Title	The shape of the human being as a function of time : time, transplantation, and tolerance in Peter Brian Medawar's research, 1937–1956
Author(s)	Park, Hyung Wook
Citation	Park, H. W. (2010). The shape of the human being as a function of time: time, transplantation, and tolerance in Peter Brian Medawar's research, 1937–1956. Endeavour, 34(3), 112-121.
Date	2010
URL	http://hdl.handle.net/10220/9942
Rights	© 2010 Elsevier. This is the author created version of a work that has been peer reviewed and accepted for publication by Endeavour, Elsevier. It incorporates referee's comments but changes resulting from the publishing process, such as copyediting, structural formatting, may not be reflected in this document. The published version is available at: [http://dx.doi.org/10.1016/j.endeavour.2010.07.002].

"The Shape of the Human Being as a Function of Time": Time, Transplantation, and Tolerance in Peter Brian Medawar's Research, 1937-1956

Hyung Wook Park

Division of General Studies, Ulsan National Institute of Science and Technology, Ulsan, South Korea, 689-798

Corresponding author: Park, H. W.

(park0717@gmail.com. Phone: 82-52-217-2018)

Summary: Using tissue transplantation, the British scientist Peter Brian Medawar showed how extrinsic cells could be permanently integrated into an animal's body without provoking immune responses. With his study of this phenomenon—which he called "actively acquired tolerance"—Medawar was awarded the Nobel Prize in Medicine and Physiology in 1960 along with the Australian scientist Frank Macfarlane Burnet, who theoretically predicted the possibility. The monumental work of Medawar stems from his long and deep interest in the nature of living organisms' changes over time, such as growth, aging, and evolution. In particular, his concern on the phenomenon of *decline* played a critical role in his research design regarding tolerance and its interpretation.

Keywords:

Peter Brian Medawar, tolerance, tissue transplantation, time, growth, aging, evolution, decline

Abbreviations:

PBM Peter Brian Medawar Papers, Wellcome Library, London, United Kingdom

RAF Ronald A. Fisher Papers, University of Adelaide Archive, Adelaide, South Australia, Australia

NAUK National Archives of the United Kingdom, London, United Kingdom

Growth and Aging

On December 6, 1951, during his inaugural lecture as Jodrell Professor of Zoology at University College London, Peter Brian Medawar explained how the evolutionary process accounted for the origin of aging. According to Medawar, senescence had been an enigmatic phenomenon to biologists and medical researchers for a long time. None of the current scientific theories could satisfactorily explain its origin and cause. In this state, Medawar claimed, his new evolutionary theory could provide a firm basis for tackling the "unsolved problem of biology." Indeed, aging was an issue "of conspicuous sociological importance" as well, because "the center of gravity of the population is shifting steadily toward old age."[1] This altering demographic structure changed "the principal causes of death" from infectious to chronic diseases, incurring serious "economic consequences." A scientific approach to senescence was thus urgently needed in Western countries which were enjoying longer average lifespan.

But aging was not Medawar's major research subject at that time. His team was then deeply involved in a seeming unrelated project, tissue transplantation, which led to the landmark 1953 paper on "actively acquired tolerance." Nevertheless, a close analysis of his works shows Medawar's persistent concern on the dynamic aspects of life which governed both aging research and immunological investigation. Even while he was not thinking about aging, his preoccupation with life's changing features over time, including age-dependent transformations, was a critical element of his science.

This dimension of Medawar's work resulted from his scientific training and academic networks. Born in 1915, he was educated in Magdalen College at Oxford University from 1932 to 1935 (Figure 1). There he finished his undergraduate degree in zoology and worked as a demonstrator and research fellow before being appointed Mason Professor of Zoology at the University of Birmingham in 1947.

[Figure 1]

During this period, he learned to investigate the living organism as a constantly changing entity, whose nature could be revealed primarily through careful observation and systematic analysis that often relied upon mathematical tools. It was certainly possible for him to study the living organism as if it had been a static being, just as many physiologists and geneticists did at that time. However, the senior investigators he met during his scientific education and the books he avidly read led him to view life through its temporal variations, including its development, senile changes, and evolutionary adaptation.[2] A major influence on this academic standpoint was the British biologist D'Arcy Thompson, who wrote *On Growth and Form* (1917). Through his publications and personal correspondence, Thompson taught Medawar that the growth and structural relationships of various living organisms could be mathematically traced and analyzed.[3] Medawar also learned biostatistics and the new evolutionary theories after the Modern Synthesis through several eminent scientists, including Ronald Fisher, Julian Huxley, J. B. S. Haldane, Alfred Lotka, Edward Poulton, E. S. Goodrich, and E. B. Ford. He came to appreciate these scientists' quantitative way of explaining evolution in terms of random variation and natural selection. Indeed, Medawar knew many of these scholars in person, primarily through his Oxford alumni-faculty network. As Jack Morrell has described, many prominent evolutionary scientists taught and studied at Oxford University during the early and mid-twentieth century, and Medawar's 1944 article "Oxford zoology" indicates that he deeply respected these prestigious biologists and regarded himself as a member of the active academic community.[4]

Medawar's first published paper in 1937 shows how he used the approaches he learned from these scholars to analyze a biological phenomenon, namely, "ageing" of tissues explanted

from embryonic animals. In this paper, he summarized his study of the biological properties of a factor in malt extracts that had been known to inhibit the proliferation of cells. He observed that the susceptibility of explanted tissue to the inhibitory effects of the factor increased with the tissue's age. This observation led him to think that the "growth energy" of tissues could be represented as the capacity to grow under the influence of the inhibitory factor.[5] Younger tissues with more growth energy tended to proliferate at a higher rate than older tissues in the presence of the same amount of the inhibitory factor.

In 1940, Medawar studied this phenomenon further with carefully designed experiments and mathematical analyses. He stated that the growth energy of tissues increased in proportion to the concentration of the inhibitory factor that was "*just sufficiently high* to inhibit all [outgrowths] from a series of explants of differing embryonic ages."[6] He then actually measured these concentrations using explanted embryonic chicken hearts aged from 6 to 18 days, and from these data, determined the growth energy and its mathematical relation to the heart's age.

But what was more important in this paper was the "specific growth rate," together with the relationship between tissues' mass and age. Medawar thought that the specific growth rate, which was defined as the rate of change of mass divided by the current mass, was in direct proportion to the growth energy. From this idea and an equation based on it, he deduced the mathematical relationship between the mass of the embryonic chicken heart tissue and its age. This relation indicated that "the heart of the chicken grows *at a rate of continuous compound interest which itself declines by continuous compound interest.*" That is, while the growth of the tissue occurred exponentially through the duplication of existing cells, the rate of the duplication decreased exponentially over time. For Medawar, this was a characteristic of *senescence*, which proceeded even during embryo development.

