The last 40 years has been a remarkable evolution of organ transplantation from nothing to a well-established form of treatment with good short-term and tolerable long-term results. Achieving tolerance with organ transplant has always been one of the most important goals in the field of transplantation.

The acceptance of antigens from non-identical cattle twins in utero has led to the discovery of "immunological tolerance" by Peter Medawar, father of transplantation. Subsequent to that, tolerance to renal allograft has been observed in patients who also received bone marrow grafts from the same donor.

Starzl T has described tolerance to liver grafts in man. Among their 42 patients, 12 were off all immuno-suppression after 10 or more years. Of patients with good function at 5 years, immunosuppression could be weaned off successfully. However, it is important to have in-vitro testing to determine who will develop tolerance and who will reject but such in-vitro testing is currently not available.

Starzl T has pioneered the use of prednisolone and azathioprine for transplant rejection. But he has noted that azathioprine did not induce tolerance. The practice of transplantation has transformed with the use of cyclosporin in 1985. Number of liver transplants performed increased dramatically. However, despite use of all the immunosuppression available, there is still risk of developing chronic rejection. Moreover, there is problem with drug toxicity, for example, cyclosporin induced nephrotoxicity. Data showed that cadaveric organ graft survival was about 70-80% at 1 year, 50-60% at 5 year and 40-50% at 10 years. In recent years, there is other more potent immunosuppressive agent such as FK506 and rapamycin. These drugs inhibit lymphocyte proliferation. However, it is said that both drugs should not be used together as they may compete for the same binding site.

The ultimate goal in transplantation is to achieve complete tolerance with no steroid required, no side effects, maintain good graft function without developing chronic rejection and induction of graft acceptance by creating a window of opportunity for immunologic engagement without graft versus host disease or host versus graft disease (WOFIE hypothesis). Tolerance can be classical, operational or almost or "Prope" tolerance. This almost or Prope tolerance could be a major step forward providing better quality of life for patients and requiring inexpensive maintenance immunosuppression. It involves induction followed by use of minimal immun-suppression. In fact, tolerance without immuno-suppression is difficult to achieve in organ graft because of polymorphism of HLA, variability of human response and vulnerability of organ graft to develop rejection.

Following the demonstration by Knechtle and colleagues that profound cytotoxic T cells depletion in rhesus monkey treated with a CD3 diphtheria immunotoxin resulted in tolerance to renal allografting, we have used a similar depleting protocol that depletes all T and B cells in recipients of cadaveric renal transplant, using CAMPATH-1H. CAMPATH-1H is a humanized antiCD52 monoclonal antibody, targeting CD52 on all lymphocytes. The targeting site is unique and different from that of anti-CD3 and anti-CD25 monoclonal antibody. The CAMPATH-1H had a rapid depleting effect when given intravenously, 20 mg on days 0 and 1 after renal transplantation, to 31 patients. It eliminated lymphocytes from the blood for a month as confirmed by immunohistochemical studies showing complete depletion of both T and B lymphocytes in kidney,
liver and lymphoid tissue. At 48 hours after the second dose of low dose monotherapy, cyclosporin (Neoral) was given to maintain blood levels averaging 100 ng/ml. Initially no other immunosuppression was given. The degree of HLA mismatch ranged from 1 to 5. Lymphocytoxicity test was negative in all cases. With a follow-up of 24-30 months, all except one of the patients are alive, one patient was on dialysis and one patient was on FK506. There have been five rejection episodes, all responded to pulse steroid treatment. One patient had recurrence of her original disease. The remaining 28 patients had intact functioning grafts. Mean serum creatinine was 149 umol/l (range: 66-292 umol/l) at 24-30 months. Three patients developed infections including one patient with shingles, one with intra-abdominal tuberculosis and one with systemic CMV infection. One patient with severe heart failure at the time of surgery died from this condition after 11 months. Currently 28 patients are still on the original low dose cyclosporin monotherapy. The outcome for this cohort of patients is encouraging, with efficacy compares favourably to our conventional triple therapy but in most cases allows the patients to be steroid-free on low dose immunosuppressive monotherapy. The maintenance treatment has very little obvious side effects. The regimen is simple for patients, is inexpensive and should be beneficial in the content of tight budgetary constraints worldwide. Patients who do not need to be on steroid are pleased with this aspect of the protocol. This treatment protocol should gain its popularity and be considered in patients not suitable for conventional immunosuppressive treatment.

Starzl T has reported a baboon to man liver transplant years ago. The patient died about 70 days after transplant as a result of the combination of rejection, infection and metabolic problem. Next advance in transplantation may be the use of cell therapy. Pigs are cloned recently and by manipulating the nucleus, one can alter the antigen of pigs. This may hold future for xenotransplantation.

With regard to islet transplantation, since 1990, there have been 267 attempts of islet transplant in the Edmonton Center. 8.29% maintained insulin independence at 1 year. Shapeiro et al (N Engl J Med 2000) described islet transplantation in 7 patients with type I diabetes using a glucocorticoid-free immunosuppressive regimen, consisting of sirolimus, tacrolimus and daclizumab. It was noted that the regimen results in insulin independence with excellent metabolic control for over 2 years. Optimal site of islet injection include: intra-portal, subcapule of kidney and submucosal site of gut. There may be one day when we can use the patient's own cell and genetically engineered and then cultured and re-injected back to patients.