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Germs, Hosts, and the Origin of Frank Macfarlane Burnet’s Concept of “Self” and “Tolerance,” 1936-1949

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Abstract. In the early twentieth century, the living organism’s ability to distinguish its “self” from foreign entities such as bacteria, viruses, transplanted tissue, or transfused blood was a major problem in medical science. This article discusses how the Australian immunologist Frank Macfarlane Burnet arrived at a satisfactory explanation of this problem through his 1949 theory of “self” and “tolerance.” Burnet’s theoretical work began from his study of diverse factors affecting the conditions of the host and the germ for the occurrence of infectious diseases. Among them, the host’s age came to receive his attention as a crucial factor. This understanding was facilitated by his acceptance of cytoplasm inheritance theories, which emphasized the importance of the embryonic host’s changing conditions according to its age. Based on this idea, he claimed in 1949 that the “self” of the organism was defined during its embryogenesis. Peter B. Medawar and his colleagues’ demonstration of Burnet’s claim became the basis for awarding Burnet and Medawar the Nobel Prize in Physiology and Medicine in 1960. While previous histories have focused on Burnet’s “inductive reasoning” or “ecological perspective” to explain his conception of the theory of “self” and “tolerance,” this article finds the origin of his ideas within an important line of modern medical research engendered through the development of germ theories—the studies of the host body and its relationship with parasites. Keywords: Frank Macfarlane Burnet, self, tolerance, host, germ, age, cytoplasmic inheritance.
How can an organism distinguish its own molecules and cells from those of extrinsic origin? Numerous surgeons, physicians, and biologists have pondered this and related questions. How can a human or animal tell its own body components from that of viruses, bacteria, transplanted tissue, or transfused blood? During the nineteenth and early twentieth century, doctors and scientists realized that clear distinctions existed between humans and microbes, guinea pigs and rabbits, and humans with different blood types.¹ Indeed, transplantation surgery had already shown that it is extremely difficult to exchanges tissues permanently even between closely related individuals. These difficulties led many early twentieth century biomedical scientists, such as Leo Loeb, E. E. Tyzzer, and Clarence C. Little, to think that the nuclear gene was the ultimate basis upon which the immunological individuality was constructed.² According to them, the genetic difference between two individual organisms determined whether an organism or its parts could provoke defensive reactions within another organism’s body.

The Australian immunologist Frank Macfarlane Burnet (1899-1985) proposed in 1949 an entirely different and highly successful theory of immunological distinction that led him and the British scientist Peter Medawar (1915-1987) to share the Nobel Prize in Physiology and Medicine in 1960. Burnet conceived this idea after many years of theoretical studies, which culminated in his monograph, the second edition of The Production of Antibodies (1949). According to this text, the “self” of the host body is actively defined during its embryogenesis through complex interactions between immune cells and all the
other cells and molecules within an embryo. During this process, even foreign materials and organisms that accidentally invaded the embryonic body can be perceived as a part of the “self,” since every molecule in the embryo is recognized as a portion of the organism. Therefore, Burnet argued, bacteria, viruses, or genetically distinct cells that had entered the embryonic host could be indefinitely “tolerated” even after it became an independent organism. Medawar and his team supported this argument by their transplantation experiments, which provided the first demonstration that extrinsic tissues other than cornea could be successfully tolerated within a distinct individual. As historian Ilana Löwy has written, Burnet’s theory contributed to redefining immunology as the science of “self” and “nonself” recognition and provided a highly productive and successful “boundary concept” that linked basic scientists and practicing physicians in their investigation and treatment of diverse human illnesses such as allergy, autoimmune disease, cancer, and immune deficiency syndrome.

How could Burnet arrive at such a remarkably successful theory in 1949? Historians, philosophers, and scientists have already studied Burnet’s works. Immunologists Ian R. Mackay, Gustav Nossal, Alberto Martini, and Leslie Brent believe that Burnet arrived at his “self” and “tolerance” theory in 1949 simply by generalizing the observations made by zoologist Ray Owen and pathologist Erich Traub, who showed that viruses and foreign tissues which had been placed within an embryo were not rejected long after its developmental phases had ended. Their argument is supported by Burnet’s own retrospective remarks. In his autobiography, Burnet wrote that Owen’s and Traub’s observations played an important role in guiding his “intellectual pilgrimage” toward the discovery of immunological tolerance.

Yet Burnet’s own remarks offer an incomplete account of the actual pathway of his conceptual work. Whereas it may be true that Owen’s and Traub’s articles were important, Burnet’s and others’ accounts fail to explain why these articles, among the numerous papers
he read, attracted his attention and prompted him to develop a new theory. Indeed, many historians have warned that scientists’ autobiographical stories may not be a reliable guide for understanding past events.\textsuperscript{10} We should also notice that historians have found few scientists who used inductive generalization as the only scientific method in their theory-making, especially when the observational “data” used to construct a theory was obtained by other researchers. In Burnet’s case, we need to understand the \textit{pathway} of his conceptual development by placing it amid various influences that guided his theoretical works. In this paper, I focus on the factors that shaped Burnet’s immunological thinking including Traub’s, Owen’s, and other medical researchers’ studies as well as Burnet’s own works.

