Sir Peter Brian Medawar and the Genesis of Transplantation Immunology*

Bodhisatta Nandy

Organ transplantation is now a regular practice, saving the lives of countless people across the world every single day. Even bone marrow replacement is becoming more accessible to people every year. However, advances in organ transplantation, even skin grafts, are relatively recent advancements in medical science. A few decades ago, such transplantations were mostly unsuccessful, with most attempts resulting in fatal graft rejection. Many brilliant biologists turned this around, leading to more successes. Sir Peter Brian Medawar was the one to start this revolution back in the 1950s. Known largely for his seminal contributions to the foundation of modern ‘Transplantation Immunology’, he was also, to many, a great inspiration, an embodiment of scientific temper, and one of the sharpest minds known.

Early Life and Education

Born (February 28, 1915) in Petropolis, near Rio de Janeiro in Brazil, Peter Medawar was the third child of Nicholas Agnatius Medawar and Edith Muriel. His father was Lebanese, and his mother was British. Brazilian by birth, he was registered as a ‘natural-born British’, which later turned out to be a blessing for him. At the age of 18 years, he was called up for a mandatory tenure in the army, as dictated by the Brazilian nationality law. His application for exception was denied. However, he was able to forego the military tenure by giving up his Brazilian citizenship. Along with his brother, Phillip, he moved to England to complete his schooling. In those days, schools, even in England, 

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were grossly neglected, especially in non-urban areas. He was fairly disappointed by his school experience. He described his prep school as follows:

“All that was needed was a large rambling Victorian house of the kind that had already become unsaleable as a private residence, and a bank loan to make it possible to buy the cheapest possible school furniture, iron bedsteads, rickety desks made from unseasoned wood, and the like. Staff were easy to raise and quite cheap, for unemployment was rife and no qualifications were called for other than those they professed to possess already.”

Peter managed to finish his school and went to Marlborough College, Wiltshire. Even there, his experience was not great. Though he was resentful of the college experience, this turned out to be a turning point in his life as he met a very influential teacher—Ashley Gordon Lowndes. Unhindered by his relatively poor dissection skills, Medawar went on to join Magdalen College of the University of Oxford for an honours degree in zoology in 1932. Not only did he secure a first-class in the honours, but he was also awarded the Christopher Welch Scholarship and a Senior Demyship. He eventually completed his doctoral dissertation from Magdalen College in 1941.

Interestingly, he declined the PhD (D. Phil. according to Oxford terminology) although his thesis was accepted for the degree, presumably because he could not afford it. Having a PhD degree was not essential for continuing with research. During his D. Phil., he collaborated with John Z. Young (another brilliant zoologist and former student of Ashley Gordon Lowndes) to work on ‘nerve glue’. The discovery of nerve glue was far more important than it appears, both in terms of its application as well as in terms of how it influenced the trajectory of Medawar’s career. While he was absorbed in little scientific problems, primarily driven by curiosity, J. Z. Young, his tutor at that time, realised that he was capable of doing much more than pursuing relatively easy problems.

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Skin Grafts and Introduction to Transplantation Immunology

The trigger that started Medawar down the path of transplantation immunology was a rather dramatic event. After his D. Phil. adventure, Medawar was working on tissue culture techniques and animal development and even taught himself mathematics. When World War II broke out, the university insisted that he should teach the medical students and carry out research on clinical issues so that it could have some tangential benefit to the war effort. The closest Medawar came to achieving that was when he tested the efficacy and toxicity of some antibiotics on flesh wounds that soldiers at the war front might typically face. In the laboratory of Sir Howard Walter Florey (a Nobel laureate himself) in the Department of Pathology, he was first introduced to a new problem of treating burn wounds. One day during this time, a British pilot crashed his plane almost into his backyard. The pilot survived the crash but suffered a 60% third-degree burn. Dr John Barnes of the Department of Pathology was to attend to his care. He strongly insisted that Medawar study the patient and come up with some clever idea to treat him.