In a broader perspective, Medawar's conclusion challenged the traditional notion of the aging process and gave support to the American embryologist Charles Minot's paradoxical statement in 1908. Based on his measurement of the growth rates of guinea pigs and other animals, Minot argued that the rate of the decline of the growth rate was the highest in the early phase of an organism's life and gradually declined in its later course (Figure 2). Since Minot regarded the decline of the growth rate as a symptom of aging, his observation led to his conclusion that aging not only occurred during early life, but also proceeded then at the highest speed.[7]

[Figure 2]

This was a fundamentally new way of approaching the phenomenon of aging. While it had been thought that humans went through the periods of "growing up" and "growing old," Minot's claim implied that such a distinction might not be meaningful in the scientific understanding of senescence. Aging proceeded even in the earliest stages of life. In 1941, Medawar cited this idea of Minot and argued that his tissue culture experiment supported it. The phenomenon of senescence was no longer limited to the later portions of life, because growth always accompanied senile changes. Moreover, his calculation using the specific growth rate indicated that the "specific acceleration of growth d/dt (dw/Wdt), while always negative, rises progressively to zero during the course of life."[8] In mathematical terms, this result vindicated Minot's claim that "organisms age fastest when they are young."

Another paper published in 1944, titled "The Shape of the Human Being as a Function of Time," shows how Medawar tried to describe age change—whether it meant growth or senescence—in mathematical terms. While his previous works concerned only the cell's growth

and aging, this article dealt with those of the whole human being, particularly the change of the relative proportion of its parts with development. Citing the books of Thompson and Huxley whose methodology Medawar adopted in the paper, he suggested a mathematical way to describe the growth of a man in accordance with his age. Using a picture showing his growth process only as the changing bodily proportion without altering the actual height (Figure 3), he traced the distance of four portions of the body (the fork, navel, nipples, and chin) from the base-line in mathematical terms using a function of time.

[Figure 3]

According to his equation, if two variables—time and the initial distance of a body part from the base-line—were known, it was possible to predict the relative location of the part within the body at that time. Medawar thought that by creating this equation he succeeded in describing each part's growth "as a single process of continuous deformation in time." Moreover, a further analysis of the developmental process and the equation describing it revealed that "the rate of change of shape of the human being falls off progressively in time from the 5th month of foetal life to maturity."[9] As he learned from his tissue culture experiment, growth and senescence occurred simultaneously in early life.

Starting Tissue Transplantation

Medawar's deep scientific concern on growth and aging could also be seen in a different project related to a more urgent problem. As is well known, Medawar came to join medical research program after the beginning of World War II along with many other young scientists who were requested by the government to participate in war-related research. Even though his works in

these programs differed from his previous study, his original perspectives and methodologies could still be seen.

Medawar's first wartime medical project was his research on the restoration of severed peripheral nerves. He simultaneously investigated other related issues, such as the effects and toxicity of sulfonamide drugs and the proper way of using fixatives for the treatment of burned skin. But the most important job for him at the time was research on homograft transplantation pursued with Thomas Gibson and Leonard Colebrook at the Glasgow Royal Infirmary. In fact, the safest way of skin transplantation for burned patients was to use their own skin from unharmed body parts. Yet the use of skin homograft—a piece of skin from an unrelated individual of the same species—was attempted in various hospitals, because many patients did not have enough of their own skin to cover their damaged surface. This attempt, however, invariably led to unsatisfactory consequences. As many surgeons had already known, tissues from unrelated people could not be successfully transferred except for some special cases such as corneal transplantation.[10] Although transplantation between monozygotic twins was an acceptable alternative in this state, most people did not have such a twin brother or sister. Yet homograft transplantation brought forth many intriguing academic and clinical questions, and Medawar became interested in the issues after his work at Glasgow. Indeed, he received a research grant from the Medical Research Council to tackle various topics regarding homograft problems, such as the biological nature of rejection response, the relevance of skin dosage to transplantation, and the influence of age upon the length of time of tissue survival.[11]

Like his studies of tissue culture and growth, Medawar's way of approaching these topics reveals his persistent interest in the changing features of the living organism, especially the phenomenon of decline. In most of his transplantation experiments, he traced the declining number of skin patches on an animal's body rather than merely observing the final outcome of

rejection response. Medawar hoped to approach the homograft rejection through its dynamics, not statics. In particular, he attempted to infer the "tempo" of homografts' breakdown from the changing number of surviving skin patches. In one of these experiments, he used four groups of rabbits (Figure 4).

[Figure 4]

The first was the group that received "lower-dosage" homografts from different rabbits, whereas the second was that which bore "high-dosage."[12] The third and fourth groups were those which experienced grafting of the same foreign tissues twice. Their difference was that while the third group received the second-set homograft at a body part different from the place where the first skin patch was transplanted the fourth had the second-set homograft attached to the very place where the first from the same donor was attached. He arrived at three conclusions from this experiment. First, the homograft rejection by the host was a systemic response involving its whole body rather than a local cellular response, as the relatively small difference between the third and fourth groups indicated. If it had been a local response, a much faster process should have been observed in the fourth group. Second, as several researchers had already pointed out, the nature of this rejection response was actively acquired immunity. This was obvious, since the second-set homografts in the third and fourth groups were broken down more rapidly than the first-sets in the first and second groups. After the first-set homograft was broken down, the rabbit acquired stronger immunity against the same kind of tissues. Third, the amount of grafted tissue had something to do with the pattern of rejection, as could be seen in the difference between the first and second groups. But what was the precise nature of this difference? To answer this question, Medawar used C. I. Bliss' statistical method of expressing "the percentages of graft

mortality as areas of the normal curve of error in terms of the normal deviate." With this method, Medawar was able to calculate the "probit mortality," which, to put it simply, is the probability that a randomly chosen skin homograft would be dead by a specific date. By comparing the rate of the increase of the probit mortality of the first and second groups, Medawar concluded that "the *tempo* at which breakdown proceeds, once the process has started, is the same for both: the difference between them lies in the length of the latent period which must pass before the homograft reaction becomes effective." The amount of skin tissues influenced only the brief period before the actual rejection process.

