

The curious case of the 1960 Nobel Prize to Burnet and Medawar

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Summary

The 1960 Nobel Prize was awarded to Macfarlane Burnet and Peter Medawar for immunological tolerance. The Nobel Archives reveal that the two were never nominated together by anyone; Burnet had repeatedly been nominated for his virology studies, and the Medawar group (including Rupert Billingham and Leslie Brent) had been nominated independently for their transplantation work. A review of the 1950s literature suggests that tolerance had not yet, by 1960, reached the level of acceptance and acclaim in the immunological community to appear to justify the award. Burnet probably should have received the Prize for his virus work, and perhaps also for his Clonal Selection Theory, whereas Billingham and Brent should have shared in a Prize with Medawar for transplantation. If a Prize were to be given for tolerance, most agree that Ray Owen should have shared in it, for his work on cattle chimerism. It is suggested that the 1960 Nobel Prize to Burnet and Medawar for immunological tolerance may have been given for the wrong reasons and to the wrong associates.

Keywords: Burnet; Medawar; Nobel Prize; tolerance; transplantation.

The award

The 1960 Nobel Prize for Physiology or Medicine was awarded to Sir F. Macfarlane Burnet and Peter B. Medawar 'for discovery of acquired immunological tolerance'. In his ceremonial presentation, Prof. Sven Gard of the Karolinska Institute stated that,

...so far, however, the principal importance of the discovery has been in the field of research. It has been said that it has opened a new chapter in the history of experimental biology.

Sir Macfarlane Burnet. Doctor Peter Brian Medawar. Immunity is our perhaps most important defence against a hostile surrounding world. By penetrating analysis of existing data and brilliant deduction, and by painstaking experimental research you have unveiled a fundamental law governing the development and maintenance of this vital mechanism.

On behalf of the Caroline Institute, I extend to you our warm congratulations, and ask you to receive the Nobel Prize for Physiology or Medicine from the hands of His Majesty the King.

It is generally accepted that Nobel Prizes are awarded for those advances in a discipline that are broadly recognized as of ground-breaking importance by contemporaries, and that combinations of recipients (to a maximum of three) will usually be nominated jointly, and for the same central reason. In this respect, the award of the 1960 Prize would appear to represent some curious anomalies.

The contributions

What, precisely, were the contributions of these awardees? Macfarlane Burnet, Director of the Walter and Eliza Hall Institute in Melbourne, Australia, had carried out world-class research in virology during the 1920s and 1930s, but had become interested in immunology in the 1940s. He wrote a book on antibody formation in 1941¹ and, with his collaborator Frank Fenner, revised it in 1949.² By this time, Burnet had become aware of Ray Owen's remarkable observation of the inability of non-identical cattle twins with shared circulations to reject one-another's different blood groups (chimerism),³ and of the earlier story that newborn mice with congenitally acquired lymphocytic choriomeningitis virus could not mount an immune

response against that virus.⁴ This led the imaginative Burnet to postulate that the fetal recognition of 'self-markers' would justify the following sentence on p. 103 of his second edition,

If, in embryonic life, expendable cells from a genetically different race are implanted and established, no antibody response should develop against the foreign antigen when the animal takes on an independent existence.

Erling Norrby, whose book *Nobel Prizes and Nature's Surprises*⁵ presents the most thorough discussion of the 1960 Nobel Prize, and of how the Nobel Committee arrived at its decision, would comment that, 'It was this brief statement that served as the basis for his 1960 Nobel Prize.'

Peter Medawar, trained in zoology, had been exposed during the war to the general failure of skin grafts from unrelated donors onto burn victims, and made the study of the science of transplantation his life's work, first at the University of Birmingham and then at University College, London. Originally working alone, he was joined early by Rupert Billingham and then by Leslie Brent, and it was this threesome whose work would soon define the science of transplantation biology. Aware of Owen's work and of Burnet's suggestion, Medawar's group in 1953 devised an experiment⁶ in which fetuses of one inbred mouse strain were inoculated with cells from a second, transplant-incompatible strain. Once the mice reached adulthood, skin homografts from the original donor strain were now accepted, but grafts from a third, unrelated mouse strain were rejected, showing the specificity of the tolerance induction. Even more to their credit, the Medawar group had earlier shown that non-identical cattle twins would also fail to reject one another's skin grafts,⁷ in further confirmation of Owen's observation. These results supported the notion that 'self' was somehow defined during embryonic development, as Burnet had hypothesized. The early work on tolerance by the Medawar group was summarized in their 1956 opus.⁸