The most obvious treatment approach was to use skin grafts. Essentially, the burnt skin could be replaced by pieces of skin from the same (autograft) or a different person (holograft). The latter usually generated a severe reaction—a type of inflammatory reaction that eventually resulted in the skin graft being ‘rejected’. Only in the case of identical twins (i.e., when the donor was an identical twin of the recipient) would such grafts be ‘accepted’. The former was not a feasible option when the patient was severely burnt. Hence, this was a significant challenge, especially given the war. Perhaps more importantly, the reason for this law of nature, which seemed to dictate what kind of skin (or any organ) could be ‘accepted’ as a graft, was not known. Therefore, even academically, it was a great puzzle. In Peter Medawar’s words:

“This conjunction of events had first made me aware of the body’s exquisite powers of discrimination also fixed my career as a scientist.”
As he was practising tissue culture, his first idea was to harvest some of the available skin and expand it by tissue culture before using it as grafts. This approach turned out to be of no use. In fact, the patient could not be helped by anything Medawar came up with. Note that these techniques may sound very simple, especially if you have been seeing them in some Hollywood movies, but in reality, they are not. Everything, starting from assessing the wound to harvesting skin, growing skin in tissue culture, etc., needs a precise understanding of histology, physiology, and chemistry. Nonetheless, thanks to the expert work of a Spanish plastic surgeon, and not by the effort of Medawar, the patient eventually survived. However, importantly, Medawar now had a clear idea of the problem—the homograft conundrum, as he called it.

Briefly, as mentioned above, grafts from a different person usually do not work unless the donor is the identical twin of the recipient. Even if the donor happens to be a close relative, parent or sibling, it would often not work. Typically, the recipient’s body initially seems to accept the graft, but eventually, the graft fails. If this is attempted again from the same donor, the graft rejection is even quicker.

Medawar started working at the burn’s unit of the Royal Infirmary at Glasgow. He collaborated with a rather gifted surgeon—Tom Gibson, to study homografts in humans. They studied a patient who was a burn victim and needed skin grafts. Medawar himself carried out the grafting, the sectioning, and eventually, the microscopic observations. They soon noted that the process of graft rejection starts with a whole lot of white blood cells (those involved in providing immunity to invading pathogens) migrating into the grafted tissue. This was followed by the usual inflammation that culminated in the destruction of the graft, typical of graft rejection. They also found that a second set of grafts from the same donor met with an even swifter, almost instantaneous rejection characterised by the migration of white blood cells. This was the first demonstration of the physiological events underlying graft rejection. Suddenly, the ‘nature’s rule’ was a physiological
phenomenon, an immune response albeit of a special kind. However, Medawar understood that basing such an enormous claim upon observations carried out on a single human subject would not be appropriate. Hence, he turned to animal experimentation. There was now a hypothesis to test. Once back in Oxford, eventually, data from almost six hundred grafts from twenty-five rabbits completely upheld the hypothesis. There was little doubt that graft rejection is indeed an immunological phenomenon. The immune system of the recipient treats the skin graft (or any other organ) from a donor as a ‘non-self’ entity, much like it recognises an invading pathogen. The results of these experiments were published in two very long articles in the *Journal of Anatomy* in 1944. This is now common knowledge and part of any standard immunology textbook.

**Immunological Tolerance and Acceptance**

The study of homograft remained a major emphasis of Medawar’s research for many subsequent years, through his tenure at Oxford (until 1947), as Mason Professor of Zoology at Birmingham (1947–1951), and as Jodrell Professor at the University College of London.

It was a monumental discovery both in terms of the fundamental understanding of the immune system as well as from the clinical point of view. Once it was established that graft rejection is an immune response, a clear clinical possibility began to emerge. The approach was to weaken immunity altogether, either through the use of radiation (total body irradiation destroys the tissues that form the cells of the immune system, thereby knocking the system out) or by using adrenal corticosteroids (steroid hormones secreted by the adrenal cortex tend to weaken or suppress the immune system). However, both these treatments were highly unsafe—after all, how could shutting down the immune system be safe!

Once again, Medawar and his colleagues came up with a brilliant solution. After almost nine years of the publication of the
Since autografts (grafts from the same individual) were usually accepted and homografts were rejected except between identical monozygotic twins (twins originating from the same fertilised egg) and between individuals in highly inbred strains of mice and guinea pigs, it was a fairly straightforward deduction that the rejection has something to do with inherited genes.

