ELSEVIER

The Discovery of Immunologic Tolerance

Leslie Brent

ABSTRACT: The phenomenon of tolerance can be said to have begun with the seminal observations in 1945 by R. D. Owen that cattle dizygotic twins display red cell chimerism—mosaicism as he called it—in adult life. Owen interpreted this extraordinary finding in terms of the much earlier discovery by F. R. Lillie that the placentae of cattle dizygotic twins undergo anastomosis early in fetal life, and he speculated that this would have permitted blood cells *and their precursors* to move from one twin to the other. Owen's discovery came out of the blue and it was ignored by immunologists until F. M. Burnet and F. Fenner highlighted it four years later in their influential monograph *The Production of Antibodies,* in which they predicted the existence of tolerance as a general phenomenon and developed their notion of "self-markers" to explain why the body does not react against self. Though it was Medawar's group that showed conclusively in 1953 that tolerance can be experimentally induced in fetal mice and in chick embryos, their entry into this field came from a totally different direction, an attempt to distinguish between mono- and dizygotic cattle twins by the exchange of skin grafts. This led to the seemingly paradoxic result that grafts exchanged between dizygotic twins were *accepted* (1951) and it was not until their cattle experiments had been virtually completed that they became aware of Owen's earlier discovery. Following the work of Billingham, Brent, and Medawar, and of Hašek, tolerance became incorporated into general immunologic theory and it helped to explain the fact that mammals do not normally suffer from injurious autoimmune manifestations. Ray Owen's discovery therefore has a secure place in the history of immunology. *Human Immunology 52, 75–81 (1997).*

RAY DAVID OWEN: THE MAN

Ray was born on a dairy farm in Wisconsin in 1915 and remembers that "a farm was a great place to grow up." He attended Genesee State Grade School—all of two teachers coping with eight grades—and later commuted to Waukesha High School. Before and after school hours he was expected to do his bit on the farm. This was followed by Carroll College, a liberal arts college in Waukesha, where he majored in biology. In 1937 he entered graduate school at the University of Wisconsin and completed his Ph.D. in genetics in 1941. Now began his studies on the inheritance of blood groups in cattle, work that was to lead to his most important discovery and which was to shape his future career in genetics and immunology. Following a year as Gosney Research Fellow at the California Institute of Technology he became Associate Professor of Biology at that august institution in 1947, where he has remained ever since.

During the 1960s he served as Chairman of the Division of Biology and later he became Dean of Students and Vice President of Student Affairs, as well as Professor of Biology. His chairmanship of a Caltech committee on the freshman year led to major changes, including the admission of women students. Ray has therefore served Caltech in several capacities and always with total commitment and great distinction. He has published numerous papers, of which his 1945 *Science* paper was by far the most important and influential, but arguably an equally important contribution to the field of immunogenetics has been through his influence on a long line of unusually able research students and post-docs, an association that he enjoyed and valued and that also inspired those who worked with him.

Ray has been a longstanding member of the National Academy of Sciences, the American Philosophical Society, the American Academy of Arts and Sciences, and many other bodies. He was President of the Genetics Society of America, a member of the Board of Directors of the American Society of Human Genetics, and a member of the Editorial Board of the *Annual Review of Genetics.* His many other national responsibilities included Chairmanship of the Genetics Study Section of the National Institutes of Health, the Genetics Training Committee of the National Institute of General Medical Sciences, and the Advisory Council of the National Institute

From the Transplant Unit, St. Mary's Hospital, London, United Kingdom.

Present address: Prof. Leslie Brent, 30 Hugo Road, London N19 5EU, United Kingdom.

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of Allergy and Infectious Diseases; and he was the "Scientist-Member" of the small President's Cancer Panel that advised Presidents Nixon and Ford. These duties were onerous both in terms of responsibility and time and, together with the never-ending stream of scientific papers and grant applications that came his way for reviewing, they eroded the time he had for active research.

Among many honors bestowed on Ray Owen are several honorary degrees, the 1966 Gregor Mendel Medal by the Czechoslovakia Academy of Sciences, an honorary Fellowship of the American Academy of Allergy and Immunology, and an Award for Teaching Excellence from the Associated Students of Caltech. This last was by no means the least valued by Ray, for his interactions with students and the special relationship he forged with them gave him a great deal of satisfaction throughout his life as a teacher.