Tolerance in the 1950s

I was first stimulated to an interest in the 1960 awards to Burnet and Medawar while reviewing a paper on Burnet, written by several Australians. These authors made more of the critical importance to *contemporary* immunological thought of Burnet's postulate of fetal tolerance (and of the Medawar group's experimental confirmation of it) than I remembered from the 1950s, or from having later written variously on the history of those times.⁹ Having in my library most of the immunological texts then in use, and most of the proceedings of the more prominent international meetings on immunology during that

period, I read through them carefully and could find only little mention of Burnet's 1949 concept or of the Medawar's group's 1953 experimental finding. Some immunologists studied what they variously termed 'unresponsiveness' or 'tolerance' to protein antigens in both very young and older animals, almost as a curiosity of the immune response. Transplantation researchers hoped that it might be used to mediate organ transplant survival, but most studies of the phenomenon seem to have shed little light on the process.

In his 1956 book *Enzyme, Antigen, and Virus*,¹⁰ Burnet mentions tolerance only briefly, as one of the 20 'essential characteristics of the antibody response', and its possible mediation by 'self-markers'. Tolerance is also mentioned briefly in the 1959 series of *Science* articles on antibodies by David Talmage (who had independently advanced a selectionist theory of antibody formation¹¹), and by Nobel Prize winner microbial geneticist Joshua Lederberg,¹²⁻¹³ but these are primarily devoted to the cellular dynamics, specificity considerations, and the genetics of Burnet's current pride, his clonal selection theory. In his 1959 book *The Clonal Selection Theory of Acquired Immunity*¹⁴ Burnet touches upon tolerance, but would only fully explain it a decade later in his 1969 *Cellular Immunology*¹⁵ (of which the first section was reprinted under the more significant title *Self and Not-Self*¹⁶).

It should be noted, in the present context, that the Medawar group only began to consider themselves immunologists in the late 1950s (probably not until after Medawar's 1957 Harvey Lecture,¹⁷ as both Rupert Billingham and Leslie Brent confirmed to me (Billingham RE, personal communication, 1987, confirmed also by Brent L, personal communication, 1987); earlier, they had spoken of tolerance primarily to the transplantation researchers). Hence, the Medawar group spoke on tolerance at the first New York Academy of Science transplantation conference¹⁸ in 1954 with few immunologists attending, but already at the second transplantation conference in 1956 mainstream immunologists had begun to take an interest in the rejection of transplants as an immunological process. Two papers were presented on tolerance, by Michael Woodruff¹⁹ and by Melvin Cohn.²⁰ 1956 also saw a Royal Society conference on tolerance²¹ organized by Medawar and Burnet. This brought together those investigators interested in the suppression of the immune response both to simple proteins and to transplants. Again, in the rapidly developing field of immunopathology, where the characteristics of the immune response and autoimmune diseases are central, tolerance was scarcely mentioned in the several late-1950s volumes edited by Grabar, Miescher and Vorlaender.^{22,23}

Perhaps three highly significant international conferences, attended by many of the world's leading immunological researchers, may be used to define the state of