Since autografts (grafts from the same individual) were usually accepted and homografts were rejected except between identical monozygotic twins (twins originating from the same fertilised egg) and between individuals in highly inbred strains of mice and guinea pigs, it was a fairly straightforward deduction that the rejection has something to do with inherited genes. When it failed, it was also often between a graft from a male donor to a female recipient. I leave it to the readers to deduce what this failure might imply. A glorious exception to the homograft rejection rule (apart from monozygotic twins or highly related individuals) was if the grafting was done in an embryo. It turned out that embryos accepted even cross-species grafts!

Medawar and Billingham, working on cattle, found that all cattle twins accepted grafts from each other. Since it was impossible that all those twins were monozygotic, this was very surprising. They repeated the experiments with non-twins to confirm that graft rejection did take place in cattle. In 1945, it was shown by Ray D. Owen, an American agricultural geneticist, that all twins in cattle shared embryonic blood during development and hence shared circulating red blood cells that were genetically their own as well as those genetically identical to their twins—a form of genetic chimerism. Medawar and colleagues, in 1951 and 1952, published their discovery that skin grafts could be readily exchanged between cattle twins. Immunological tolerance of the grafts seemed to be natural for cattle twins. Medawar theorised, with characteristic insight, that the intolerance to ‘foreign’ grafts takes time to develop.

Towards the end of 1951, Medawar moved to University College London along with his student Rupert Billingham, and Leslie Brent joined the group. In the 1953 paper, Medawar and colleagues took this natural immunological tolerance to the next level,
arguing that tolerance could also be induced artificially. The trick was to infuse donor blood/tissue at the embryonic stage of the recipient. The team went on to carry out experimental observations, first on laboratory mice and then on cattle, to show that this method could induce the recipient to accept a skin graft from an unrelated donor, thus creating an induced mosaic. They named this induced tolerance *acquired immunological tolerance.* Essentially, if an embryo is infused with antigenic entities (non-self molecules that can generate an immune response in the body), the individual develops to be severely compromised in terms of its ability to (immunologically) respond to that antigen. Medawar and team had discovered a fundamentally important characteristic of the vertebrate immune system. The self/non-self recognition physiology takes time to develop in a developing embryo.

At this point, a reader might think this to be an achievement without any clinical implication. However, bear in mind that this was the first time the homograft conundrum was cracked wide open.

I do not want this to sound like a remarkable success story without any setbacks and pitfalls because science almost never progresses in an uninterrupted, straight line. A few years after the publication of the landmark article on acquired immunological tolerance, Billingham and Brent discovered something called ‘graft versus host disease’ through a series of exquisitely designed experiments. It turns out that, at times, the graft tissue can contain immune cells and may hence be capable of mounting an immune response itself. Now, in the case of induced tolerance, the recipient’s immune system is neutralised for the donor factors such that the recipient or the host would not mount an immune response against the graft. However, the immune cells present in the graft can still mount a reaction against the host tissue, which is essentially defenceless. This was a significant challenge in converting the laboratory finding about induced tolerance to clinical application. However, this was not an end to the induced tolerance. Medawar–Billingham–Brent predicted in 1954 that a good genetic (HLA match: human leukocyte antigen) match between the donor and the recipient would be needed to ensure safe, donor-
specific tolerance. In the late 1960s, sustained, safe bone marrow transplantation in human patients was achieved by following HLA type matching.

Medawar, along with Frank Macfarlane Burnet, an Austrian immunologist, was awarded the 1960 Nobel Prize in Physiology and Medicine “for discovery of acquired immunological tolerance”. The British government knighted him in 1965.

Theory on Senescence

Though heavily absorbed in the research on homograft problems discussed above, Medawar had diverse interests—ranging from animal development to evolutionary theory. His interest in evolutionary theories is of particular interest to me (and also to a more wider audience). He once wrote—“For a Biologist, an alternative to thinking in evolutionary terms, is not to think at all”—highlighting his inherent thirst for a rational explanation, which for all biological phenomena, must be founded in evolutionary reasoning.

From the very early days of his life in science, Medawar was interested in ageing. Characteristically he viewed ageing from an evolutionary point of view. By the time he moved to University College London, he had already formulated a theory to explain the evolution of ageing. The theory, commonly referred to as the mutation accumulation theory of ageing, is one of the widely accepted evolutionary theories of ageing.