Medawar studied another phenomenon related to the living organism's changes over time—how the *age* of an organism influenced the regeneration of its peripheral nerves and the result of tissue transplantation. He studied the rate of regeneration of rabbits' severed peripheral nerves under varying conditions, finding that young rabbits of one month old did not differ from adult rabbits in the rate of the advancement of the axon tip of a severed nerve cell, whereas the length of time required for the functional completion and the "scar delays"—the time for a severed nerve fiber to retrogress before growing forward—were shorter in younger rabbits. He also studied how the age of skin donors and recipients influenced the outcome of tissue transplantation. As we will see, this research was a crucial early work that formed a starting point of his later studies of immune tolerance. However, this experiment itself did not seem to produce any new result that could interest Medawar. He found that young rabbits aged between 2½ and 4½ weeks old did not show any difference from adult rabbits in terms of homograft rejection. This result did not mean, however, that age was irrelevant in tissue transplantation. It simply implied that "the power of resistance to skin homografts is fully developed in rabbits ranging between 2½ and 4½ weeks in age."[13]

Embryogenesis, Individuality, and the Relations of Biological Changes

When, then, was the critical period in an organism's life, during which "the power of resistance to skin homografts" was formed? Medawar suspected that the embryo developmental period was the phase when the capacity to resist foreign graft was formed. He was well aware of the early experiments by James Murphy at the Rockefeller Institute and others' works which revealed that embryonic organisms did not respond to extrinsic agents even though they ultimately rejected them after growth. Something must occur during developmental periods, and it was necessary to study the periods further to understand the nature of the changes occurring in embryogenesis and the factors making the young organism accept extrinsic agents without resistance.

For Medawar, the embryo development was significant for other reasons as well. It was related to various biological problems in which he was interested. As I have shown, his early tissue culture experiments revealed the progress of senescence during embryogenesis. It was also significant that the study of embryogenesis was a way to appreciate the repair process after injury, because the two processes—embryogenesis and tissue regeneration—resembled each other very closely. Since both entailed rapid cell proliferation in accordance with the shape of the body, the study of embryo growth was expected to produce results that could help his wartime projects on the regeneration of tissues.[14] Another work highlighting the significance of embryo development was the project of Rupert Billingham, a student of Medawar at Oxford. In his dissertation, he discussed how a dark skin patch transplanted into a white skin area blackened the neighboring cells. Billingham, along with Medawar, interpreted this phenomenon as an irreversible transformation of cellular traits through the migration of color-determining hereditary cytoplasmic materials from dark to white cells.[15] This interpretation was significant at that time, because it could be considered a case of cellular heredity that did not follow the Mendelian laws concerning the nuclear genes. As historian Jan Sapp has shown, several scientists in the early

twentieth century claimed that cytoplasmic inheritance explained cell differentiation during embryogenesis, when the identical nuclear gene sets in all somatic cells did not appear to control the creation of distinct cell types.[16] In this situation, Billingham and Medawar's work seemed to show another case of non-Mendelian heredity relevant to embryogenesis, although their study did not directly deal with developmental phases.

Medawar's notion of immunological "individuality" also had a significant bearing on embryogenesis. The fact that most adult animals could not accept others' tissues due to their immunological barrier meant that each organism maintained a kind of "individuality." In fact, similar ideas—including Frank Macfarlane Burnet's concept of "self"—had already been proposed by several scientists, and it is probable that Medawar was influenced by one of them.[17] His first statement on immunological individuality during his lecture in 1946 revealed the formation of his perspective amid these earlier conceptions. According to him, the homograft rejection phenomenon and the problem of blood group incompatibility were two classical examples of the consequence of this individuality. They obviously indicated that individuality had a genetic basis, since it was well-known that the blood groups were genetically determined and that homograft rejection phenomena did not occur among highly inbred animals. But he stressed that the formation of immunological identity depended upon developmental processes together with genes. According to him, "Individual differentiation or *self-specificity* develops," as could be seen from the fact that "the chick, before the eighteenth day of incubation, is almost indiscriminately hospitable" to extrinsic agents.[18]

Medawar argued that immunological individuality had an evolutionary as well as embryological dimension. He wrote that the rejection response toward a different individual's tissue was a byproduct of evolution, during which animals developed mechanisms of protecting themselves against invading microbes. While such mechanisms successfully increased the rate of

survival of the individual and was thus selected during evolution, it came to frustrate surgeons' efforts to transplant homograft.

Remarkably, Medawar thought that there was a connection between these evolutionary and embryological dimensions of immunological identity construction. He wrote that "lower" animals in the evolutionary scale did not reject homografts just as "higher" organisms in their embryonic and fetal periods failed to resist extrinsic agents. According to him, "the rule that skin cannot be transplanted between individuals of the same species is known to be true only of higher vertebrates—from adult frogs and upwards." This implied that "individuality" or "self-specificity" was something that developed over time during both embryogenesis and evolution. In a language reminiscent of the old recapitulation theory of the nineteenth century— which postulated that an organism's embryogenesis "recapitulated" its evolutionary history—he thus argued, "As self-specificity develops [during embryogenesis], so also it evolves."

This statement showed that Medawar implicitly assumed the hidden interrelatedness of all kinds of biological changes. Just as the relationship between aging and growth became manifest through their simultaneous occurrence in early life, the correlation between growth and evolution was observed by the former's recapitulation of the latter. Since the recapitulation theory was generally discredited by the scientific community in the mid-twentieth century, Medawar's use of this theory in his study reveals his conceptual standpoint very well. In 1951, he also published an article on the relationship between evolution and embryogenesis. Through his observation, he argued that *Amphioxus* (lancelets) and the ascidian (sea squirts) were very close in the evolutionary pedigree because they shared significant portions of the developmental pathway.[19] The overlapping growth process of the two species meant that they shared their evolutionary history as well.

Evolutionary Theory of Aging and Time-Chimeras

But Medawar, who was sensitive to the new trends in contemporary biology, did not rely on the recapitulation theory in his other works. Rather, he tried to use the new evolutionary biology created through the Modern Synthesis. As I have written, Medawar knew many distinguished British evolutionary scientists through his education at Oxford and his professional networks. From them, he absorbed the newly established notion that evolution was contingent upon random genetic mutation and natural selection within an environment where an organism happened to live.

Medawar's evolutionary theory of aging published in 1946 was heavily indebted to the novel evolutionary theory and its contributors. His archived manuscripts show that he employed the ideas of Fisher, Ford, Huxley, Haldane, Lotka, and George Simpson in developing his theory.[20] Using these resources, Medawar initially postulated a hypothetical group of animals that began reproduction immediately after birth and died only of predation and natural disasters rather than through aging. Since the force of natural selection upon the group gradually weakened over time through the decline of the number of individuals due to accidents and predation (Figure 5), the time for the expression of the genes that could not confer selective advantages tended to shift toward later life. In contrast, the genes that could enhance the chance of survival would be expressed in earlier phases of life through natural selection.