immunology at the close of the 1950s, and so clarify the contemporary position of tolerance in the field. In the 1958 Henry Ford Hospital Symposium on *Mechanisms of Hypersensitivity*,²⁴ there are various presentations on ‘unresponsiveness’, ‘tolerance’ and ‘paralysis’ as suppressions of the immune response. Experiments are described to specifically inhibit future immune responses by feeding allergenic chemicals, by neonatal injections of simple proteins, or by injecting large amounts of pneumococcal polysaccharide, but there is no discussion of mechanism, nor of any deeper implications. Indeed, in a section on Tolerance and Rejection of Tissue, Leslie Brent²⁵ does not even mention the word tolerance. The second significant international meeting was at the 1958 New York Academy of Medicine, on *Cellular and Humoral Aspects of Hypersensitivity States*,²⁶ Medawar spoke of transplantation tolerance; after summarizing its known characteristics, he would conclude that, ‘When it comes to interpreting the phenomenon of tolerance, in transplantation immunity and other immunological systems, all is guesswork.’²⁷ Finally, at the 1959 Prague conference on *Mechanisms of Antibody Formation*, Burnet’s introductory lecture to the conference fails to mention tolerance.²⁸ At the same conference, Richard Smith describes his studies on the induction of tolerance to simple proteins,²⁹ but does not cite either Burnet’s suggestion or the Medawar groups’ confirmation, nor does he discuss the broader implications of the phenomenon.

It would therefore appear that up until 1960, tolerance provided interesting experimental models, but its mechanisms and broader implications remained unclear. Only Melvin Cohn (that inveterate seeker of deeper explanations) had raised some preliminary questions of its possible broader significance.²⁰ It is interesting that whereas Medawar presented his Nobel Lecture on the phenomenology of tolerances,³⁰ Burnet’s title was ‘The Immunological Recognition of Self’,³¹ a theoretical discussion of molecular genetic possibilities and their evolution – a prelude to his future preoccupation with the significance of self–non-self discrimination.

It is true that transplant surgeons would refer repeatedly to tolerance in their late 1950s publications as holding the promise of facilitating organ transplant acceptance – they still do! Now, half a century later, advances in this area have less to do with acquired tolerance than with immunosuppressants and modifications of peripheral regulatory mechanisms. This is not to say that the discovery of the phenomenon of tolerance was not important for the discipline of immunology; it would contribute significantly to an understanding of the ontology of the immune response, of the full significance of MHC restriction, self–non-self discrimination, and the development of cellular immunology. But this wider appreciation would only come later.

The ultimate rise of tolerance and of the ‘immunological self’

Interest in tolerance expanded markedly during the 1960s and 1970s, rapidly becoming a more familiar concept in immunological meetings and publications due, perhaps in part, to the celebration of Burnet and Medawar’s Nobel Prize. But there was one presentation that provides a highly interesting sidelight to the tolerance story. In 1961, Milan Hašek and colleagues at the Czechoslovak Academy of Sciences published a grand review of the phenomenology of tolerance in volume 1 of *Advances in Immunology*.³² But the chief purpose appears to have been to call the attention of the immunological tolerance community to Hašek’s long-term studies on the consequences of the joining together of the vascular systems of several chick embryos (parabiosis) (note the similarity to Owen’s cattle twin chimera observations described above). These were first published in 1953 in Russian, and in a rather obscure Czech journal.³³ This was the same year that saw the Medawar group’s confirmation of Burnet’s theory, and in fact Hašek’s work would have served also as such a confirmation had he interpreted it in the context of immunology. But Hašek, a devout communist in the early 1950s, analysed his data politically to confirm the Stalinist genetic theories of Lysenko and Michurin. Only later, when introduced to the Medawar group’s studies, did he acknowledge the immunological implications of his work – too late to share in the glory of discovery. This story is told in detail by Brent in his *History of Transplantation Immunology*.³⁴ Following the Hašek review, Richard Smith explored in detail the phenomenology of tolerance induction to non-living antigens,³⁵ again with no speculation on its broader significance.

The volume of research reports grew increasingly large in both transplantation studies and in the response to simple proteins. Humphrey and White devote an entire chapter to tolerance in the second edition (1964) of their *Immunology for Students of Medicine*,³⁶ and mention of it occurs in five different chapter contributions to Max Samter’s 1965 book *Immunological Diseases*.³⁷ It would soon take its place as a topic of interest in all broadly based international symposia and congresses. As a prime example, one might cite the 1967 Cold Spring Harbor Symposium *Antibodies*,³⁸ where tolerance/unresponsiveness were discussed in six presentations, and mentioned also in Niels Jerne’s summary of the meeting (although, interestingly, Burnet failed to mention the topic in his opening remarks, discussing instead his clonal selection theory).