Using a hypothetical example of the laboratory glass test tubes, Medawar argued that the strength of natural selection acting on heritable variation is a function of the age at which the variants are expressed. Imagine a laboratory that has started off with 1000 test tubes, which accidentally and randomly break at a rate of 10% per month. If an equal number of new tubes is added every month, the number is maintained at 1000. Now, supposing this process continues for some time, one can visit the laboratory at any point in time and find that the age distribution of the tubes follows a particular pattern—the youngest most common, followed
by a steady decline. Now, if we imagine these non-living tubes to be alive and hence reproduce at a fixed rate, an interesting pattern emerges. The youngest tubes (i.e., the most recently added) will always contribute the most to the pool’s (i.e., population’s) reproduction—i.e., they will always have the highest ‘reproductive value’, which will, thereafter, successively reduce with age. Thus far, the model has considered an immortal organism (biologically, immortality simply means that there is no limit to life, death happens simply by accident) with a fixed rate of reproduction. If we now consider, instead of immortality, a certain intrinsic property by virtue of which a tube simply disintegrates on its own (i.e., death), the abundance of tubes with such property will depend on the age at which it is expressed. If the disintegration effect kicks in after five years, it has virtually no effect as by that time, it has made almost as many copies of itself as it is anyway expected—after all, very few tubes are expected to remain intact for five years. Hence, the abundance of tubes with such a property can be expected to be independent of its harmful nature. In contrast, if the disintegration effect kicks in after one month, when its reproductive value is expected to be very high, the effect is expected to be very catastrophic. It is because it had only one cycle of reproduction. Tubes with such tendencies will rarely be found in the pool.

Translated in biological terms, even in a simple population of unitary organisms, the efficiency of differential survival and reproduction (i.e., natural selection) of removing deleterious heritable tendencies (genes or alleles) is expected to decline with age at which the deleterious effect is expressed. Hence, mutations (you can also use alleles/genes in place of mutations) that have harmful effects (such as reduced survival, reduced reproduction) late in life, i.e., at advanced ages, would escape the purifying effect of natural selection. Over many generations, the abundance of such late-acting deleterious mutations is expected to increase, eventually leading to poorer survival and/or reproduction of older individuals. Thus, such mutation accumulation can explain the evolution of an age-dependent decline in survival and/or reproductive rate.
in other words ageing.

Although Medawar himself could not test the validity of his theory through experimentation, over the last four decades, the mutation accumulation theory has been extensively studied. The general validity of the theory is now widely recognised. Some of these tests can be found in a previously published article in Resonance [1].

**Personality, Family, and Late Life**

Medawar had wide-ranging interests that included opera and cricket. Even when he was extraordinarily busy with various activities in the 1950s, he tried to find time to play, although he was not particularly good at it. He referred to his role in the team as an “all rounder” and defined the term as—“a technical term in village cricket referring to someone equally lacking in proficiency in all branches of the game”. To him,

“The game gave one opportunity to spend at least an afternoon in the open and usually in very pleasant surroundings, enjoying the prospect and retrospect of lunch or tea accompanied by a pint of ale.”

Medawar was known for his sense of humour and wit. J. B. S. Haldane once described him as, “He smiles and smiles, and is a villain”. He was extraordinarily tall (6.5 ft) and handsome. He met Jean Shinglewood Taylor during his Oxford days and got married in 1937. They had four kids—two sons and two daughters. He was passionate about the truth and was extremely critical of anything that could not be verified by experimentation.

In 1969, during the annual meeting of the British Association, he suffered a stroke that led to severe impairment of his speech and movement. Though he survived, the recovery took a lot of time and was incomplete. He resumed work, albeit in a severely limited capacity. He spent a considerable amount of time writing books and essays on a variety of topics. He eventually passed away on October 2, 1987. Although there has been some de-
bate about the timing of the 1960 Nobel Prize, as transplantation immunology had not yet reached its peak of importance at that time and needed contributions from many more, there is little disagreement that Peter Brian Medawar was truly the pioneer of transplantation immunology. Without his seminal contributions, the world would probably have had to wait longer to see transplantation outside science fiction, and the delay might have cost us innumerable lives.

Suggested Reading


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