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Special Feature

Reminiscences of Sir Peter Medawar: In Hope of Antigen-Specific Transplantation Tolerance

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Peter Medawar's career in medical research (he always described himself as a medical research scientist) began as a student of zoology in Oxford. He obtained a first class degree in 1936, aged 21, and undertook postgraduate studies with Florey. His work was anchored in a broad field; he was adept at addressing novel questions in the context of prior ideas and knowledge. His earlier interest in growth, driven as much by mathematics as biology, gave way to transplantation at the beginning of World War II, treatment of burns patients being the driver. He interpreted the results of grafting autologous and allogeneic human skin, observed clinically and microscopically, as immunological; he identified accelerated donor-specific reactions to subsequent grafts as 'second set', and described cell (lymphocyte) mediated infiltration of allo- but not auto-grafts following initial vascularization, both in the patient context and in experimental animals. He became intrigued by the consequences of hematopoietic chimerism, from which his landmark discoveries on the induction of transplantation tolerance derive. These results, his interpretation and dissemination of them, gave hope to transplant surgeons that donor-specific transplant tolerance would be achievable. Many immunosuppressive drugs later, we are now reapproaching this hope, from various angles.

Key words: biography, tolerance, transplantation, chimeras, skin, Nobel prize

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Introduction

Peter Medawar died on 2 October 1987, a week before the publication of Bjorkman's illuminating paper in *Nature* on the crystal structure of an HLA class I molecule (1). He would have enjoyed those pictures. He was a scientist who took enormous pleasure in discoveries that brought previous observations into a new conceptual framework, whether they were his own or those of others. He would have been fascinated at this illuminating view of MHC restriction: although Zinkernagel and Doherty's 1974 description of this centrally important phenomenon (2), and the identification by Townsend and his colleagues of short viral peptides as the cognate targets (3) came many years after Peter Medawar's pioneering work on tolerance, both were in turn built on his earlier discoveries of the link between transplantation and the immune system (4–6). He described the work he carried out as 'transplantation biology': it brought together surgery and immunology, and gave 'hope of progress' to the clinical application of tissue and organ transplantation.

Personal Reminiscence: The National Institute for Medical Research, Mill Hill, London and the Clinical Research Centre, Harrow

My knowledge of Peter Medawar is from 1968 to 1987. As Institute Director he recruited me to the National Institute for Medical Research (NIMR) in Mill Hill, and I joined the team investigating the effects of long-term administration of antilymphocyte serum. This was a golden time at NIMR, with immunologists, cell biologists, biochemists, parasitologists and microbiologists ebbing and flowing into each other's labs, and meeting over coffee, lunch and at the bar at the end of the day, planning experiments, discussing results, challenging ideas and interpretations. In addition to the scientists Medawar had brought or recruited to the Institute, many were attracted to spend their sabbaticals there, as well as young scientists on post-doctoral fellowships, from the United States, Australia and Europe; there were also many visiting scientists passing through, giving seminars and joining in the life of the Institute. Lively debates centered around questions of 'germ line versus mutation' for generation of immunoglobulin diversity, the separation of lymphocytes into T and B compartments and how they 'helped' each other (7), of the subsets of T cells (8) and the nature of their antigen-specific receptors, how effector cells were developed during an immune response, and how they might be controlled (9).

Peter Medawar led some of these debates, contributed to others, but was always there, in the background, encouraging and supporting us all, incorporating each one into various social activities—games of cricket, swimming

during the summer holidays at the outdoor pool of a nearby school, parties at his house in Hampstead, trips to the opera. He spent 2 days during the week, and Saturday morning, at the bench, which for him more often than not was skin grafting of mice, reading the grafts and guiding his small team of technician, Ph.D. students and visiting surgeons. The administration of the institute, his visits outside it to various meetings, committees and advisory groups, in the United Kingdom and abroad, were done in the interstices of his lab-centered time. He also found time to write books (10) and make radio broadcasts, and was one of the most effective communicators of science to the public. He was helped by the support of his colleagues, members of his own lab and the administrative staff of the institute, and of course his family.

