Attempts at transplanting tissues such as the skin go back a very long way, certainly to the 16th century. Although the Italian surgeon Gaspare Tagliacozzi was credited with the successful transplantation of noses from slaves to their masters, he was healthily sceptical about grafts transplanted from one individual to another — the so-called allografts. Interest in transplantation goes back further than that, but here we are entering the grey area of mythology; thus there is reference to transplantation in Egyptian papyri and in the Hindu Susruta. Likewise, the transplantation of parts of the body of an animal of one species to that of another may be found in classical mythology, giving rise to the lamassu, chimera, griffon, hippocamp and cockatrice. Of these the chimera is best known — part lion, part goat and part serpent — and it is no accident that those who discovered immunological tolerance chose to describe as cellular chimeras animals which, as a result of an experimental stratagem, sustain in their bodies the cells of another individual.

Whilst there was considerable interest in skin and tumour transplantation in the 19th century, the field really began to open up towards the beginning of this century. The early trigger for this was the aspiration of some intrepid surgeons, mainly in German-speaking countries, who thought that they might rescue patients suffering from terminal kidney disease by providing them with a healthy kidney. At that time it was unthinkable to use human cadaveric kidneys, so they began to graft kidneys between animals, both allografts and grafts from other species — xenografts. Some surgeons were quicker than others to realise that their experiments were doomed to failure, handicapped as they were by an almost complete lack of knowledge of the mechanisms of graft failure and, of course, by the absence of immunosuppression. Nonetheless, a few transplants survived for several weeks, almost certainly due to the patients’ uraemia, and the principle that transplanted kidneys can secrete urine was established. This encouraged the French surgeon Alexis Carell, first working in France and later in the United States, to establish a method of anastomosing the blood vessels of transplanted kidneys with those of their hosts and to show beyond doubt that such kidneys were, for a while, fully functional.

Even the kidneys so skillfully transplanted by Carell and CC Guthrie failed sooner or later, and so interest in transplantation as a surgical panacea waned. It was revived during the second world war when Peter Medawar’s experimental studies in both humans and rabbits showed, beyond a shadow of a doubt, something that had long been suspected: the cause of graft failure was immunological. The science of transplantation immunology was born and, like Topsy, it grew and grew.

I would not want to weigh in the balance which country has made the most telling contribution to the development of transplantation immunology. It would, however, be false modesty for us not to acknowledge that the British have been a major force, beginning with Peter Medawar’s seminal studies in the mid-1940s and with Peter Gorer’s, which began even earlier. These two men were pioneers and, together, they lifted British immunology to quite dizzy heights.

The eight British individuals I have chosen to describe are, of course, not the only ones who have made their mark — the UK is fortunate to have spawned a large number of outstanding transplantation immunologists and transplant surgeons.

Peter Brian Medawar

Peter Medawar (Fig 1) had a Lebanese father and an English mother and was born in Brazil. He was educated at Marlborough College — an experience he detested, though it instilled in him a decisive love for biology. He met his wife Jean at Oxford, where he took a degree in Zoology as well as his DPhil. It was in Oxford that there began his lifelong interest in the biology of tissue transplantation. From Oxford he moved to Birmingham to become Professor of Zoology and four years later, in 1951, he was appointed Jodrell Professor of Zoology at University College, London. He was accompanied by his post-doctoral Fellow, Rupert Billingham, and by myself as his postgraduate student, and here began his second marvellously creative period in the laboratory. In 1962 he moved on to become the distinguished and much admired and loved Director of the National Institute for Medical Research, a position he occupied until some years after his disastrous brain haemorrhage, which occurred in Exeter in 1969 at the annual meeting of the British Association for the Advancement of
Science, soon after he had given his Presidential address. He remained physically greatly handicapped although his intellectual recovery was quite remarkable – sufficient to enable him to supervise research carried out by colleagues and to write a number of popular books that earned him a devoted readership among the general public. His last book, which was autobiographical (Memoirs of a Thinking Radish), was published in 1986 after several further disabling strokes. He died in 1987.

Medawar's clear thinking and his genius for devising innovative experiments that usually came up with decisive answers gave the field of transplantation a huge impetus, and it came as no surprise when he was elected as the first President of the Transplantation Society. While he made his presence felt in many branches of the field – for example, he laid the foundations of modern reproductive immunology with a brilliant review in 1948 discussing the immunological relationship between mother and fetus – the studies for which he will be best remembered are two-fold.