Finally, the one constant factor in Ray's life has been his long and happy marriage to June, with whom he now lives in semiretirement in Pasadena. Indeed, it is impossible for his friends to think of Ray without also thinking of his life's companion who has given him her unfailing and rock-solid support. They had two sons, David and Griffie; the latter tragically died in a road accident as a teenager.

THE DISCOVERY OF IMMUNOLOGICAL TOLERANCE

The Beginnings

Although J. B. Murphy [1] showed as early as 1914 that foreign tissues grow on the chorioallantoic membrane of the chick embryo because of immunoincompetence, a state that he succeeded in reversing by the concomitant transplantation of adult spleen cells, and although embryologists interested in tissue differentiation had long taken for granted that chick embryo limb buds could be successfully transplanted to other embryos (see [2]), the beginning of the tolerance story is firmly linked to the year 1945. It was in that year that R. D. Owen [3] published his carefully observed and correctly interpreted findings that cattle dizygotic twins possess, in adult life, red blood cells that are genetically their own but also other red cells that could only have come from their twin partner. No quantitative data were given, but because as many as 40 cattle blood group antigens had by then been identified the occurrence of identical specificities in twins that were definitely not monozygotic led Owen to speculate that "some mechanism is operating to produce frequent phenotypic identity of blood types in genetically dissimilar twins. The vascular anastomosis between bovine twins, known to be a common occurrence, provides an explanation." Owen went on to quote F. R. Lillie's [4] anatomical findings of placental anastomosis in cattle twins some three decades earlier.

Ray Owen drew the following conclusions. First, ". . . the critical interchange is of embryonal cells ancestral to the erythrocytes of the adult animal. These cells are apparently capable of becoming established in the hematopoietic tissues of their co-twin hosts and continuing to provide a source of blood cells distinct from those of the host, presumably throughout life." And second, "Several interesting problems in the fields of genetics, immunology and development are suggested by these observations. Most of them are still largely speculative and will not be considered here. An application that may be mentioned is the tool now provided by the blood tests for selecting, with a high degree of reliability, those heifers, born twin with bulls, that are potentially not freemartins. . . ." Freemartins, it should be added, are the sterile female twins of male partners, sterile because of exposure to male hormones early in embryonic development thanks to the placental anastomosis. Thus, the son of a farmer, working in a State with reputedly more cows than people, had solved a problem of considerable agricultural importance: at last freemartins could be identified at an early stage, enabling the farmer to exclude them from his dairy and breeding herds.

Together with H. P. Davis and R. F. Morgan, who were both Professors of Dairy Husbandry at the University of Nebraska, Owen [5] published a follow-up paper a year later in which they described how a red Shorthorn cow called Old Glory "was turned out to pasture" on a Nebraskan farm and how it gave birth to a succession of five calves, which were given the names of the countries at that time represented on the Security Council—United States, England, Russia, China and France. Anatomical examination suggested that the quintuplets had originated from at least four fertilized eggs. Owen used a battery of antisera recognizing 40 inherited red cell antigens and found those of the calves to be identical, with the dam and sire being similar to each other and different from the calves by only two antigens. The authors stated that "The homogeneity of these quintuplets . . . indicates a very thorough intermixture of at least two different cell-types among the quintuplets as embryos . . ." and they concluded that all five calves must have had a common fetal circulation, bringing about the free circulation of red cell precursors and the establishment of these cells in the hemopoietic tissues of each calf. The data therefore not only confirmed Owen's original findings but they did so dramatically.

Enter Burnet and Fenner, and Medawar's Group

Although Owen published his original observations in *Science*, a journal with a wide and international circulation, its significance remained unnoticed for several years until F. M. Burnet and F. Fenner [6] published their monograph in 1949. The importance of this book and the wide-ranging speculations made in it have, to my

mind, been inappropriately belittled in M. Cohn's [7] recent "personalized account of some of the important conceptual contributions to immunology." Be that as it may, Burnet and Fenner, in developing their "self marker" hypothesis to explain the absence of autoimmunity in mammals and birds, highlighted Owen's discovery as to "what is at present a unique natural example" of what they had in mind. They wrote: "A very interesting field for direct experimentation is opened up by this finding, particularly if the same type of phenomenon can be induced by intravenous inoculation of foreign embryonic blood cells in chick embryos." They also quoted the earlier work of E. Traub [8], which showed that mice infected with lymphocytic choriomeningitis virus became healthy carriers of the virus, with their young infected *in utero* but without clinical signs of illness and with resistance to intracerebral challenge in the absence of neutralizing antibodies. "These phenomena are obviously complex but there is the development of a *tolerance* (my italics) to the foreign microorganism during embryonic life. . . ." Burnet and his colleagues later attempted to induce tolerance in chick embryos to viral antigens but failed.