Philosopher Alfred I. Tauber and his colleagues have provided a persuasive account in this respect, by pointing to the diverse intellectual traditions in which Burnet’s predecessors and contemporaries worked. Chief among these are evolutionary, dynamic, and holistic thinking, which Burnet inherited from several scientists including the Russian zoologist Elie Metchnikoff.\textsuperscript{11} Tauber has argued that Burnet, after a complex trajectory of thinking stemmed from diverse contemporary biological theories and discoveries,\textsuperscript{12} finally arrived in 1949 at the conclusion that an organism’s “self” was dynamically defined through cellular interactions within the whole developing embryo. This conclusion, emphasizing \textit{process} and \textit{interaction}, clearly revealed Burnet’s strong commitment to dynamic and holistic philosophy.\textsuperscript{13} Owen’s and Traub’s observation was only one part of the various factors that guided Burnet’s thinking.

While generally agreeing with this explanation, I found that it misses an important aspect of Burnet’s intellectual development. Although Tauber persuasively showed Burnet’s philosophy in regard to the evolutionary ideas and other scientific issues, he did not analyze the problems in \textit{medicine} Burnet had inherited from the “Golden Age” of medical bacteriology and virology—the nature of infectious disease, its causation, and the relationship between host and parasite. Indeed, Burnet was a medical doctor who had been trained at the
University of Melbourne Medical School and the Lister Institute of Preventive Medicine. Moreover, as I will show in this essay, he was deeply interested in clinical as well as experimental problems. While it is very true that Burnet thought in terms of evolution and ecology, he was not a professional ecologist or evolutionary biologist, and his topics were always derived from contemporary issues in medical research and practice.

Thus, this essay will analyze Burnet’s conception of “self” and “tolerance” through the problems in medicine engendered after the establishment of the germ theory as its paradigm. Indeed, Louis Pasteur, Robert Koch, and others opened a new era of medical research and public health by establishing the germ as the causal agent of infectious disease. As Pasteur and Koch themselves knew, however, the existence of a germ was not enough to cause an infectious disease, and many other factors influencing the conditions of the host and germ were also involved.14 Hence, as medical historians have pointed out, early twentieth century bacteriologists and epidemiologists became increasingly interested in these factors, as their disciplines were transformed by their investigations on the complex ecological relationship between the host and parasite.15 I argue that Burnet’s theory of “self” and “tolerance” originated from these investigations within medical research and practice. Particularly, I will show that Burnet’s study of the relationship between the age of the hosts and the occurrence of infectious disease was a crucial factor for the maturation of his ideas on “self” and “tolerance” in 1949. In this respect, my essay can be placed among the recent historical works that trace the development of medical research on human diseases after the birth of the germ theory.16 While not neglecting the importance of germs, early twentieth century studies of their nature and human diseases revealed more complex aspects—the host body as well as the germ emerged as causes of diseases and bacteria were no longer regarded as specific and unchanging pathogens. Ultimately, infectious diseases were understood as arising from the disturbance of “equilibrium” between the germ and host, rather than from the “invasion” of the former into the latter. I will explain the development of Burnet’s
immunology within the intellectual context of this changing notion of disease causation.

Host’s Body and its Symbionts

Born in 1899 into an Australian family of Scottish descent, Burnet received his medical degree in Melbourne and his Ph.D. in London, where he worked on bacteriophages and Salmonella with leading microbiologists at the Lister Institute of Preventive Medicine. Forty years later, as a successful medical scientist and a Nobel Prize Winner, he recollected his early motivation for this career as a microbiologist in his 1968 autobiography, Changing Patterns.

When I was younger and had time to read an occasional long and scholarly book, I read most of Creighton’s History of Epidemics in Britain....[I]t was immensely worth reading as a truly scholarly study of epidemics by a man who did not believe in the Pasteurian germ-theory of disease. Until I read Creighton I did not realize how naïve were the early bacteriologists. Diphtheria is due to the diphtheria bacillus, the diphtheria bacillus causes diphtheria and when one finds a diphtheria bacillus in a healthy throat it must be something else, a diphtheroid bacillus.17

