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Peter Brian Medawar and the discovery of acquired immunological tolerance

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ABSTRACT

The immunological tolerance was described for the first time with the seminal observations made in 1945 by R.D. Owen, demonstrating that cattle dizygotic twins display red cell chimerism in adult life. F.M. Burnet and F. Fenner highlighted the Owen's discovery in their monograph "The production of Antibodies" published in 1949. In 1953, P. Medawar and his co-workers showed that tolerance can be experimentally induced in fetal mice and in chick embryos. In 1960, Medawar in recognition of the significance of his 1953 and 1956 papers was awarded the Nobel Prize in Physiology or Medicine with Burnet for their discovery of acquired immunologic tolerance.

1. Biographic profile

Peter Brian Medawar was born on February 28, 1915, Rio de Janeiro Brazil, to businessperson Nicholas Medawar and the former Edith Muriel Dowling. After the conclusion of the First World War in 1918, the family moved to England. Medawar studied zoology at Magdalen College, Oxford, completing his undergraduate studies with first class honours in 1935. The same year he accepted an appointment as Christopher Welch Scholar and Senior Demonstrator at Magdalen College. He was named a fellow at Magdalen in 1938 and remained at Oxford until 1947, when he accepted an appointment as Mason professor of Zoology, at the University of Birmingham.

When World War II broke out in Europe, the Medical Research Council asked Medawar to concentrate his research on tissue transplants, primarily skin grafts. In these years, Medawar together with Rupert Billingham and Leslie Brent at the University College in London investigated the use of skin grafts to determine whether cattle twins were monozygotic or dizygotic. He observed that the rejection time for donor grafts was noticeably longer for initial grafts, compared to those grafts that were transplanted for a second time. Medawar formed the opinion that the body's rejection of skin grafts was immunological in nature.

From 1951 to 1962, Medawar served as professor of Zoology and Comparative Anatomy at University College London. In 1962, he became the Director of the National Institute for Medical Research (NIMR), Mill Hill (Fig. 1), where he continued his study of transplants and immunology.

In 1960, Medawar was awarded the Nobel Prize in Physiology or Medicine with Sir Frank Macfarlane Burnet (Fig. 2) for their discovery of acquired immunologic tolerance. Medawar's Nobel prize award was in recognition of the significance of his 1953 and 1956 papers [1,2, the alphabetical order of their names was Medawar's convention and acknowledgement of their team work] on induction of transplantation tolerance, experimentally providing supporting evidence for Burnet's hypothesis of self/non-self discrimination.

In 1969, Medawar suffered a stroke, the first of several, that left him partially paralyzed and forced him to step down as Director in 1972. On October 2, 1987, at the age of 72, Medawar died at the Royal Free Hospital in London as a consequence of a last severe stroke.

He was made a Fellow of the Royal Society in 1949 and received many other honors throughout his career. Medawar was also a philosopher and a gifted science communicator.

2. The influence of Burnet

In 1945, Raymond Owen (Fig. 3) discovered that chiamerism in cattle twins protected red blood cells (RBCs) of both animals in

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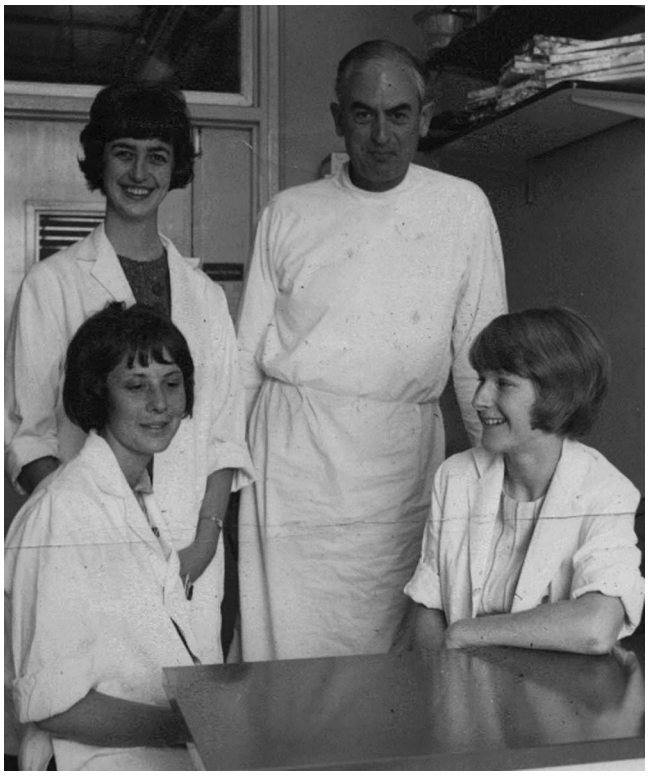

Fig. 1. Peter Medawar with colleagues at National Institute for Medical Research (NIMR).

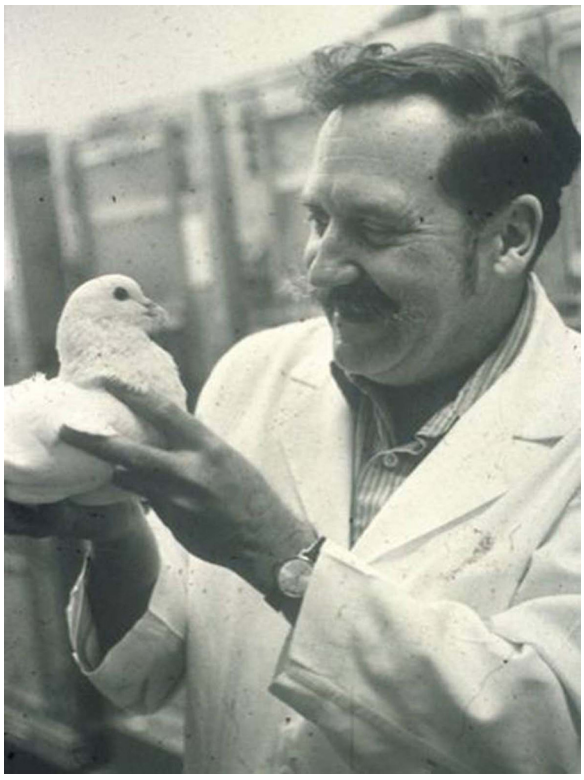

Fig. 3. A port trait of Raymond Owen.

Fig. 2. A port trait of Sir Frank Macfarlane Burnet.

each of them. He made the observation that non-identical (dizygotic) twin cattle, which shared the same placental circulation and whose circulations were thereby linked, grew up with appreciable numbers of RBCs from the other twin in their blood: if they had not shared the same circulation at birth, red cells from the twin injected in adult life would be rapidly eliminated by an immunological response [3]. This paper was significant with regards the hemopoietic stem cell research as well. When Medawar was awarded the Nobel Prize, he wrote a letter to Owen in which he declared that: " 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 that 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 Phyl. 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." [4].

From this finding Burnet and his colleague Frank Fenner conceived the notion that potential antigens which reach the lymphoid cells during their developing immunologically immature phase in the perinatal period can specifically suppress any future response to that antigen when the animal reaches immunologically maturity.

As Burnet said: "In the first edition of "Biological Aspects of Infectious Disease" (1940), I first used the concept that once the simplest animals evolved, the related requirements for mutation (by the digestion of other organisms) and for protection from bacterial infection, required a capacity to distinguish between the chemical structure characteristic of self' and any sufficiently different chemical structure which is recognized as 'not self'. Self' must remain undamaged by the enzymes and other mechanisms that can digest and destroy 'not self'. This is the concept basic to modern immunology but no one applied it seriously until 1949." [5].