As I have recounted in my book *A History of Transplantation Immunology* [2], Medawar did not read Burnet and Fenner's monograph until 1950, when in fact he reviewed it anonymously for *Nature*. By that time he, together with R. E. Billingham and several other colleagues, had embarked on yet another study in an attempt to distinguish identical from fraternal twin calves. They approached the problem from another angle altogether in that they exchanged skin grafts between dizygotic twin calves in the hope that rejection of the grafts would set them apart from monozygotic twins long before it was possible to sex the animals on morphologic grounds. To their astonishment, the great majority of grafts survived very happily, and it was only when someone drew their attention to Burnet and Fenner's monograph that they began to realize the reason for their unexpected results. The data were duly published in 1951 [9], with a follow-up a year later [10]. They found that the majority of cattle twins at birth and for long after were fully tolerant of grafts of each other's skin and they cited Owen's work as the key to their interpretation. Naturally, they realized that skin grafting could not, after all, provide a solution to the farmer's freemartin dilemma but that the serologic reagents used by Owen could.

Historically, it is fortunate that the Medawar group had remained unaware of Owen's serologic findings until their study had been almost completed, for had they known of it they would hardly have embarked on their cattle work. As it was, the cattle findings led them directly into experiments to show that tolerance could be induced experimentally in mice.

Actively Acquired Immunologic Tolerance

In 1951 Medawar moved from Birmingham to University College, London, taking with him his postdoctoral Fellow R. E. Billingham and L. Brent, a postgraduate student. Together, they immediately began skin transplantation studies in inbred strains of mice and, having standardized survival times and established the main parameters of the immune state following graft rejection and the adoptive cellular transfer of immunity to syngeneic mice, they embarked on a sustained series of experiments to show that tolerance to skin allografts could be induced experimentally. These and subsequent events have been described in detail in chapter 5 of my book [2] and I will focus here on their findings as they related to Owen's work and on the fulsome acknowledgments they made to Owen.

The first publication by Billingham, Brent, and Medawar [11] was in 1953, in which they described their early data. Some mice inoculated *in utero* with a mixture of donor strain cells, including spleen cells, failed to reject donor strain skin grafts when these were transplanted 6 to 8 weeks after birth. Graft survival could be permanent or transient and it was strain-specific. Preliminary experiments with chick embryos were also reported: embryos inoculated intravenously with allogeneic adult blood exhibited varying degrees of tolerance, with fully tolerated Rhode Island Red grafts displaying a luxuriant crop of red feathers against the white background of the White Leghorn recipients. The discussion referred to Fenner and Burnet's speculations, cognitive phenomena, and Owen's previous findings. They wrote: "An exactly comparable phenomenon has been described by Owen, who found that the majority of dizygotic cattle twins are born with, and long retain, red blood cells belonging genetically to the zygote lineage of its twin . . . There is no reason to doubt that this is because cattle twins, being synchorial, exchange blood in foetal life. . . ."

In their full write-up of the tolerance studies three years later, including experiments showing that tolerance could be abolished in adult animals by the adoptive transfer of normal or presensitized lymphoid cells, Billingham et al. [12] also demonstrated that Owen's natural tolerance in cattle had its exact counterpart in birds. Thus, chicks that had been laboriously hatched out of fertile double-yolked eggs were shown to be chimeric for red cell antigens with serologic reagents provided by Owen, and they were found to be tolerant to each other's skin grafts. It was no accident that the injection of trypan blue into the chorioallantoic circulation of one chick proved that it was confluent with that of the other embryo. Billingham et al wrote: "For the first clear demonstration of an example of tolerance we are indebted to the work of Owen. . . ." Similar results were obtained by

Medawar's group by the artificial parabiosis of chick embryos (see below).