Then three things happened to focus greater attention on tolerance. The first was the slowly growing appreciation of the mechanisms involved in autoimmune diseases, and the wonder about why such diseases should

occur – or rather, what prevented everyone and all organs from undergoing such attacks. The second occurred with the discovery of T and B cells, focusing attention on whether tolerance operated on either one or both of them. The third event was in 1969, when Burnet published his book *Self and Not-Self*,¹⁵ and the speculations on the significance of tolerance began to expand exponentially. In the decades that followed, many international symposia were organized on the topic, covering such subjects as methodological approaches, fundamental mechanisms, and clinical implications.

Soon, tolerance and the significance of self–non-self discrimination involved not only immunologists, but also philosophers, sociologists and even journalists. Books were written on ‘the immunological self’, such as Jan Klein’s *Immunology: The Science of Self*,³⁹ Rem Petrov’s *Ya Ily Nye Ya (Me or Not Me)*,⁴⁰ and W.R. Clark’s *In Defense of Self: How Immunology Really Works*,⁴¹ among many others. International symposia were organized on the subject, such as *Soi et Non Soi (Self and Non-Self)*⁴² in 1990; an internet symposium on *Self-Nonself Revisited* in 2000;⁴³ and *L’Identité, la Part de l’Autre: Immunologie et philosophie (Identity, the Role of the Other)*⁴⁴ in 2010. As befits an important thesis, antitheses soon appeared, such as Alfred Tauber’s *The Immune Self: Theory or Metaphor?*⁴⁵; Irun Cohen’s *Tending Adam’s Garden*,⁴⁶ Silverstein and Rose’s *On the mystique of the immunological self*,⁴⁷ and Thomas Pradeu’s *The Limits of the Self: Immunology and Biological Identity*.⁴⁸

Perhaps the leading theoretical underpinning supporting the broad significance of ‘tolerance’ and its subsequent transformation to ‘self–non-self discrimination’ was the article by Peter Bretscher and Melvin Cohn in 1970, entitled ‘A theory of self–nonself discrimination’.⁴⁹ This thesis has been expanded and repeatedly defended by Cohn in many different articles. And on a more practical level, the potential importance of immunological tolerance was best pointed up by Leslie Brent who, in his Presidential Address to the Transplantation Society,⁵⁰ would call tolerance ‘the holy grail’ of transplantation research (and would devote an entire chapter to immunoregulation and tolerance as the holy grail 20 years later in his *A History of Transplantation Immunology*⁵¹).

The decision

The Nobel Committee will generally not make an award until the accomplishment is widely acknowledged as important by the general community of scientists in that field. From the immunological literature before 1960 outlined above, this seems not to have been the case for tolerance! Indeed, it would require a decade or two beyond 1960 for ‘tolerance’ and ‘self’ to achieve broad currency and significance within the immunological community.

How, then, was the decision made by the Nobel Committee to combine Burnet and Medawar in 1960, in the context of an award for their work on immunological tolerance. Here is what the recently opened Nobel archives, as carefully detailed in Erling Norrby’s book on the 1960–62 Nobel Prizes, would suggest:⁵²

Nominations of Macfarlane Burnet for a Nobel Prize had already started in the late 1940s; these had nothing to do with his immunology, but rather they were for his highly admired virological studies during the 1920s and 1930s. None of these early nominators even mentioned immunology, as nearly as I can tell. As is the practice of the Nobel Committee, all nominations are preliminarily assigned to experts for evaluation, to reduce the list to the more serious candidates. Early on, it was recognized that Burnet was ‘prize-worthy’ (what the Italians might call ‘*papabile*’). But it is the general practice not to make an award during the first year or two of eligibility. Burnet continued to be nominated for his virology and to be prize-worthy, and even went up in the esteem of the Nobel reviewers during the succeeding years, but each time some other candidate edged him out. It appears to be the practice of the Committee that after being passed over for 4–5 years, a candidate’s chances decrease thereafter, even despite continuing nominations and a continuing strong report. Then, toward the end of the 1950s, the occasional nomination might even mention, in addition to his virus studies, Burnet’s immunological theories and especially his 1957 clonal selection theory.⁵³ In 1958, the Medawar group (Peter Medawar, Rupert Billingham and Leslie Brent) were nominated by transplantation biologists for their studies that had put tissue and organ transplantation on the scientific and clinical map. Although the Committee’s expert reviewer Prof. Bernt Malmgren recommended Medawar as prize-worthy, he deemed Billingham and Brent to be too junior to share in the prize.