This paragraph reveals Burnet’s recollection of the state of the germ theory in the early twentieth century and his perspective on it. He wrote that he was in sympathy with the British physician Charles Creighton (1847-1927), a renowned critic of the germ theory.18 According to Burnet, Creighton pointed to the existence of the “healthy carrier” and the serious problem it had suggested for the validity of the germ theory. If healthy people carried the same germ in their throat as diphtheria patients did, can we still say that that germ was the cause of diphtheria? Burnet ridiculed “the early bacteriologists” who simply avoided this problem by hypothesizing the existence of another microbe whenever they found in a healthy body a
germ which had been regarded as the cause of a particular disease. Since such a hypothesizing was “logically beneath contempt,” the strict causal relationship between a germ and a disease could not be established.\(^{19}\)

But we may suspect that this depiction is historically incorrect, because it grossly simplified the standpoints of “the early bacteriologists.” While it may be true that Louis Pasteur, Robert Koch, and other early contributors of the germ theory emphasized that a specific germ was the most important cause of a specific disease, they generally knew that the existence of a germ was not enough to cause a disease. Although Koch argued that the causal relation of a germ to a disease could only be established when that germ, in a pure culture state, could replicate the original disease in a healthy animal body, this replication experiment was not always successful due to diverse factors influencing the state of the host and germ.\(^{20}\) Pasteur and his French colleagues also recognized that the condition of the host influenced the outcome of infection by germs, as he noticed that chickens contracted anthrax only when their body temperature was sufficiently lowered.\(^{21}\) Furthermore, Pasteur’s colleague Elie Metchnikoff pointed out that the host body had an active capacity of resisting infection with germs.\(^{22}\) The intrusion of a germ into a host body provoked a disease only when this capacity did not function properly.

In fact, according to the recent historical research, the “germ theory of disease” Burnet mentioned in his autobiography did not exist as a single and unified approach. As historians Nancy Tomes and John Harley Warner have pointed out, it may be historically misleading to assume that there was such a unitary approach that could be called “the germ theory.” Instead, recent publications in medical history have offered more complex pictures on the development of diverse germ *theories* that had been constructed in various ways by many local actors in their particular social and cultural environments.\(^{23}\)

However, we can infer from Burnet’s autobiography that there were persistent controversies and research on the role of a bacterium or virus in the causation of a disease,
and this controversial state of medical research influenced his early works. Indeed, we can find this influence in his Ph.D. training in London. There he was exposed to the British germ theories and bacteriology which seriously took into account the host as a causal factor for infectious diseases. Even in the early twentieth century, as Michael Worboys has persuasively shown, British medical scientists and health workers maintained their traditional emphasis on the importance of constitutional and environmental factors for the occurrence of infectious disease, and regarded germs as a necessary but not as a sufficient cause. Among these British researchers, Burnet’s dissertation supervisors, J. C. G. Ledingham and J. A. Arkwright, were the chief influence on young Burnet’s thinking. According to Olga Amsterdamska, they were the leading investigators in England on the problems of bacterial variability, which began to be observed with the rising difficulties of infectious disease diagnosis. This observation led them to depart from Koch’s notion of bacterial monomorphism and to find more complex features in the microbial world. Moreover, in their book, *The Carrier Problem in Infectious Disease* (1912), they found the “carrier problem” as a highly problematic issue that “has necessitated considerable modification of our conception of the nature of infection,” and reviewed the contemporary research on it. This review included the investigations of immune reaction within the human body that might be responsible for the carrier state. According to them, one important reason that a germ did not cause a diseased state in some people could be found in the defense mechanism embedded in their constitutions. Indeed, Burnet, after finishing his dissertation under Ledingham and Arkwright’s supervision, also became deeply interested in these constitutional factors and the carrier state. As I will describe in this essay, his interest in them was one of the most significant elements that guided his research on “self” and “tolerance.”

Burnet’s dissertation on bacteriophage also led to an investigation that shed light on the relationship between the host and parasite and the occurrence of disease. As Burnet continued his study of bacteriophage, he encountered a
controversy between the French-Canadian microbiologist Félix d’Herelle and the Belgian immunologist Jules Bordet on its nature and character. Although Burnet thought that Bordet’s theory—that the bacteriophage was a bacterial intracellular enzyme—was partially right, he supported d’Herelle’s idea that it was an organism that could be distinguished from, but could live symbiotically with the bacterium. Through his own work, Burnet concluded that the lysogeny of bacteriophages within a bacterium was a kind of symbiosis between the two organisms that had evolved independently.\(^{29}\) What is striking is that Burnet later interpreted the nonsymptomatic carrier states of herpes and rickettsial infection in humans also as a result of symbiosis between humans and microbes.\(^{30}\) Both human “healthy carriers” of pathogens and the bacteria carrying lysogenic phages were examples of the symbiotic relationship of the host and parasite, because phages could live in a bacterial body without causing its lysis, just as germs could reside within the human body without causing any disease. Infections, including both microbial infection of human and phage infection of bacteria, did not always lead to the diseases or destruction of the host.