I have not yet mentioned the work of Milan Hašek. More or less at the time Medawar's group was carrying out its experimental study, Hašek was engaged in experiments in chickens that were designed to prove a politically correct phenomenon known as "vegetative hybridization." He developed the ingenious technique of embryonic parabiosis, involving the anastomosis of two allogeneic chick embryos by allowing their chorioallantoic membranes to fuse, resulting in a free exchange of fetal blood from about the 10th day of incubation [13]. Using this technique he demonstrated that, after hatching, the parabionts were less able to form antibodies in response to each other's serum proteins. Although he later realized that this was yet another example of actively acquired tolerance he at first believed that the parabiosis had brought about an "approximation" between the parabionts, i.e., the development of acquired characteristics alleged in the Soviet Union to have come about in plants and animals following various experimental procedures. Such an explanation was fashionable in Eastern Europe at a time when Michurin and Lysenko dominated Soviet biologic thinking. Hašek subsequently met Medawar and Brent at an international embryology meeting and thereafter interpreted his data in terms of acquired tolerance. Hašek and his school in Prague made many contributions to the development of tolerance, especially in relation to xenogeneic antigens, and their technique of chick embryo parabiosis was used by other laboratories, foremost among them that of Medawar's group. His role was not, however, decisive in that the tolerance bandwagon had by then already gained momentum in Britain and in other western countries.

Why Was the Discovery of Tolerance Important?

The induction of tolerance depended on the presentation of allogeneic antigens to animals before they had become immunologically mature, in practice either during fetal or neonatal life. (The parameters of tolerance induction have been fully discussed elsewhere—see ref. [2], chapter 5—where detailed references to the events described in this article may be found.) It had therefore always been clear that it could have no direct applicability to the human situation, although some attempts to induce tolerance in human neonates with allogeneic blood were made. So far as transplantation is concerned, the tolerance studies were important in two respects. First, the immunologic barriers erected during the course of evolution against allografts, however secondarily this may have arisen, were breached for normal tissues for the first time. (The phenomenon of enhancement [see ref. [2], chapter 6] was at that time thought to apply only to tumors.) This gave encouragement and hope both to experimentalists and to transplant surgeons and it provided a benchmark by which future attempts to induce tolerance in adults were to be judged. Second, it encouraged the development of the field of immunoregulation, especially once it became clear that tolerance was often not because of clonal deletion but because of immunoregulatory mechanisms such as suppressor cells and antiidiotypic antibodies (see chapter 6 of ref [2]). It also led directly to the discovery of graft-versus-host disease (see ref. [2], chapter 8).

Once it had been shown that tolerance was a universal phenomenon that transcended the boundaries of allo- and xenotransplantation—the first intimation that tolerance could also be induced to soluble proteins came from Hana and Oyama [14], Cinader and Oubert [15] and Dixon and Maurer [16]—it became central to immunology and theories of antibody production had to take it into account. Especially important was its effect on notions about autoimmunity, for it provided an explanation for tolerance to self and the normal absence of autoimmune manifestations. Thus, when Doniach and Roitt [17] in 1957 described thyroid-specific auto-antibodies in the serum of patients suffering from Hashimoto's disease directed against thyroglobulin, they were able to relate their findings to tolerance. They wrote: "The concept of immunologic tolerance provides a rational basis for the phenomenon of auto-antibody formation, since animals may fail to acquire this tolerance for constituents which do not gain access to the sites of antibody formation during the critical period. . . ." The danger of autoimmunity therefore provided a raison d'etre for tolerance, and Brent and Medawar [18] discussed this relationship and its implications in a wider context at some length.

MECHANISMS OF TOLERANCE

This will have been discussed by others at this Symposium and it has been considered at length in my book [2]. I will confine myself here to a few general remarks. Medawar's group [10, 11] had, fortuitously, carried out their main tolerance studies with mouse strains that later proved to differ only for class I antigens. These workers had come to the conclusion that tolerance induction was brought about by a central failure of the immune response. In such mice, tolerance was shown to be brought about by clonal T lymphocyte deletion, an option that was much later shown to be a realistic one when clonal deletion within the thymus had been demonstrated [19–23]. However, following the discovery of suppressor T lymphocytes by R. K. Gershon and K. Kondo, several groups, prominent among them those of M. Hašek and J. W. Streilein, found such cells to play an important role in many examples of neonatally induced tolerance, especially when the donor and recipient strains differed for

class II antigens (see ref. [2], Chapter 5). Thus, the fortuitous choice of inbred mouse strains by Billingham et al. permitted the concept of clonal deletion to be developed although it probably delayed the recognition of suppressor T cells and other active mechanisms.