Then, finally in 1960, among several further nominations of Burnet for his virological studies came one by Nobel laureate Joshua Lederberg. Although this nomination concentrated on Burnet’s virological studies, it also mentioned in passing his significant immunological speculations. (One will remember that Lederberg had spent time with Burnet at the Hall, Institute in Melbourne, and had recently collaborated closely with Burnet and with David Talmage to publish their three 1959 *Science* articles on clonal selection.) Also in 1960, for the first time, there came a nomination of Burnet by Jorgen Birkelund, now restricted to his immunological theories including that on tolerance. Apart from his nomination of Burnet, Lederberg also submitted separately a nomination of the Medawar group for their transplantation studies. A similar nomination of the Medawar group for transplantation came also from Norwegian immunologist Sverre Henriksen, who also emphasized their experiments on tolerance. In the earlier review of the Medawar nomination, the

Nobel Committee's specialist bacteriologist Malmgren had mentioned also that Medawar's work on tolerance should not be considered without reference to Burnet's earlier theory.

With these strong (but separate) nominations, the Nobel Committee was pleased (and perhaps relieved) to have found a basis upon which to revivify and recognize the worthy but long-deferred Burnet. Hence, it was the Nobel Committee rather than the nominators who had paired the two recipients in the context of immunological tolerance, setting aside Burnet's work in virology and Medawar's more extensive transplantation studies. Most of those involved with tolerance studies would agree that Ray Owen should have been included in any prize for tolerance. It is also probably safe to say that within the immunological community, by 1960 both Billingham and Brent were viewed as full contributors to the Medawar team's overall success. However, even if this view were shared by the Nobel Committee, the two could not be added, since the Nobel rules restrict each award to a maximum of three recipients. In the event, Medawar did share his monetary award with his two colleagues.

Comment

It would appear, then, that the award to Burnet and Medawar for tolerance (minus the unfortunately missing Ray Owen) was premature in 1960. They had each been nominated separately, but for other advances, and had never been nominated jointly for tolerance. Beyond this, it would take another decade or more for the full theoretical and practical implications of tolerance to be realized within the immunological community, as it engaged organ transplantation, autoimmunity and the important process of self–non-self discrimination. This is not to say that the two individuals did not merit Nobel recognition. Surely Burnet deserved a prize for his earlier non-immunological studies in virology, and he would appear to have deserved one for clonal selection, which soon became the ruling paradigm of the discipline. And Medawar (together with Rupert Billingham and Leslie Brent) certainly deserved a prize for their studies which opened up transplantation immunology as one of the great stories in modern medical science.

We may note in passing that Burnet later implied that he had received the Prize for the wrong reason – not for his virology, nor even for tolerance, but rather for his clonal selection theory. In my own later discussions with Billingham and with Brent, I received the impression that they felt that tolerance was merely one of many steps in the Medawar group's grand contributions to transplantation biology. I recall also, in this same vein, that Merrill Chase (Karl Landsteiner's long-time associate) mentioned that Landsteiner also felt that he had been recognized by

the 1930 Prize for the wrong reason – for his discovery of blood groups, rather than for his more favoured immunochemical specificity studies. Immunologists interested in the history of their field might also be interested to learn that in 1960, Albert Coons was nominated for the Nobel Prize for his perfection of the fluorescent antibody labelling method, so important to contemporary studies of the localization of antigens and antibodies – but was not considered 'prize-worthy'!

Finally, the story of the 1960 award on tolerance to Burnet and Medawar suggests further that a somewhat similar process might have been at play within the 1984 Nobel Committee on Physiology or Medicine, which added Niels Jerne (for his theories) to the team of César Milstein and Georges Köhler (for monoclonal antibodies) – an even more disparate combination. But we will not know the answer to this until the Nobel Committee Archives are opened by statute after 50 years, in 2034.

Disclosures

There are no competing financial or commercial interests.

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