[Figure 5]

This changing pattern eventually constructed a certain temporal pattern of gene expression. The genes for development, which were critical for proper biological functions, would move toward earlier portions of lifespan, while the genes responsible for the symptoms of senescence—such as

wrinkled skin, chronic diseases, and menopause—would shift toward later stages. Yet these aging genes would not usually have an opportunity of expression in wild nature, because most individuals would die before experiencing any senile symptoms. Through civilization, however, humans and their domestic animals with better housing, food, and healthcare could live long enough to see the expression of the genes of old age.

Medawar's evolutionary theory of aging clearly illuminates his view of the connections among growth, aging, and evolution. In his theoretical scheme, the hypothetical group did not have a clear distinction between development and senescence, because the group reproduced itself immediately after birth. Each member in the group underwent the concurrent processes of growth, reproduction, and senile changes right after its creation. Moreover, these processes were equally subject to the force of natural selection, even though the force would eventually become weaker in later periods. In this scheme, the distinction between growth and aging were just a byproduct of the evolutionary change.

In his 1946 paper, Medawar proposed an experiment that could reveal the nature of the changes brought forth by this process. To him, transplanting tissues between young and old organisms was a useful tool for unraveling their physiological differences engendered through aging. This experiment could answer many questions like the following.

How, then, does tissue transplanted from a baby animal to a dotard develop in its "old" environment? Does it rapidly mature and age, or does it remain like a new patch on an old pair of socks? Conversely, what is the fate of tissue grafted from old animals into youngsters?[21]

The "time-chimera" was the term he coined to designate these artificial organisms made through the surgical combination of two body parts of distinct ages.

Tolerance, Decline, and the Null Period

But Medawar did not make such a "time-chimera" to study aging. In fact, he did not pursue any further research on senescence for the remainder of his life, even though he occasionally participated in the meetings of the British Society for Research on Ageing and the Nuffield Gerontological Research Fellowship Committee. Whereas his theory played an important role in the later developments of evolutionary research on senescence, he himself did not continue his original work.[22] Interestingly, the creation of time-chimeras crucially contributed to an apparently unrelated work in immunology, as we will see.

It may be possible to find a reason why Medawar did not continue to study senescence. As I have written elsewhere, aging hardly attracted British scientists' attention during the mid-twentieth century due to the weak social and financial support.[23] In contrast, tissue transplantation emerged as a highly fascinating subject in the same period with its relevance to various biomedical problems. While staying at Birmingham from 1947 to 1951, Medawar, together with his former student Billingham, spent most of his time and energy in tissue transplantation, which led him to explore a large number of intriguing study subjects. After moving to University College London, Medawar accounted for this broader applicability of tissue transplantation in a review paper. According to him, the transplantation of skin was "used for the study of a wide variety of biological problems," such as the nature of pigmentation, the effect of freezing and drying upon the viability of tissues, the immunological effect of cortisone, and the role of different skin layers in engendering tumors under the influence of certain chemicals.[24] Medawar and his team were funded by several patrons for implementing these projects, such as the Medical Research Council, the Department of Plastic Surgery at Oxford, and the British

Empire Cancer Campaign. The scope of tissue transplantation research, which had begun as a wartime project, was thus substantially expanded.

In 1952, Medawar discussed how such varied uses of tissue transplantation could inform the problem of immunological individuality. In particular, he described an interesting medico-legal case in which tissue transplantation was used as a critical means to settle down a dispute about a man's monozygotic twin sons. One of his twin children, who had been given to a wrong person due to a mistake after birth, found his biological parents and twin brother through tissue transplantation. The twins could exchange their skin without having any immunological reaction. Medawar, however, did not claim that immunological individuality was genetically determined as this episode might indicate. It was "a property that comes into being during the course of development."[25] Admittedly, he had already claimed in 1946 that individuality was formed during development and evolution. Yet his argument in 1952 came to have a different twist with his research at Staffordshire as well as his reading and citing of the American scientist Ray Owen's 1945 paper.

In his Wisconsin laboratory, Owen conducted an extensive blood testing of cows that had twin brother or sister coming from a distinct egg. Knowing that the "freemartin," the infertile young female cow, was made through connected blood vessels between dizygotic twin calves during embryogenesis and fetal phase, he argued that the shared blood circulation during these periods also explained why many dizygotic twin calves had identical blood types.[26] This was interesting with respect to immunology, because it was known that two genetically distinct cows could hardly have the same blood type due to a large number of different kinds of blood antigens in cattle. Based on this fact and other evidence, Owen concluded that the dizygotic twins' identical types of blood cells descended from the embryonic cells that had been exchanged between the two fetuses in a uterus. While they were in the mother's uterus, the cattle learned not

to respond to the blood cells of distinct genetic constitution coming from their dizygotic twin brother or sister.

Although Medawar did not state explicitly in his 1952 paper, this observation by Owen implied a considerable change in the concept of immunological individuality. While the individuality of 1946 was something that merely grew during developmental periods, it was now what was actively *defined* in these stages. Whereas Medawar in 1946 had thought that all genetically extrinsic entities would ultimately be rejected by an animal which had retained them during growth periods, he found in 1952 that such entities could be completely integrated into the adult host that could readjust the boundary of its individuality through development. In this process, it was difficult to find any clear roles assigned to nuclear genes.

There were other publications with a related implication. Perhaps the most important work for Medawar was the second edition of *Production of Antibodies* (1949) written by Burnet and his colleague Frank Fenner. In this book, the authors argued that immunological "self" was defined during embryogenesis and that any entities that had entered the host body at that time would be permanently tolerated as a part of the host's "self." Indeed, as several historians have pointed out, this argument was partially indebted to Owen's article, and it is possible that Medawar, too, came to know of Owen's research through Burnet.[27] After writing this book, Burnet's team conducted an experiment on immunological tolerance using viruses and red blood cells, although they did not obtain a result that fit with his theoretical expectation.[28] Another interesting work was published in 1952 by Jack Cannon and William Longmire at the University of California.[29] They arrived at a more successful result using chickens' skin homograft rather than employing viruses and red blood cells as Burnet did. In this experiment, Cannon and Longmire found that the age of the chicken was closely related to the length of homografts' survival time in a new host. While about thirteen percent of the chickens that had received a

homograft patch right after hatching retained it by the eighth week, only one percent among those that had acquired a homograft from the fourth to the sixth day after birth still kept it in the same week. The younger the host organism was at the time of surgery, the longer the extrinsic transplant could survive on the skin. An older paper published in the 1920s also showed an interesting result. In 1929, C. H. Danforth and Frances Foster at Stanford University argued that twenty-nine among one hundred and eighty-eight chickens that had received a graft from a different individual "on the day of hatching or within a few days thereafter" could retain it almost indefinitely.[30] Since twelve among these twenty-nine chickens had obtained a graft from the same strain, the number of surviving homografts from completely unrelated individuals was seventeen, which was still quite impressive.