First, he showed decisively that the rejection of skin allografts is an immunological event. In a paper published in 1943 with the Scottish plastic surgeon Thomas Gibson, they demonstrated that a set of second skin grafts from the same allodeme donor was rejected more quickly than the first set; they pointed out that this kind of secondary response was highly typical of an actively acquired immunity. Medawar proved this point by skin grafting experiments in rabbits. Grafts from genetically unrelated donors were invariably rejected within eight days and, following their destruction, further grafts from the same donor, but not from other donors, were again rejected more quickly. His histological examination of allografts at various times after transplantation revealed an infiltrate of mononuclear cells, mainly lymphocytes, but at that time his thoughts about the causes of rejection were still dominated by serum-borne antibodies directed against the foreign tissue. He later helped to found the cellular school of graft rejection, which attributed the role of villain to the body's small lymphocytes.

Although others before him had suspected that the immune system was involved in allograft rejection, especially of tumours, this was such an incisive demonstration that it could not be ignored. By sweeping away other less plausible notions, it suddenly made the study of allografts amenable to all manner of investigations, including the use of x-rays and drugs to suppress the immune system.

Medawar's second vital contribution was to provide experimental proof of the phenomenon of immunological tolerance. The American immunogeneticist RD Owen had demonstrated in 1945 that cattle dizygotic twins possessed not only their own red blood cells but also those of their twin partner. Owen was aware of a previous finding by an American embryologist that such twins almost invariably have a vascular placental anastomosis in utero, and Owen deduced that this had led to an exchange of red blood precursor cells that continued to produce erythrocytes of their own genetic lineage.

The doyen of immunological theorists, Macfarlane Burnet, seized on this finding several years later and built it into a theoretical framework that assumed the existence of immunological tolerance when he published his influential monograph, together with Frank Fenner, in 1949. According to them, foreign cells or organisms such as bacteria or viruses introduced into fetal mammals when their immune systems are still immature should prevent their hosts from ever developing the ability to recognise the foreignness of their antigens. In other words, they postulated the existence of the phenomenon of immunological tolerance.

Interestingly enough, Medawar, Billingham and their colleagues came to a similar conclusion when they realised that cattle dizygotic twins usually accept skin grafts transplanted from one to the other. It was Burnet and Fenner's monograph which, quite late in their investigations, drew their attention to Owen's prior work and they postulated that graft acceptance had been caused by the in utero establishment of cellular chimerism. Evidently the exchange of cells in utero had led to the induction of tolerance. At this point Medawar, together with Billingham and myself, set out to prove this experimentally and beyond doubt.

Our first paper was published in Nature in 1953, and in it we described the experimental induction of tolerance by the inoculation of adult allogenic cells directly into mouse fetuses. When such mice were given a skin graft later in life, when they could be expected to be immunologically fully mature, the grafts from the donor who had provided the inoculated cells were frequently not rejected. However, a
graft from an unrelated strain was rejected normally, showing that the tolerance that had been induced was highly specific to the cell donor. Even now, more than four decades later, tolerance is still a hot subject: its mechanisms remain under scrutiny, and attempts are being made to expedite the induction of tolerance in clinical transplant recipients by augmenting the organ graft with donor bone marrow cells. The hope is that by increasing the level of cellular chimerism, which TE Starzl’s team has uncovered in many liver and kidney recipients, the hypo-responsiveness or tolerance sometimes observed after the passage of time will come about more quickly and in a higher proportion of patients.

The experimental induction of tolerance was important for several reasons. First, it showed for the first time that the immunological barrier preventing the transplantation of normal allografts could be breached, even though the strategy depended on the use of immunologically immature animals. It raised the hope that one day this might be applicable, in some way, to adult animals and to humans, and this has proved to be the case. Second, it encouraged a great upsurge of interest in transplantation, both in the laboratory and the clinic, and it gave some encouragement to the new wave of surgeons anxious to try their luck with kidney transplantation, this time with the help of some form of immunosuppression. Third, it helped to explain why autoimmunity is a relatively rare event, for exposure of the developing immune system of any one individual to the body’s own tissue molecules would be expected to lead to tolerance and thus to the prevention of autoimmune responses later in life.