SOME RECENT DEVELOPMENTS

I was asked especially to relate the older literature to some recent developments and I have chosen two topics.

Microchimerism—Cause or Effect?

Billingham et al. [12] had shown conclusively that neonatal tolerance achieved in mice by the inoculation of allogeneic lymphoid cells was almost invariably accompanied by the presence of donor cells in the lymphoid organs of the tolerant animals: evidently there was a clear link between functional tolerance and cellular chimerism. However, split tolerance—the termination of functional tolerance to skin allografts with persisting cell chimerism—was sometimes encountered. Nonviable or anucleate cells incapable of replication did not induce tolerance. For example, Mitchison [24] found that tolerance induced in chick embryos or newly hatched chicks to allogeneic red blood cells was maintained only by regular transfusions of red blood cells, and that tolerance broke down 3 to 4 weeks after the last transfusion. A similar observation had been made by Simonsen [25], and the conclusion that the maintenance of tolerance required the presence of replicating donor cells was strongly reinforced by the observations of those working with soluble proteins: tolerance persisted only for as long as the animals were given regular doses of the appropriate protein.

Some early observations left little doubt that in neonatally induced tolerance the persistence of chimerism was essential to the maintenance of skin allograft tolerance. Lubaroff and Silvers [26, 27] destroyed the donor cells of rats or mice tolerant to MHC-incompatible skin grafts in two ways: by the inoculation of specific antisera against the donor strain antigens, and by the transplantation of MHC-compatible cells sensitized against the donor strain into tolerant mice bearing healthy MHC-incompatible skin grafts. In the latter case, the transferred cells eliminated the chimeric cells of the tolerant animals but they were eventually themselves rejected by a response against minor histocompatibility antigens. In both experimental situations skin graft tolerance broke down, suggesting very strongly that the chimeric cells had played an essential role in maintaining tolerance. On the other hand, in certain immunoregulatory protocols established in *adult* rodents by pretreatment with cell-free donor strain tissue extracts and short-term immunosuppression, where cell chimerism could not possibly be involved, long-term tolerance to skin allografts was likewise achieved (see, for example, [28]): here the antigenic stimulus maintaining the tolerance emanated exclusively from the skin graft and the tolerance was driven by T suppressor cells.

The question of whether tolerance develops in long-term organ transplant recipients and the role played in this by the donor cells has recently been raised by Starzl et al. [29–31] following their demonstration that donor cells can be found in the tissues of allogeneic liver and kidney recipients. Starzl and his colleagues went on to develop the hypothesis that it was the persisting donor cells that were responsible for whatever tolerance ensued in such patients. They have argued that, far from preventing donor cell migration, everything possible should be done to enhance it.

The clinical inferences have derived further support from the experimental work of Sharabi et al. [32], who again showed that the removal of donor cells led to the abrogation of tolerance. On the other hand, Bushell et al. [33] have found in a mouse model that tolerance induced by a single dose of irradiated donor blood, under cover of anti-CD4 antibody, induced a specific, stable, and long-term tolerance to cardiac allografts despite the inability of the cells to replicate and to survive for very long in their hosts. It seems possible that whether or not chimeric cells are important depends on the particular tolerance mechanism involved.

Is Tolerance and Self/Nonself Discrimination Still a Valid Concept?

Very recently the concept of tolerance and self/nonself has been challenged by Ridge et al. [34], apparently supported by studies published in the same issue of *Science* by Sarzotti et al. [35] and Forsthuber et al. [36]. The three papers were accompanied by an overenthusiastic and uncritical article by a scientific journalist [37] making sweeping claims on behalf of the authors that would appear to go far beyond the experimental evidence provided. This is not the place to enter into a full discussion of these communications but I will briefly summarize the data. Ridge et al. [34] reexamined neonatal tolerance induced to the minor histocompatibility antigen, H-Y, which is present only in male cells. Because they were able to prevent tolerance induction to H-Y by using cell inocula enriched for dendritic cells, and because tolerance could be induced in adult mice with the aid of very large doses of male B lymphocytes, these workers concluded that there was nothing very special about the neonatal period and that "tolerance is not determined by the self or nonself origin of the antigen but rather by the conditions under which it is introduced." Their conclusions were firmly linked to the "danger" hypothesis of cell activation proposed earlier by Matzinger [38], according