In the early 1950s, Medawar was aware of Burnet's book and article, but there is no evidence that he read the papers by Cannon, Longmire, Danforth, and Foster. Cannon and Longmire's article came out in 1952 when Medawar was conducting his landmark research that would be published in 1953. Since Medawar's archival collection does not have any correspondence with them, it is unlikely that they exerted any influence upon Medawar. In contrast, Danforth and Foster's older experiments had been performed in the 1920s, and it is thus possible that Medawar had known of it. Yet Medawar did not cite their works in his crucial papers on tolerance published during the early 1950s. Indeed, the aim and design of Medawar's experiments were different from theirs. While Danforth and Foster merely tried to show that tissues could survive for a long time in a foreign host when they were transplanted onto it in its early age, Medawar aimed at investigating whether the host could *remember* the structure and pattern of the molecules and cells—some of which could have a foreign origin—within its body during its early developmental phase. In this sense, his aim pertained to a larger question on how

an organism's immunological boundary could be defined by recognizing its extrinsic as well as intrinsic constituents.

The first study guided by this aim was Medawar and his colleagues' experiments using dizygotic twin calves conducted at Cold Norton Farm in Staffordshire. According to Medawar, this research was initiated when Hugh Donald, head of the Agricultural Research Council's Animal Breeding and Genetics Research Organization, asked him how he could distinguish monozygotic and dizygotic twins.[31] While it was often believed that skin transplantation would easily reveal their difference, his team obtained a distinct result. They found that that "all two-egg twins show some degree of tolerance to homografts transplanted from one to the other," and that "thirty-six out of 42 cattle of two-egg twin birth were found to be completely tolerant to skin homograft."[32] Tissue transplantation could hardly be used for distinguishing identical from non-identical twin calves.

This result not only corroborated Owen's blood testing study but also deepened its immunological implication in at least two respects. First, Medawar's experiment revealed that the actual scope of the phenomenon that Owen showed was broader than his paper implied. It indicated that the calves might be able to remember the whole body's pattern of their dizygotic twin brother or sister as a part of their own constitution. Indeed, while the result of the blood testing clearly implied that embryonic blood cells were shared between dizygotic twins through connected blood vessels, it was still not immediately obvious that skin cells' precursors also migrated simultaneously through the same route. Since the experiment showed that this was indeed the case, it could then be further construed that the skin cell was just one of those that had been shared in developmental phases. Other types of cells must have been exchanged as well, and perhaps all kinds of cells might have been shared and remembered by the dizygotic twins. Second, Medawar's experiment revealed more complex aspects of the tolerance phenomenon

than Owen's. It was found that "the degree of tolerance" among the calves was "widely variable." While complete tolerance toward their dizygotic twin's skin was found in the thirty-six cattle among the forty-two, the six individuals also showed varied degrees of tolerance, measured by the number of days during which the skin patch survived on the host body. Moreover, it was found that the "grafts from one twin to the other may be tolerated although grafts of the reciprocal transplantation are eventually destroyed." These findings indicated that tolerance was a highly complex phenomenon, and it was necessary for Medawar to study the varied dimensions of the problem systematically using more standardized laboratory organisms, such as the mouse. In addition, a highly meaningful result would be gained, if experimenters could actually insert a group of foreign cells into an embryonic animal instead of just supposing the occurrence of this process through connected fetal blood vessels as Owen did.

In designing his new study, Medawar returned to the issue of the age of experimental organisms. If a skin patch was grafted to an unrelated adult animal, it was invariably rejected due to the host's immune response. But the above experiments using cows and Owen's observation implied that an extraneous entity could be tolerated if the host organism was in its embryonic or fetal stage. In fact, the papers by Danforth, Foster, Cannon, and Longmire revealed that the host could be slightly older, since some newly hatched chickens also accepted external tissues. What, then, happened during these early periods of an animal? Unlike Burnet, Medawar was not interested in making a detailed theory on the mechanism of the immune system formation during growth phases. Indeed, he read Burnet's *Production of Antibodies*, but did not attempt to discuss the mechanism proposed by him. Medawar simply mentioned that there might be "the more profound theoretical reasons" as Burnet wrote.[33] To Medawar, what was important was to analyze observable phenomena rather than to postulate hypothetical molecular mechanisms, and, in this respect, his own previous research was enough as a guide to further investigation. As I

have written, he already found in 1945 that young rabbits aged between 2½ and 4½ weeks old did not differ from older rabbits in terms of immune response to homografts. From this finding, he concluded that the ability to recognize foreign materials had already developed before the rabbit reached 2½ weeks of age. This conclusion indicated that an earlier phase of an organism's life, including embryonic period, held a key to the puzzle of immunity. It is also quite remarkable that Medawar was thinking about "time-chimeras" again. While completing his experiment on the effect of freezing on the viability of cells in 1952, he stated that "one possible approach to the problem of the causes of senescence is to graft tissue from a young animal to its own self when it has grown older."[34] It was possible to detach tissues from a young animal and to store them in a freezer until the organism became older. Then, the frozen "young" tissues could be thawed and regrafted to their original host to investigate the process of aging.

Medawar, Billingham, and Leslie Brent's well-known research in 1953 started from making this time-chimera, although it was a genetic chimera as well. He injected a "suspension of adult tissue cells" of an A-line mouse into six fetuses within the uterus of a CBA mouse.[35] These chimeras between the young CBA and the older A-line mouse grew well except one which died before birth. After these remaining five mice became eight weeks old, they received A-line skin grafts. Remarkably, two among the five mice showed complete tolerance toward these grafts, while other two mice quickly rejected them. The remaining one "underwent a long-drawn-out 'spontaneous' involution" which resulted in a "complete breakdown shortly after the 91st day" after transplantation. Medawar's team also found that tolerance was highly specific by observing that a third strain's tissues grafted upon the chimeras were rapidly rejected. Moreover, the two chimeras could lose their tolerance toward A-line tissues if "fragments of lymph node from normal CBA mice which had been actively immunized against A-line skin" were inserted into

them. The phenomenon implied that tolerance depended on the lymph node that learned not to respond to the cells belonging to a specific strain.