Toward the end of 1969 Peter Medawar suffered a severe stroke, whilst giving the Presidential address to the British Academy in Exeter Cathedral. Whilst he made a remarkable recovery, it left him hemiplegic and with no left visual field. He learned to walk again, and to compensate for his visual impairment, but he did not regain effective use of his left arm. The support of his colleagues, his secretary and his family, particularly his wife Jean, allowed him to return to work, but he resigned as Director of NIMR in 1971, and moved his lab to the newly formed MRC Clinical Research Centre (CRC) in Harrow, within the Division of Surgical Sciences to which his former student Eugene Lance had been appointed as head. Here Medawar, with typical bravery and lack of complaint, continued to write books (11) and returned to an area of research related to some of his previous work in Oxford, embryology, but this time to explore its link with the anaplastic growth of tumors. He found experimental evidence for the re-expression on tumors of 'embryonic antigens', and argued that immune responses to these might account for the epidemiological findings that pregnancy lowered the risk of breast cancer (12). He became interested in immunopotentiation in relation to cancer, and in the late 1970s organized a discussion meeting at the Villa Serbelloni in Italy to which Thierry Boon contributed, setting out his novel approach for the identification of tumor antigens recognized as MHC-restricted peptides, as a prelude to attempting immunotherapy (13). In 1973 Peter Medawar had encouraged me, by then an independent scientist within his Transplantation Biology group, in my plans to initiate *in vitro* work on the immune responses of T cells to the male-specific transplantation antigen, HY. This could be regarded as a surrogate tumor antigen, hence the interest in Thierry Boon's work. Peter took great pleasure in following the progress of my HY work through MHC restriction, immune response genes and chromosome mapping studies, combining *in vitro* with *in vivo* approaches, of which skin grafting, learnt from him, was the most probing. Sadly, he did not live to see our molecular identification of HY genes and peptide epitopes to which the T cell work led us (14), and which has provided a novel route into the use of HY peptides to induce donor-specific transplantation tolerance (15).

Transplantation and Immunology, Actively Acquired Tolerance: Oxford, Birmingham and University College, London

Peter Medawar's extraordinary influence on clinical transplantation, however, stems from the work he did before he became the famed Director of NIMR. Research under the auspices of the War Wounds Committee of the MRC was commissioned to determine if treatment of burns (war injuries common in pilots) with skin grafts could be improved. Medawar did this in collaboration with Thomas Gibson, a Glasgow surgeon (4): the treatment of a badly burned epileptic patient was carried out using a combination of 'pinch' grafts taken from the patient herself (autografts), and those from another unrelated individual (allografts in current parlance). In addition, a second set of grafts was later transplanted from the same donor. The grafts were observed visually and, following appropriate biopsies, histologically. Surprisingly, this was the first systematic study of the process of rejection; using his background from studying morphology at Oxford, Medawar examined the histological sections as well as observing the grafts macroscopically. The results showed that rejection of the first set of allografts was preceded by a latent period, with healing-in and vascularization indistinguishable from the autografts. However, rejection of the second set of allografts from the same donor took place much more rapidly, a hallmark of an immune response.

These results established that the underlying basis of skin allograft rejection could be regarded as immunological rather than due to surgical problems or vague physiological incompatibilities (4). He took this investigation further in experiments performed on outbred rabbits, confirming the specificity of second set rejection of grafts from the same donor as the first, and determining that graft rejection was preceded by an intense infiltration of lymphocytes, suggesting it was a 'cell-mediated' response (5,6). He also established that leucocytes could be used to immunize rabbits for second set graft rejection, implying antigens shared by skin and blood cells (16). However, further exploration of this notion required a move to inbred mice, for whom the genetics of transplantation antigens as measured by rejection of allogeneic tumors, and by anti-H2 antibodies, were becoming clearer from the work of George Snell and Peter Gorer at the Jackson Laboratory. However, that move was also propelled by the results of an experiment in which skin grafts were exchanged between twin calves, in the expectation of distinguishing dizygotic from monozygotic twins. This produced the unexpected result that each pair, whether of the same sex or not, failed to reject the co-twin's graft. In view of the report by Owen (17) that twin calves had mixed blood circulation via the shared placenta in utero, and Burnet's citation of this (18), proposing that such animals would be tolerant of each other's blood antigens, Medawar and his colleagues interpreted their skin graft results with cattle twins as providing evidence that chimerism in the hematopoietic compartment induced

tolerance also to skin grafts, implying the sharing of transplantation antigens between these two tissues (19).