Peter Medawar was not only the leader of his team, comprising Billingham and myself and others, but the leader in the rapidly developing field of transplantation in the 1950s and 1960s. He received many honours, and the Nobel Prize, shared with Macfarlane Burnet in 1960, was unquestionably his greatest accolade. He was not only a great experimental scientist and theoretician but also a brilliant lecturer, a felicitous and elegant writer and a witty conversationalist. Many will remember him for the fortitude and good humour which characterised the last fifteen years of his life.

JW Dempster

The contributions of Jim Dempster (Fig 2) in the 1950s tend to be overlooked because he faded from the transplantation scene prematurely; he now lives in retirement in Hampshire. He was a surgeon at the Hammersmith Hospital and he deserves recognition for his early experimental observations on the fate of canine kidney allografts, which he subjected to critical scrutiny both macro- and microscopically. Dempster’s conclusions based on kidney rejection supported those of Medawar with skin: that rejection was essentially an immune phenomenon and, like Medawar before him, he invoked serum antibodies as the mediators of rejection. He published several reviews on kidney transplantation in the early 1950s and these helped to encourage others to enter the fray, even though he himself regarded the transplantation of human kidneys as premature at that time. Later, he took part in the kidney transplantation programme initiated by R Shackman and others at the Hammersmith Hospital.

Dempster’s name is associated with two other issues, one practical and the other theoretical. He and his colleagues were the first to show that not only delayed-type hypersensitivity reactions – exemplified by the tuberculin reaction – but also the response to skin allografts could be suppressed in animals by whole body x-irradiation. This was an important finding because whole body irradiation was used in the early clinical attempts to transplant human allogeneic kidneys. The theoretical issue was this. When examining the histology of kidneys undergoing rejection Dempster noted that there was not infrequently a perivascular accumulation of round cells – small lymphocytes – and he interpreted this as a possible reaction of cells within the graft against the host. A similar observation and interpretation was made at roughly the same time by a Dane, Morten Simonsen, who, like Dempster, was pioneering kidney transplantation in dogs. Thus both anticipated the concept of graft-versus-host responses. However, their observations were undoubtedly misinterpreted because it was subsequently shown by others that the cells they had identified had come from the graft recipient and were an indication of a reaction by the recipient against the graft. At that time the role of lymphocytes in graft rejection was not understood. Nonetheless, Dempster
and Simonsen had recognised that graft-versus-host reactivity might occur in certain circumstances.

**Peter Alfred Gorer**

In the 1930s, Peter Gorer (Fig 3) published his first papers on what seemed to be a somewhat obscure red cell antigen in inbred strains of laboratory mice\(^{12,13}\). He recognised this antigen with the help of crude antisera and called it antigen II. It was a weak immunogen and Gorer and his colleagues had to devise a special technique that enabled them to detect the agglutination of mouse erythrocytes carrying the antigen. Antigen II seemed to be associated with rejection of sarcomas. Meanwhile the American geneticist, George Snell, working at Bar Harbor, had become interested in the genes and antigens responsible for the rejection of tumours and he produced a series of highly inbred strains of mice within which tumours could be transplanted without inciting immune responses. Gorer and Snell became aware of each other's interests, recognised that they were complementary and arranged for Gorer to spend a sabbatical year in Bar Harbor. This collaboration resulted in a seminal publication in 1948 in the *Proceedings of the Royal Society*\(^4\), in which they and S Lyman showed, among other important observations, that Gorer's gene coding for a red cell antigen was identical with Snell's tumour resistance gene. It was given the label H and subsequently it became known as H-2. This was the beginning of our understanding of histocompatibility antigens - the antigens that trigger alloresponses. Snell died in June 1996 at the age of 93.

The H-2 gene proved to be highly complex, comprising a large number of alleles which were later found to be grouped in a series of subloci. H-2 antigens were soon found to be responsible for the acute rejection not only of tumours but also of skin and other types of allografts. In the late 1950s the human counterpart, HLA, was discovered by the Frenchman Jean Dausset and by others, and it became clear that its organisation was every bit as complex as that of H-2 and astonishingly similar. As each gene was shown to express one HLA molecule and the array of genes was large, the diversity of histocompatibility antigens in man, as in the mouse, proved to be staggeringly high. The need for tissue typing in organ transplantation for the major histocompatibility complex (MHC) antigens therefore became apparent, though for organs such as the liver and kidney the tissue typing effect is no longer as great as it used to be thanks to the advent of modern immunosuppressive drugs. However, in bone marrow transplantation tissue typing remains an absolute requirement.