Medawar's team made time-chimeras for inducing chicken's tolerance as well. But these time-chimeras were of a different sort. Whereas adult cells were inoculated into a mouse embryo as foreign entities, embryonic cells whose age was the same as that of the host were used for the same purpose during the chicken experiment. In this study, the time-chimera was made in a different stage. The donor, after being used as a source of foreign cells, had to die and its tissues were stored in a frozen state until the host finished its embryo period. Then this host became a genuine time-chimera by receiving the donor's tissues that were thawed from their frozen state. Why, then, was this procedure necessary? Citing their previous paper on freezing and time-chimeras, the authors wrote that since chicken strains were not genetically standardized it was impossible to use a distinct individual of the same strain as the donor of the second set-graft.[36] The only way to test tolerance in this state was to use the same individual's cells frozen until the hatching of the host. Despite this different procedure, the study of chickens' tolerance produced the same result as the mouse experiment. Two tolerant chickens were created among the seven that had received foreign cells during embryogenesis.

This observation illuminated the significance of growth phases, during which the scope of the specificity of tolerance seemed to be determined. He wrote,

The effect of this first presentation of foreign tissue in adult life is to confer 'immunity', that is, to increase the host's resistance to grafts….But if the first presentation of foreign cells takes place in foetal life, it has just the opposite effect: resistance to a graft transplanted on some later occasion, so far from being heightened, is abolished or at least reduced. Over some period of its early life, therefore, the pattern of the host's response to foreign tissue cells is turned completely

upside down. In mice….this inversion takes place in the neighborhood of birth, for there is a certain 'null' period thereabouts when the inoculation of foreign tissue confers neither tolerance nor heightened resistance.[37]

Medawar and his team conducted an experiment to confirm the existence of this "null period" using ninety-six newly born mice. When these very young mice were inoculated with foreign cells and were later challenged with the tissues from the same donor after they became adults, only nine among them showed tolerance towards the extrinsic tissue in any degree. A large portion of the remaining mice showed neither tolerance nor immunity in terms of the number of days of tissue survival. According to Medawar, this result implied that the "null period" did exist as a stage in an animal's life course and that age was a key factor in the growth of immunological identity and tolerance.

But the meaning of this null period was not yet clearly articulated in the 1953 paper. What did it mean that a mouse showed neither immunity nor tolerance? Medawar clarified this question through his extensive experiments published in 1956.[38] In this work, he readopted the probit transformation techniques to calculate the median survival time (MST) of homografts. During the initial set of experiments, the MST was calculated from the time of the death of a large number of foreign tissues attached on animals' body. It was then set as a standard through which he determined whether the host's response was immunity or tolerance in subsequent transplantation experiments. If the MST was shorter than the time of the survival of the tissues grafted upon an animal that had previously received foreign cells, it could then be stated that the tissues were being tolerated (Figure 6).

[Figure 6]

In contrast, if the MST was longer, the tissues were provoking immune response. It was also possible that the two time spans were approximately the same in length. In that case, it should be concluded that the foreign cells were inoculated during the null period and the subsequent tissue grafts induced neither tolerance nor immunity. The data from his experiments showed that these three phenomena were observed in a highly ordered manner over an animal's lifespan. The animals' body showed the gradual shift from the phase of tolerance to that of immunity via the null period. In fact, this shifting of phases was the reason why he called the phenomenon he studied "actively acquired tolerance," which was "the exact inverse of" actively acquired immunity.

In 1956, Medawar tried to provide a more detailed basis of this age-dependence of tolerance. He inoculated two groups of mouse fetuses before and after the eighteenth day of conception with the same foreign cells. While a slightly higher percentage of mice with initial tolerance were found in the group that received the foreign cells at a later stage, the group that was inoculated before the eighteenth day was eventually revealed to have a larger proportion of individuals with long-term tolerance toward tissues "in an entirely normal condition for upwards of 50 days." Considering the difficulty of inoculation into a very young fetus before the eighteenth day of conception, these results clearly showed that it was easier to induce tolerance to external agents in younger organisms. Citing Cannon and Longmire's article as well, Medawar and his colleagues thus claimed that these experiments revealed "the progressive decay, with increasing age, of the power of an antigenic stimulus to confer tolerance."[39] The ability to develop tolerance would "decay" until the null period, and then the ability itself was converted to that of immunity, which was a kind of "negative tolerance."

This idea of Medawar will remind many readers of his reference to Minot's thesis in his 1941 paper on tissue culture. While Medawar's research subject in 1956 was very different from what he studied in 1941, his view of aging as a phenomenon that proceeded even in the earliest part of life could still be seen in the above remark. In a deeper sense, Medawar found one of his favorable research subjects, namely, a process that entailed both growth and senescence. Like cells' proliferative capacity, the ability to incorporate extrinsic agents underwent a rapid decline during the developmental period.

Medawar, Burnet, and Dynamics of Life

The fact that Medawar shared the Nobel Prize with Burnet due to his experimental confirmation of Burnet's theory may lead some people to think that Medawar's work merely resulted from his efforts to test Burnet's idea. Elsewhere, I have tried to show why this view is misleading, although Medawar was certainly inspired by Burnet in some degree.[40] First, the archival records show that the two scholars hardly exchanged correspondence regarding their study subjects during the 1940s and early 1950s. They were mostly worked in their own research environment with little mutual communication. The fact that Medawar and Burnet expressed their wish to share the Nobel Prize with different people may also indicate their substantial difference. Burnet hoped a joint award with Niels Jerne who proposed the "natural selection theory of antibody," while Medawar wished that his collaborators, Billingham and Brent, should have been awarded along with him.[41] Second, Medawar and Burnet approached the immunological problems in highly different ways. To Burnet, who was trained as a virologist and microbiologist, tolerance was the most common outcome of microbe-animal interaction. Indeed, several microbiologists after Louis Pasteur and Robert Koch claimed that infectious disease and death were merely unusual consequences of microbial infection resulting from disturbed natural balance. To these

scholars, evolutionary forces tended to maintain peaceful coexistence among species including humans and various microbes. But Medawar, who was not trained in microbiology, was not aware of these recent discussions and studies. Following more traditional standpoints, he took it for granted that humans' contact with bacteria and viruses led to infectious disease and other health problems. This view was combined with his tissue transplantation experiment which showed that most cases of transplantation should fail. To him, microbial infection and tissue transplantation were similar because both involved pathogenic intrusion of extraneous entities into an animal's body. According to this perspective, tolerance—which for Burnet was a natural outcome of microbe-animal interaction—was an extraordinary phenomenon that had to be forged only through sophisticated experimental manipulation.