In 1947, Peter Medawar had been appointed Mason professor of zoology in Birmingham, where he continued his transplantation studies, with Rupert Billingham and Leslie Brent. He was elected to the Royal Society in 1949. Following his appointment as Jodrell professor of zoology and comparative anatomy at University College, London in 1951, he embarked, again with Billingham and Brent, on the critical work in inbred mice, to test whether experimentally induced chimerism would also result in tolerance to skin grafts from the donor strain. They first established the normal median survival time of A strain skin on CBA mice (11 ± 0.3 days). Then, via a laparotomy they injected a litter of CBA mice in utero with tissues from A strain mice. The five young recipient mice were grafted when they reached 8 weeks of age with A strain skin, while three of them accepted for more than 2 months. One mouse rejected the graft chronically between days 75 and 91; the other two were tested for susceptibility to rejection by transfer of lymphoid tissue from CBA donors immunized with A strain tissue. This adoptive transfer of immune cells caused rapid rejection of the previously tolerated grafts, showing that recipients made chimeric in utero had 'actively acquired' their tolerant state, rather than the grafts themselves having adapted, becoming resistant to rejection. This experiment was reported in detail in the original *Nature* paper (20), together with others to establish the specificity of tolerance with third-party grafts, which were rejected, and testing tolerance in mice injected with A strain tissue after birth, rather than in utero, resulting in a smaller percentage retaining test skin grafts. They also include in this paper results with White Leghorn chick embryos made chimeric by injection of allogeneic blood from a Rhode Island Red chicken into the chorioallantoic vein. The resultant birds as young adults accepted skin grafts from the donor, identified by growth of pigmented feathers.

Medawar's key paper (20) fully supported Burnet and Fenner's idea of adaptation of 'recognition of self' in the developing immune system. It was followed in 1956 by a monograph (21) exploring the parameters of both tolerance and immunity to allogeneic transplants, and showing they were 'cell mediated' rather than humoral. The mechanism of tolerance was at the time assumed to be clonal deletion, but later Medawar (9) raised the possibility of the potential effectors being present but 'inactive' in tolerant mice—prescient in view of current hypotheses about anergy and regulation. The 1956 monograph (21) is most beautifully written, in Medawar's characteristic, lucid, witty style, and is profusely illustrated with beautiful photographs of mice, chickens and a duck. These results profoundly affected the perception of those caring for patients in end-stage organ failure, e.g. kidney, since they raised the possibility of transplantation of allogeneic kidneys under a regime that protected them from immune attack, in the knowledge that actively acquired tolerance was a possible outcome. These results also contributed greatly to basic immunological knowledge, and allowed further development of the field of cellular immunology, which is, as Leslie Brent points out in his 'History of Transplantation Immunology' (22), essentially based on transplantation studies.

The Nobel Prize, Directorship of NIMR and Civil Honors

Peter Medawar was awarded the Nobel Prize, jointly with Burnet, in 1960, for his work on transplantation tolerance. In 1962 he became Director of the NIMR, where his experimental work became focused on how to induce donor-specific transplantation tolerance in adults. He continued to use his mouse models, with skin grafting as the readout. He explored the use of a biological reagent, antilymphocyte serum (ALS), prepared from rabbits injected with mouse thymocytes. Mice treated with ALS around the time of grafting retained their skin grafts for longer than the controls, and under some circumstances, for example if made chimeric by injection of donor-strain spleen cells, or given low doses of irradiation, could be made tolerant (9). This approach foreshadows more recent work by Waldmann and his colleagues using monoclonal antibodies to defined molecules, such as CD4 and CD8, expressed on T lymphocytes, to 'reset' the adult immune system, making it susceptible to tolerance induction (23), as well as that using monoclonal antibodies to induce co-receptor blockade (24).

The recognition of Peter Medawar as a scientist of great originality and distinction was also marked by the award of civil honors: a C.B.E. in 1958, a Knighthood in 1965, a C.H. in 1972 and an O.M. in 1981. He enjoyed these, but perhaps even more the knowledge that he had contributed crucial knowledge for rational progress in the practice of transplantation in clinical medicine. He was a brilliant communicator, able to discuss results and ideas in a way which made them accessible to whatever audience he was addressing, including gatherings of the International Transplantation Society, of which he was President in 1966, learned scholars of both science and philosophy (he was an admirer and friend of the philosopher Karl Popper), as well as radio audiences—he gave the Reith lectures in 1959, entitled 'The Future of Man'. His outlook was always one of hope and optimism, of the ability of rational, scientific thought to solve problems, including those caused by science.

It is perhaps disappointing that donor-specific tolerance has to date been so difficult to achieve in the clinical transplantation setting, as it could avoid many of the toxic and non-specific effects of chemical immunosuppressive agents. However, the potential of biological reagents such as selected monoclonal antibodies and peptide antigens, perhaps used initially in tandem with non-toxic doses of

irradiation or drugs, currently holds out great hope, of which Medawar would certainly approve.

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One important source of reference in preparing this article is the Biographical Memoirs of Fellows of the Royal Society (25) written about Peter Medawar by another friend and colleague, Avrion Mitchison, whom I thank. His article is a good source too for those also interested in the various topics other than transplantation biology, on which Peter Medawar worked during his career. I would also like to thank my eagle-eyed secretary, Vivien Tikerpäe, for her proof reading of my text.

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