Eventually the precise chemical and molecular structure of H-2 and HLA antigens was uncovered. It was clear from the outset that MHC systems had not evolved in order to frustrate the ambitions of 20th century transplant surgeons, and in 1974 a vital discovery by Rolf Zinkernagel and Peter Doherty\(^{15,16}\) provided a powerful raison d'être for them. They found that, in the mouse, viral antigens could be recognised by the immune system only when associated with a particular mouse H-2 antigen, giving rise to the notion that the primary role of the histocompatibility molecules is to present peptides derived from viral and other antigens to T lymphocytes. (Zinkernagel and Doherty were recently awarded the Nobel Prize for their important discovery.) Much later, in the 1980s, it was shown how peptides bound by MHC molecules are presented to the T cell receptor. One of the triumphs of molecular immunology was the visualisation, in the late 1980s, of the variable peptide-holding groove of MHC molecules. Using crystallisation and x-ray diffraction techniques of a human MHC molecule, the Wiley-Strominger group, with Pamela Björkman, was able to construct a three-dimensional picture of the groove and to identify the electron-dense material within it as a peptide\(^17\). These and numerous other investigations convincingly explained precisely how the MHC molecules allow cells of the immune system to communicate with each other and to trigger immune responses.

My account gives a mere glimpse of what profound and wholly unexpected consequences flowed from Peter Gorer’s early observation. There is no doubt that he would have shared the Nobel Prize with Snell and Benacerraf in 1980 had he lived longer. Alas, being a heavy cigarette smoker he died of cancer of the lung in 1961 at the age of 54. He was elected to Fellowship of the Royal Society and was appointed to a Professorship - sadly, only shortly before he died at the height of his powers. Peter Gorer was, without doubt, a highly original thinker who was much admired and loved by his students and collaborators.
Rupert Everett Billingham

Rupert Billingham (Fig 4) collaborated with Medawar in the skin-grafting study in cattle dizygotic twins and he was intimately involved in the experimental tolerance work at University College, London. He was a superb experimentalist and highly inventive in devising techniques that enabled him to get to the core of any problem. For example, together with myself, he devised the technique of intravenous inoculation of cells into newborn mice, a development that not only made the analysis of the phenomenon of tolerance far less laborious but also paved the way for the recognition of graft-versus-host disease. His interest in immunologically privileged sites led him to construct an alnymphatic but vascular skin pedicle in guinea pigs, on to which he placed skin allografts in order to ascertain the role of lymphatic drainage on graft rejection. By making many interesting observations on the immunological interactions between mother and fetus and neonate, he became the father of reproductive immunology. It was no accident that he became the first president of the international society devoted to the immunology of pregnancy.

However, one of his most telling contributions was the discovery of tolerance and the recognition that a graft comprising immunologically active cells can react, often with disastrous consequences, if it is transplanted to a host unable to reject it for genetic or other reasons. Medawar, Billingham and I had been puzzled about the high fetal mortality that ensued when allogeneic cells such as spleen cells were injected directly into fetuses, and for several years we attributed this mortality to technical factors. It was only when Billingham and I had begun to use the intravenous route in newborn mice as a means of exposing immature mice to foreign antigens that it began to dawn on us that the delayed deaths – two to three weeks after inoculation – were brought about by an immunological reaction of cells in the inoculum against the antigens of the recipient. Our first paper on this was published in 1957, and in the same year Morten Simonsen in Copenhagen came to a somewhat similar conclusion when working on chick embryos. We drew attention to the fact that human bone marrow contains immunologically competent cells – lymphocytes – and warned that attempts to transplant human bone marrow into patients that were either genetically or experimentally rendered immunoincompetent would be highly dangerous. This warning was well justified, for graft-versus-host disease remains the biggest problem in bone marrow transplantation to this day.