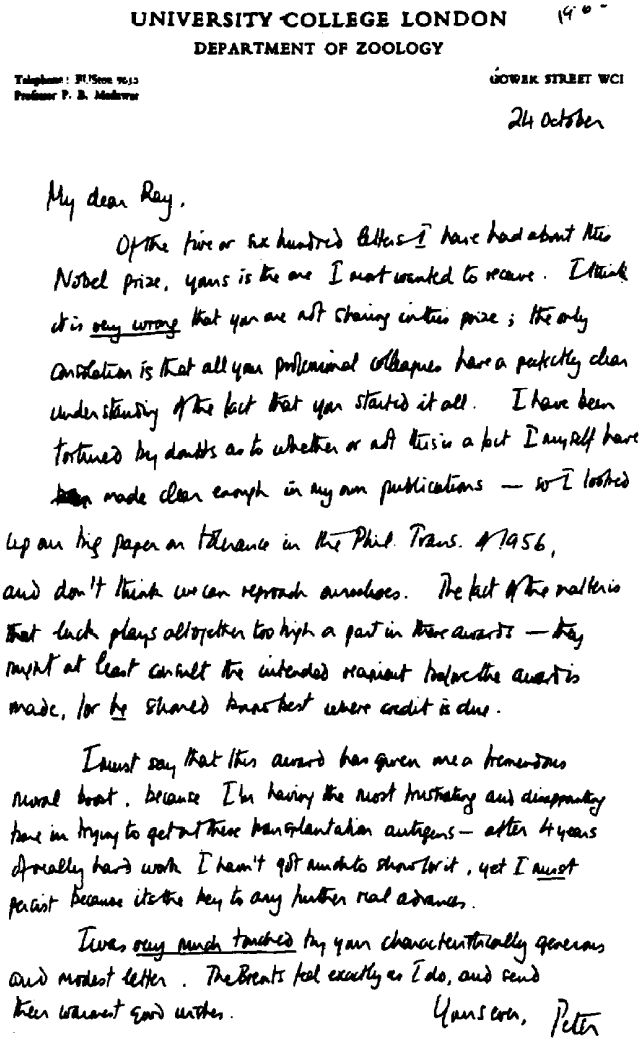
to which the critical factor was not the distinction between self and nonself but between "dangerous and harmless entities."

In a sense, Ridge et al. [34] could be accused of reinventing the wheel, for it has long been known that the introduction of exogenous IL-2 can subvert the establishment and the maintenance of neonatally induced tolerance [39], though those observations were accommodated within the theoretical tolerance framework. That there is indeed something *very* special about immunologically immature rodents so far as the ease of tolerance induction is concerned has been so widely documented (see, for example, chapter 5 of ref. [2]) as to make it unnecessary to provide chapter and verse here. As for the "danger" hypothesis of Matzinger, there are all kinds of problems with it; for example, if only danger signals activate the immune response, why is it that a) the signals emanating from tumors do not incite effective responses and b) the signals of certain harmless antigens such as minor histocompatibility antigens, or for that matter MHC antigens, do? Although the new data are certainly of interest I feel that the overthrow of the self/nonself concept would be grossly premature. Nor do they take into account that the tolerance mechanisms do not necessarily involve clonal deletion.

The supporting paper by Sarzotti et al. [35] described how low doses of a murine leukemia virus injected into neonatal mice brought about a protective immune response rather than tolerance. Again, there is plenty of evidence going back to the 1960s to show that the dose of immunogen is indeed of great importance in deciding whether tolerance or immunity ensues. It should be noted that Sarzotti et al. are careful not to make any sweeping claims from their experimental data. Finally, the data by Forsthuber et al. [36] showed that the inoculation into neonatal mice of putatively tolerogenic doses of a protein (hen egg lysozyme) can induce the formation of a vigorous TH2 response. These workers administered the antigen in Freund's incomplete adjuvant, an artefactual strategy that could be expected to override any tolerance mechanisms that might have come into play had the protein been used on its own.

