% after the first year and about 50% after 10 years.1,2 The increased success of renal transplantation is due to increased knowledge about HLA matching, immune responses directed against graft antigens, and immunosuppressive drugs. Currently, acute rejection episodes can be treated successfully in most patients. On the other hand, about half the graft recipients encounter chronic rejection. The pathogenesis of such rejection remains uncertain and various factors might play a role, including immune-mediated damage. Chronic rejection is one of the most important challenges for successful renal transplantation.

In this issue of The Lancet, Gerhard Opelz describes, for the Collaborative Transplant Study, that panel reactive antibodies are strongly associated with long-term graft loss in HLA-identical sibling-kidney transplantation. The investigators analysed over 4000 HLA-identical (matched for A, B, and DR) sibling transplantations, compared with over 160 000 cadaveric transplantations. In the first year after transplantation, the presence of panel reactive antibodies was associated with significant reduction in graft survival in the cadaveric transplant group, but there was no effect in the HLA-identical sibling transplantations. However, long-term follow-up in the HLA-identical sibling group showed a major effect for panel reactive antibodies: in recipients with high levels of panel reactive antibodies (>50%), the number of functioning grafts was significantly lower at 10 years after transplantation. Thus the effect of panel reactive antibodies was highest in the first months after renal transplantation in cadaveric transplantations, started after the first year in HLA-identical sibling transplantations, and affected graft survival in the 10-year follow-up in the HLA-matched group.

What are the antibodies recognising? Before the transplantation, lymphocytotoxic panel reactive antibodies were assayed by incubation of serum with a panel of lymphocytes (from random donors of blood) in a dye-exclusion test. The level of presensitisation is determined by the number of donors that is recognised by the patient’s serum. The antibodies might bind both HLA and non-HLA antigens on the lymphocytes. These different reactivities cannot be discriminated with the assays used in Opelz and colleagues’ study. The effect of HLA antibodies might be more direct and result in the rapid effects found in the mismatched cadaver-transplant group. On the other hand, antibodies reactive with non-HLA antigens might be directed against minor histocompatibility antigens. The effects of these antibodies may be protracted and take years to induce damage. Alternatively, epitopes might be hidden or cryptic, and only exposed on damage to the graft. Hidden epitopes might be exposed by acute rejection episodes, as suggested by the finding that episodes of acute rejection are important risk factors for the development of chronic rejection.3 Unfortunately, data on the number of acute rejection episodes, which could partly explain the differences observed in Opelz’s study, are not available in the registry. More specifically, recent molecular analysis of kidney biopsy specimens during acute rejection revealed strong heterogeneity, including a subset with major B-cell contribution.4 These different subtypes of acute rejection showed different prognostic implications and careful examinations may yield important information for the pathogenesis of chronic rejection.

The high level of panel reactive antibodies might represent high responsiveness to antigen encounter. Previous alloantigen sensitisation (eg, during pregnancies, previous transplantations, or blood transfusions) may then be responsible for the high levels of panel reactive antibodies. Indeed Opelz and colleagues describe an association with female sex and the number of blood transfusions. Extrapolation of this phenomenon also suggests that the recipient might develop antibodies against any other antigens that are
distinct between the new kidney graft and the recipient. If, hypothetically, antigens in the kidney itself (that are not present on lymphocytes) are variable or polymorphic between individuals, this might result in an antibody response by the high-responsive recipient.

In-situ evidence for humoral involvement is derived from the finding of C4d deposits in rejected kidney allografts that correlate with circulating anti-HLA antibodies. In addition, immunosuppression with mycophenolate mofetil, which inhibits not only T-cell function but also antibody production by B cells, seems promising for long-term function of the transplant. The risk of chronic rejection is decreased in patients treated with mycophenolate mofetil. The effect of this drug is additive to the effect of HLA matching, suggesting that mycophenolate mofetil not only inhibits anti-HLA antibodies but also other antibody responses.

Antibody responses receive increasing interest in chronic rejection and specificity, affinity, and pathogenicity need to be investigated to estimate their contribution. The antigens recognised by the antibodies might be antigens on lymphocytes but may also be antigens that are specifically expressed in the graft. An example of tissue-specific antigens recognised by antibodies of patients with a specific form of chronic rejection, transplant glomerulopathy, is the glomerular basement-membrane protein agrin. Agrin is a heparin sulphate proteoglycan involved in maintenance of glomerular filtration. Antibodies against the side chains of agrin can induce proteinuria and duplications of the glomerular basement membrane. Antibodies against agrin were not found in patients with chronic allograft nephropathy; however, these patients might have antibodies with other specificities.

The results described by Opelz and colleagues support a search for antibodies in renal transplant recipients with chronic rejection.

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We declare that we have no conflict of interest.