Billingham went to the United States in 1957 and has worked and lived there ever since. He worked for some years at the Wistar Institute in Philadelphia, became Professor and Chairman of the Department of Medical Genetics at the University there, and in 1971 was appointed Professor and Chairman of the Department of Cell Biology and Anatomy at the University of Texas. There he remained until his retirement in 1986 and he now lives with his wife on Martha’s Vineyard. Like Medawar his first degree was in Zoology and he was one of the early Presidents of the Transplantation Society. His many honours include election to Fellowship of the Royal Society in 1961 and the Medawar Prize in 1994.

Michael Francis Addison Woodruff

Michael Woodruff (Fig 5) was a distinguished transplant surgeon who also made a name for himself as a transplantation immunologist. His parents were British but he was born and educated in Australia. An extraordinarily formative, though painful, experience during the last war was his capture by the Japanese and his internment in a prisoner of war camp in Singapore. He had managed to save a copy of RH Maingot’s Postgraduate Surgery and was astonished to read that human skin grafts initially healed but were then destroyed. He resolved there and then to study this problem after the war, which is precisely what he did.

Woodruff became an early pioneer in human renal transplantation and he performed the first transplant, from an identical twin, in Britain – having become Professor of Surgery and Director of the Nuffield Transplantation Surgery Unit in Edinburgh. In 1960 he published a massive tome on the Transplantation of Tissues and Organs, which still makes interesting reading. He made his greatest impact in 1963 when, together with NF Anderson, he revived interest in antilymphocytic serum (ALS) by showing that, administered to rats, it could substantially prolong the survival of skin allografts. Because the range of immunosuppressive drugs was at that time very limited, Woodruff’s observations released the floodgates for further research and for clinical application. Anti-
lymphocyte globulin (ALG) – the purified globulin moiety of ALS – was for many years effectively used in renal transplantation both as a prophylactic agent and for the resolution of rejection crises. It has been largely displaced by monoclonal antibodies but some centres continue to use it when drugs fail to resolve a rejection crisis.

Woodruff became yet another British President of the Transplantation Society, received a knighthood and was elected to Fellowship of the Royal Society. He had the reputation of being combative in discussions at meetings and for asking searching questions such as: ‘is there such a thing as a tolerant cell?’ (as opposed to a tolerant animal). He later turned his attention to tumour immunology. Woodruff is a keen and expert sailor and now lives in retirement with his wife in Edinburgh.

Nicholas Avrion Mitchison

Avrion Mitchison (Fig 6) was, until his retirement from the Jodrell Chair of Zoology at University College, London (UCL), one of Britain’s foremost basic immunologists. His tutor at New College, Oxford had been Peter Medawar and he was much influenced by him. His DPhil thesis was in part devoted to the transfer of living lymphocytes to other mice of the same inbred strain. When the cell donors had been sensitised to foreign histocompatibility antigens, this sensitivity was transferred to the cell recipients so that they now rejected tumour grafts in accelerated fashion even though they had never encountered the antigens of the tumours. This adoptive transfer of immunity, as Medawar’s group came to call it when they had shown that the same was true for skin allografts, had an extraordinary impact on the development of transplantation research and it is still being used as a test for the immunological competence of living cells.

When working at the National Institute of Medical Research, before going to UCL to follow in Medawar’s footsteps, Mitchison carried out some singularly important studies in mice which showed, with the aid of pure, soluble protein antigens, that tolerance could be induced at both high and low doses. He was also responsible for basic studies on the cooperation between the T and B lymphocyte subpopulations; and for the discovery that T lymphocytes can ‘speak’ to each other by secreting lymphokines.

Mitchison retired from his Chair at UCL to become Director of a newly formed Rheumatology Institute in Berlin. He influenced numerous students, many of whom have had distinguished careers. He is – like his uncle JBS Haldane – something of an eccentric; at international meetings he appeared to slumber through many a talk, only to ask the speaker the most searching questions at the end of the paper. He, too, has received many honours and was elected to Fellowship of the Royal Society in 1967. He now divides his time between Islington, where he lives with his wife, and Washington DC.