TOLERANCE AND THE NOBEL PRIZE

Discussing the pros and cons of individual Nobel Prizes is a rather sterile exercise and it can be highly invidious (see, for example, p. 28 of Cohn's [7] recent reminiscences). I remember how embarrassed I was when J. Hamburger, in introducing me as the incumbent President of The Transplantation Society many years ago, expressed his strong belief that R. E. Billingham and I should have shared the Nobel Prize with Medawar. Nonetheless, returning to the person in whose honor this



UNIVERSITY COLLEGE LONDON 19 60
DEPARTMENT OF ZOOLOGY

Telephone: [illegible] Professor P. B. Medawar

GOWER STREET WC1

24 October

My dear Ray,

Of the five or six hundred letters I have had about the Nobel prize, yours is the one I most wanted to receive. I think it is very wrong that you are not sharing in this prize; the only consolation is that all your professional colleagues have a perfectly clear understanding of the fact that you started it all. I have been tortured by doubts as to whether or not this is a fact I myself have made clear enough in my own publications — so I looked up our big paper on tolerance in the Phil. Trans. of 1956, and don't think we can reproach ourselves. The fact of the matter is that Lwoff plays altogether too high a part in these awards — they might at least consult the interested majority before the award is made, for he showed himself best where credit is due.

I must say that this award has given me a tremendous moral boost, because I'm having the most frustrating and disappointing time in trying to get at these transplantation antigens — after 4 years of really hard work I haven't got much to show for it, yet I must persist because it is the key to any further real advance.

I was very much touched by your characteristically generous and modest letter. The Brents feel exactly as I do, and send their warmest good wishes.

Yours ever, Peter

FIGURE 1 Copy of a letter written in 1960 by P. B. Medawar to R. D. Owen, after the latter had congratulated him on his share (with F. M. Burnet) in the 1960 Nobel Prize.

article came to be written, one could—and I will—make out a perfectly logical case for the inclusion of Ray Owen in the Nobel Prize awarded to Medawar and Burnet in 1960. It was without a shadow of a doubt he who set the ball rolling, who encouraged Burnet and Fenner to speculate on self and nonself, and whose work provided the key to the critical cattle skin grafting experiments of Medawar's group.

However, it was not to be and, as this is a historic contribution, I shall reveal—with the very reluctant permission of Ray Owen—the contents of a letter Peter Medawar sent to Ray soon after the Nobel award was made (Fig 1). It reads:

"My dear Ray,

Of the five or six hundred letters I have had about the Nobel Prize, yours is the one I most wanted to receive.

I think it is *very wrong* that you are not sharing in this prize; the only consolation is that all your professional colleagues have a perfectly clear understanding of the fact that you started it all. I have been tortured by doubts as to whether or not this is a fact that I myself have made clear enough in my own publications—so I looked up our big paper on tolerance in the Phil. Trans. of 1956, and don't think we can reproach ourselves. The fact of the matter is that luck plays altogether too high a part in these awards—they ought at least consult the intended recipient before the award is made, for *he* should know best where credit is due.

I must say that this award has given me a tremendous moral boost, because I'm having the most frustrating and disappointing time in trying to get out these transplantation antigens—after 4 years of really hard work I haven't got much to show for it, yet I *must* persist because it is the key to any further real advances. [Author's note: see chptr. 4 of ref. [2].]

I was very much touched by your characteristically generous and modest letter. The Brents feel exactly as I do, and send their warmest good wishes.

Yours ever,

Peter"

I have included this letter because it is, in my view, of historic interest and because it reflects great credit on both these men, on Ray Owen because his congratulations were totally sincere and not in the least self-serving, and on Peter Medawar because he clearly felt very strongly that Owen *should* have shared the prize with him. That Ray Owen genuinely felt that he had not deserved to be included is evident from a letter he sent to Dr. D. Götze of Springer-Verlag KG in response to a letter by Dr. I. Weissman to Götze. He wrote: ". . . I want to say as emphatically as possible that I do not share, and honestly never have, Irv's impression that an injustice was done when I was not included in the Nobel Prize, and I very much hope that feelings will not emerge . . . the work by Medawar and his group that put the concept on an experimental foundation clearly justified the Prize, and Medawar's many other contributions over a long, productive career confirm it . . . I have never felt that the twin cattle studies would have justified the uncritical adulation that is so often accorded to Nobel laureates. . . ."

History may well take a different view with, to quote M. Cohn [7], "the wisdom of hindsight."

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