Despite this difference, both Medawar and Burnet had a dynamic view of life which was significant in immunology's transformation in the mid-twentieth century. Although pursued with different standpoint, their perspectives on life, together with their impact upon their discipline, reveal how important it was to study the living organism through its temporal dimensions in modern biomedicine. Ultimately, their contributions altered the direction of immunology's development from chemical studies of antigen-antibody reactions to biological investigations into living organisms and their continuously shifting physiological states.[42] As a major contributor to this significant scientific transformation, Medawar's persistent concern on decline played a critical role in his works. It was a phenomenon unique to living organisms, associated with a variety of his research subjects pertaining to biological changes, including tissue culture, the evolution of aging, and the induction of immunological tolerance.

Acknowledgment: I am very grateful for the helpful comments by the anonymous referees as well as by Sally Kohlstedt, John Eyler, and Andreas-Holger Maehle. This paper stems from the latter half of my

chapter, "Germs and Tissues: Frank Macfarlane Burnet, Peter Brian Medawar, and the Immmunological Conjucture," in Annette Barton (ed.) *Host-Pathogen Interactions: Genetics, Immunology, and Physiology* (Hauppauge, New York: Nova Science Publishers, in press).

---

[1] Medawar, Peter Brian (1952) *An Unsolved Problem of Biology: An Inaugural Lecture Delivered at University College London, 6 December 1951* (London: Lewis), pp. 3-4. At that time, Medawar was certainly aware of his contemporary political discourse on aging. See Thane, Pat (2000) *Old Age in English History: Past Experiences, Present Issues* (Oxford: Oxford University Press), pp. 336-342; Soloway, Richard A. (1990) *Demography and Degeneration: Eugenics and the Declining Birthrate in Twentieth Century Britain* (Chapel Hill: University of North Carolina Press), pp. 226-258.

[2] The significance and meaning of the dynamic perspectives in biological and biomedical research has been extensively studied. See, for example, Beurton, Peter J., Falk, Raphael, and Rheinberger, Hans-Jörg (eds.) (2000) *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge: Cambridge University Press); Oyama, Susan, Griffiths, Paul E., and Gray, Russell D. (eds.) (2001) *Cycles of Contingency: Developmental Systems and Evolution* (Cambridge: MIT Press); Keller, Evelyn Fox (2002) *Making Sense of Life* (Cambridge, Mass.: Harvard University Press).

[3] Medawar regularly corresponded with Thompson who occasionally commented on Medawar's papers before their publication. Deeply appreciating this help and the insights he gained from Thompson's book, Medawar wrote a chapter in *Essays on Growth and Form Presented to D'Arcy Wentworth Thompson* (1945), edited by Wilfred Le Gros Clark and Medawar himself. See Thompson to Medawar, 21 February 1942, PBM, Box 2, Folder A.24.

[4] Morrell, Jack (1997) *Science at Oxford, 1914-1939: Transforming an Arts University* (Oxford: Oxford University Press), pp. 273-286; Medawar, Peter Brian (1944) "Oxford Zoology," *Biology* Autumn Term, pp. 1-4. Medawar also closely interacted with Fisher, who often read and commented on Medawar's papers and even offered his mice for his junior colleague's experiment. One of these papers was transmitted to *The Proceedings of the Royal Society* through Fisher's recommendation. See Fisher to Medawar, 25 March 1943, RAF; Medawar to Fisher, 9 September 1943, RAF. This article Fisher transmitted to the Royal Society is Medawar, Peter Brian (1944) "The Shape of the Human Being as a Function of Time," *Proceedings of the Royal Society of London: Series B. Biological Sciences* 132, pp. 133-141.

[5] Medawar, Peter Brian (1937) "A Factor Inhibiting the Growth of Mesenchyme," *Quarterly Journal of Experimental Physiology* 27, pp. 156-158.

[6] Medawar, Peter Brian (1940) "The Growth, Growth Energy, and Ageing of the Chicken's Heart," *Proceedings of the Royal Society of London: Series B. Biological Sciences* 129, p. 337.

[7] Minot, Charles S. (1908) *The Problem of Age, Growth, and Death* (New York: Putnam), p. 5

[8] Medawar, Peter Brian (1941) "The 'Laws' of Biological Growth," *Nature* 148, p. 773. In this sentence, "*W*" means mass and "*t*" means time. He used differential calculus to acquire specific acceleration of growth from specific growth rate.

[9] Medawar, "The Shape of the Human Being," p. 133.

[10] Silverstein, Arthur (2009) *A History of Immunology*, 2nd ed. (Amsterdam, Elsevier), pp. 232-233.

[11] F. J. C. Herald to Medawar, 19 January 1943, NAUK, FD 1/6959.

[12] Medawar, Peter Brian (1944) "The Behavior and Fate of Skin Autografts and Skin Homografts in Rabbits," *Journal of Anatomy* 78, p. 186.

[13] Medawar, Peter Brian (1945) "A Second Study of the Behaviour and Fate of Skin Homografts in Rabbits," *Journal of Anatomy* 79, p. 174.

[14] Medawar, Peter Brian (1945) "Biological Aspects of the Repair Process," *British Medical Bulletin* 3, pp. 70-73.

[15] Billingham, Rupert E. and Medawar, Peter Brian (1947) "The 'Cytogenetics' of Black and White Guinea Pig Skin," *Nature* 159, pp. 115-117.

[16] Sapp, Jan (1987) *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press), p. 103.

[17] About historical studies of immunological ideas on "individuality" or "self," see Tauber, Alfred I. (1994) *The immune Self: Theory or Metaphor?* (Cambridge: Cambridge University Press); Löwy, Ilana (2003) "On Guinea Pigs, Dogs and Men: Anaphylaxis and the Study of Biological Individuality, 1902-1939," *Studies in History and Philosophy of Biological and Biomedical Sciences* 34, pp. 399-423; Kroker, Kenton (1999) "Immunity and Its Other: The Anaphylactic Selves of Charles Richet," *Studies in History and Philosophy of Biological and Biomedical Sciences* 30, pp. 273-296.

[18] Medawar, Peter Brian (1946) "The Theory of the Differences between Individuals," *The Substance of a Lecture Given to the Oxford Summer School of the British Social Hygiene Council*, p. 103, PBM, Box 36, Folder E.23.