James Learmont Gowans

James Gowans (Fig 7) came into immunology from physiology. He too obtained his first degree at Oxford, where he went on to study for his DPhil at the Sir William Dunn School of Pathology. There he was strongly influenced by Howard (later Lord) Florey, who suggested to him that it might be profitable to study the biology of lymphocytes. These cells were known to appear in all manner of inflammatory reactions, from cutaneous delayed-type hypersensitivity
such as the tuberculin reaction and certain bacterial
diseases such as tuberculosis, to allografts undergoing
rejection. Virtually nothing was known of their role
and, because they were thought to be unprepossessing-
looking short-lived cells, they were considered to be of
no great importance. Gowans wasted no time in show-
ing, through a series of incisive and elegant experi-
ments, that small lymphocytes were anything but end
cells, that they can recirculate from the blood into the
tissues, from there into the lymph nodes and eventu-
ally to the thoracic duct lymph and thus back to the
blood\textsuperscript{21,22}. Gowans and his colleages showed precisely
how this comes about. Later, encouraged by Medawar,
they showed that pure populations of small lympho-
ceyes could destroy skin allografts and incite graft-
versus-host reactions by transforming into large blast
cells, which in turn divide to form more small
lymphocytes of the same specificity.

These observations were central to the development
of our modern understanding of the immune system
and, together with Jacques Miller's finding of the role
of the thymus gland as the 'finishing school' for T
lymphocytes, form the basis of modern cellular
immunology. Indeed, one may well wonder why the
Nobel Prize Committee has not seen fit to give full
recognition to the combined contribution of these two
immunologists. It was therefore especially appropriate
that Gowans and Miller should have been selected in
1990 to be the first recipients of the Transplantation
Society's Peter Medawar Prize and Medal.

Having made his seminal observations, Gowans left
experimental immunology in 1977 to become Secretary of the Medical Research Council, a post that
he held for a decade. More recently he has acted as
Secretary-General of the Human Frontier Science Pro-
gramme based in Strasbourg. He was elected to Fellow-
ship of the Royal Society and, like Medawar, Woodruff
and Calne, has been honoured by a knighthood. He
lives with his wife in Oxford.

Roy Yorke Calne

My final pioneer is Britain's outstanding transplant
surgeon, Roy Calne (Fig 8). He has spent most of his
professional life in Cambridge, though his interest in
transplantation predated his arrival there. Through
KA Porter at St Mary's Hospital Medical School,
London, he became interested in the late 1950s in a
new drug with immunosuppressive properties,
6-mercaptopurine, and in 1960 he published a paper
in the \textit{Lancet}\textsuperscript{23} in which he described the prolongation
of survival that could be achieved for canine kidney
allografts with this drug. During a postdoctoral year at
the Peter Bent Brigham Hospital in Boston, where he
worked with, among others, John Merrill and Joe
Murray, he continued with this work in dogs and took
part in the first application of the drug's analogue,
azathioprine, to human cadaveric kidney transplanta-

As Professor of Surgery in Cambridge he has
made numerous other contributions, among them the
demonstration, with Richard Binns, that pigs can be
made tolerant to kidney allografts by the inoculation
of the kidney donor's cells \textit{in utero}.

Calne's other signal contribution to clinical trans-
plantation was the introduction into renal transplanta-
tion of yet another drug with immunosuppressive
properties, cyclosporin. This had been discovered in
Switzerland and, after some trials in rabbits carried out
by a young Greek surgeon, AJ Kostakis, and by DJG
White in Calne's department of surgery, he again had
the courage and audacity to try it in clinical renal
transplantation\textsuperscript{24,25}. Despite some early fears of toxic
side effects it proved to be a success and the azathiop-
rine era was superseded by the cyclosporin era. Thus,
Calne has been instrumental in introducing into the clinic two of the three most powerful immunosuppressive drugs known.

Calne was elected to Fellowship of the Royal Society, was knighted, and was awarded the prestigious Medawar Prize. In recent years he has developed his talent as a portrait painter and has painted many of those who have been active in the field, as well as patients and nursing staff. His book on Art, Surgery and Transplantation was published recently, and includes a large number of his portraits. He is due to retire from his Chair in 1997 and lives with his wife in Cambridge.

Conclusion

More information about the work of these eight British pioneers and the historical context in which their discoveries were made may be found in my recently published A History of Transplantation Immunology. By focusing on them in this lecture I trust I have not given the impression that there were not many others, both before and after them, who made vitally important discoveries that have helped to make tissue and organ transplantation such an immensely successful therapy. Nonetheless, there can be no doubt that the contribution of these and many other British workers has been of the greatest value and significance.

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