I will try to outline the developments of immunosuppression, especially drug-induced immunosuppression and how this has influenced the practise of organ transplantation. In particular, I will discuss our work with the powerful lympholytic antibody Campath 1H originally prepared in Cambridge by Waldmann and his group. This has been used in a series of renal transplants as a pre-emptive strike as the sole immunosuppressant for the first three days, to 'wipe the slate clean' as it were, of lymphocytes and monocytes and leave the field clear for minimal maintenance immunosuppression which I have called "proper or almost tolerance". The five year results of the initial trial of 31 recipients of cadaveric renal transplants have been encouraging and a number of further trials have been initiated, with varying maintenance immunosuppression (Moore et al., 1960; Starzl et al., 1960).

The current expectations in organ transplantation have improved steadily, particularly in the last five years. The first immunosuppression was x-irradiation which proved to be very unsatisfactory with a high toxicity and a poor therapeutic index. The only long survivors were two recipients of kidneys from non-identical twins. The introduction of chemical immunosuppression with azathioprine made transplantation possible and a number of further trials have been initiated, with varying maintenance immunosuppression (Moore et al., 1960; Starzl et al., 1960).

The most effective immunosuppression so far described with a low toxicity has been a combination of FK506 and rapamycin in an important series of clinical investigations performed by McAslister in Halifax, Nova Scotia (McAlister et al., 2000). It was this combination, together
with an anti-II 2 receptor antibody that led to a complete change of attitude of the transplant community to islet transplantation in the treatment of type 1 diabetes. The series of patients treated by Shapiro and colleagues in Edmonton has now reached more than 40 with a one year success rate in terms of insulin independence of 80% and a two year success rate of 75% (Shapiro et al, 2000). The procedure usually requires at least two cadaver pancreas donors in order to get sufficient islets and this highlights the fact that cadaveric islet transplantation can never be a mainstream therapy for type 1 diabetes. Another disadvantage is that the patients require life-long immnosuppression so they substitute immunosuppression for insulin, but this can be a good trade-off if the patient is a brittle diabetic and it is hoped that the islet transplants will prevent secondary complications of diabetes.

With the progress in islet transplants together with important advances in bone marrow transplantation, especially using myelodepleting platted techniques, the stage is set for a major advance in transplantation. Hopefully non-myelodepleting bone transplantation to produce macrochimerism will result in true tolerance as has been observed in bone marrow and renal transplants between close blood relatives treated at the Massachusetts General Hospital in Boston, where the recipients had suffered from myeloma and renal failure (Buhler et al, 2002). The move from closely-matched donor to an unmatched donor will be a big step. Therefore, there is great interest in the possibility of engineering stem cells to provide large numbers of suitably differentiated cells to treat diseases such as diabetes, Parkinson’s disease and in-born errors of metabolism. Currently, it is uncertain whether adult stem cells from bone marrow or other sources will be suitable for this task or whether it will be necessary to use fully totipotent embryonic stem cells which, of course, can differentiate into any tissue. With any stem cells therapy, there is a potential danger of tumor formation and also the possibility of virus disease if a virus is used to engineer cells to produce specific proteins. Since the cloning of Dolly, the possibility of nuclear transfer to produce bespoke stem cells or differentiated cells with the unique HLA configuration of the sick recipient is another area that is being explored.

So for young investigators interested in transplantation the field continues to be exciting, particularly the possibility of producing tolerance for transplantation of whole organs on the one hand, and the development of non-immunogenic surrogate specialized cells to treat patients with diseases requiring specific cell protein synthesis.

REFERENCES