[19] Medawar, Peter Brian (1951) "Asymmetry of Larval Amphioxus," *Nature* 167, pp. 852-853.

[20] Medawar, Peter Brian, undated but written in the 1940s, "Demography: notes," PBM, Box 17, Folder C.26; "Special Case," PBM, Box 17, Folder C.23; "Population with Constant Force of Mortality," PBM,

Box 17, Folder C.23; "Natural Examples," PBM, Box 17, Folder C.23. For a more thorough discussion on this issue, see Park, Hyung Wook (2009) "Refiguring Old Age: Shaping Scientific Research on Senescence, 1900-1960" (Ph.D. Thesis: University of Minnesota), pp. 146-163.

[21] Medawar, Peter Brian (1946) "Old Age and Natural Death," *The Modern Quarterly* 2, p. 48.

[22] Charlesworth, Brian (2000) "Fisher, Medawar, Hamilton, and the Evolution of Aging," *Genetics* 156, pp. 927-931; Gavrilov, Leonid A. and Gavrilova, Natalia S. (2002) "Evolutionary Theories of Aging and Longevity," *The Scientific World Journal* 2, pp. 339-356; Holliday, Robin (1996) "The Evolution of Human Longevity," *Perspectives in Biology and Medicine* 40, pp. 100-107; Rose, M. R. and Graves, J. L. (1989) "What Evolutionary Biology Can Do for Gerontology," *Journal of Gerontology: Biological Sciences* 44, pp. B27-B29.

[23] Park, "Refiguring Old Age," chapter 4.

[24] Billingham Rupert E. and Medawar, Peter Brian (1951) "The Technique of Free Skin Grafting in Mammals," *Journal of Experimental Biology* 28, p. 385.

[25] Medawar, Peter Brian (1952) "A Biological Analysis of Individuality," *American Scientist* 40, p. 637.

[26] Owen, Ray D. (1945) "Immunogenetic Consequences of Vascular Anastomoses between Bovine Twins," *Science* 102, pp. 400-401. This paper was significant with regard to hematopoetic stem cell research as well. See Fagan, Melinda B. (2007) "The Search for the Hematopoietic Stem Cell: Social Interaction and Epistemic Success in Immunology," *Studies in History and Philosophy of Biological and Biomedical Sciences* 38, pp. 222-224.

[27] Burnet, Frank Macfarlane and Fenner, Frank (1949) *The Production of Antibodies*, 2nd ed. (Melbourne: Macmillan), p. 103. Tauber, Alfred I. and Podolsky, Scott H. (1994) "Frank Macfarlane Burnet and the Immune Self," *Journal of the History of Biology* 27, pp. 531-573; Silverstein, *A History of Immunology*, p. 56. My former paper analyzes this matter from a slightly different perspective. See Park, Hyung Wook (2006) "Germs, Hosts, and the Origin of Frank Macfarlane Burnet's Concept of "Self" and "Tolerance," 1936-1949," *Journal of the History of Medicine Allied Sciences* 61, pp. 492-534.

[28] Burnet, Frank Macfarlane, Stone, J. D., and Edney, M. (1950) "The Failure of Antibody Production in the Chick Embryo," *Australian Journal of Experimental Biology and Medical Science* 28, pp. 291-298.

[29] Cannon, Jack A. and Longmire, William P. (1952) "Studies of Successful Skin Homografts in the Chicken," *Annals of Surgery* 135, pp. 60-68.

[30] Danforth, C. H. and Foster, Frances (1929) "Skin Transplantation as a Means of Studying Genetic and Endocrine Factors in the Fowl," *Journal of Experimental Zoology* 52, p. 445.

[31] Medawar, Peter Brian (1986) *Memoir of a Thinking Radish: An Autobiography* (Oxford: Oxford University Press), pp. 110-111.

[32] Billingham, Rupert E., Lampkin, G. H., Medawar, Peter Brian, and Williams, H. L. (1952) "Tolerance to Homografts, Twin Diagnosis, and the Freemartin Condition in Cattle," *Heredity* 6, p. 211.

[33] Anderson, D., Billingham, Rupert E., Lampkin, G. H., and Medawar, Peter Brian (1951) "The Use of Skin Grafting to Distinguish between Monozygotic and Dizygotic Twins in Cattle," *Heredity* 5, p. 395.

[34] Billingham, Rupert E. and Medawar, Peter Brian (1952) "The Freezing, Drying and Storage of Mammalian Skin," *Journal of Experimental Biology* 29, p. 466.

[35] Billingham, Rupert E., Brent, Leslie, and Medawar, Peter Brian (1953) "'Actively Acquired Tolerance' of Foreign Cells," *Nature* 172, p. 604.

[36] Ibid., p. 605. The previous paper cited by the authors is Billingham and Medawar, "The Freezing, Drying and Storage," p. 466

[37] Billingham, Brent, and Medawar, "Actively Acquired Tolerance," p. 603.

[38] Billingham Rupert E., Brent, Leslie, and Medawar, Peter Brian (1956) "Quantitative Study on Tissue Transplantation Immunity. III. Actively Acquired Tolerance," *Philosophical Transactions of the Royal Society: Series B. Biological Sciences* 239, pp. 357-414.

[39] Ibid., p. 373.

[40] Park, Hyung Wook (2010, in press) "Germs and Tissues: Frank Macfarlane Burnet, Peter Brian Medawar, and the Immunological Conjuncture," in Barton, Annette (ed.), *Host-Pathogen Interactions: Genetics, Immunology, and Physiology* (New York: Nova Science Publishers). The fact that Burnet cited Erich Traub's papers while Medawar ignored them during the early 1950s is further illuminating. As I discussed in my book chapter, this reveals their different perspective very clearly.

[41] Sexton, Christopher (1999) *Burnet: A Life* (Oxford: Oxford University Press), p. 140; Medawar, *Memoir of a Thinking Radish*, p. 137.

[42] Tauber, *The Immune Self*, pp. 81-123; Silverstein, *A History of Immunology*, pp. 240-253; Löwy, Ilana (1992) "The Strength of Loose Concepts—Boundary Concepts, Federative Experimental Strategies and Disciplinary Growth: The Case of Immunology," *History of Science* 30, pp. 371-396. Also see Hamilton, David (1989) "Peter Medawar and Clinical Transplantation," *Immunology Letters* 21, pp. 9-13; Mazumdar, Pauline M. H. (ed.) (1989) *Immunology, 1930-1980* (Toronto: Wall & Thompson).