Of course, Burnet was not the first scientist to find that an animal or human could live and evolve symbiotically with bacteria. As historian of science Jan Sapp has pointed out, the idea of the man-microbe symbiotic evolution was widely discussed and debated among medical researchers and biologists during the early twentieth century.\(^{31}\) It is thus highly probable that Burnet also became familiar with the idea of symbiosis and other ecological and evolutionary issues through these discussions and debates, especially those within Britain where Burnet was trained.\(^{32}\) In fact, *The Science of Life* published in 1929 by the British novelist and biologists H. G. Wells, Julian S. Huxley, and G. P. Wells contained such evolutionary and ecological ideas, which were used to interpret several important microbiological problems.\(^{33}\) In this book, Wells and his coauthors dealt with diverse features of the living world—such as symbiosis, succession, climax, food chain, and parasitism—in light of the contemporary ecology and evolutionary science,\(^{34}\) and criticized the prevalent
point of view that regarded bacteria “simply as creatures which cause disease.”35 Pointing out that diverse nonpathological bacteria were found living on various natural resources outside the human body,36 the authors emphasized that many of these bacteria, as evolving and changing entities,37 played an indispensable role for the economy of nature by decomposing dead organisms.38 Moreover, they pointed to the instances that parasitism might evolve into a symbiotic relationship which benefited both the host and parasite39 as well as the importance of the host’s condition for the causation of infectious disease.40 They also mentioned the existence of “carriers,” who were “congenitally protected” against the infectious disease they spread.41 What did Burnet learn from this book? As Tauber suggested, this book suggested to him a complex and dynamic picture of the biological world in which all the living and evolving organisms—including men, animals, and germs—were closely intertwined.42 Burnet later wrote that his first monograph, *Biological Aspects of Infectious Disease* (1940), “expresses the same general point of view that runs through Wells, Huxley and Well’s *Science of Life*” and argued that “the biological approach gives a better starting point for the professional study of human infectious disease.”43 Indeed, *The Science of Life* contained the arguments that frequently appeared in Burnet’s interpretations of diverse problems in medicine and public health, such as “the Bundaberg tragedy.”

This tragedy was a fatal incident that happened in 1928 at Bundaberg, Queensland, involving the death of twelve children among the twenty-one who were inoculated with diphtheria toxin-antitoxin mixture as a vaccine.44 This incident happened when Burnet returned to Melbourne as an assistant director of the Walter and Eliza Hall Institute. Charles Kellaway, director of the Hall Institute, ordered him to search for the cause of the incident through laboratory testing. While performing this duty, he discovered an “interesting example of the way a relatively harmless bacterium can be responsible for fatal infections”:45 Although it was certain that the vaccine was contaminated, the contaminating agent was a strain of *Staphylococcus*, a bacterium that was commonly found on healthy human skin. How,
then, did it kill so many children if it was only a normal bacterium living with humans? It was toxic, Burnet wrote in 1940, because “several hundred million staphylococci” suddenly appeared within the blood vessel through the inoculation, even though the bacteria themselves were perfectly benign in their natural habitat, the human skin. This discovery meant that two conditions had to be considered to explain the causation of infectious disease—the quantity of bacteria and their location within the host body. To develop a disease, more detailed requirements than the existence of a germ had to be satisfied. But what was more significant for Burnet was the fact that nine children survived the tragedy despite the injection of *Staphylococcus*. The existence of such survivors implied that the state of the host body was involved in the occurrence of this incident. In this case, the matter in question was their age; those who were not affected by the bacteria were the “older children who might be expected to have had more “training” in dealing with staphylococci.” The age of the host was as important as the invasion of the bacterium for the tragedy.

The subsequent laboratory investigation on this tragedy also gave him an insight that heightened the importance of the host body for infectious disease. Burnet inoculated staphylococcal toxoid into rabbits and observed the changing concentration of antibodies in the rabbit serum. Here, he observed “the booster effect,” a phenomenon widely known among clinicians—a second injection led to a more rapid rise of antibody titer than had followed the first injection. This effect led him to hypothesize the multiplication of a certain entity that was responsible for the making of antibodies: The boosted production of antibodies during the second contact was caused by the replication of the antibody-producing cells themselves or some kind of their sub-cellular molecules in charge of putting out the antibodies. The initial attack of staphylococcal toxoid, he thought, must have prompted the rapid multiplication of these antibody producing cells or their sub-cellular units, which could quickly make a large number of antibodies during the secondary infection. This multiplication, if proven, meant that the host body underwent a change after the initial
contact with germs, and its response to the same germ would differ after this change.\textsuperscript{52}

Finishing this investigation of the Bundaberg tragedy, Burnet started experimental studies of various infectious diseases at the Hall Institute in Melbourne and the National Institute of Medical Research in London. During the 1930s, his main research subjects included the diseases involving diverse viruses and rickettsiae, such as canary pox, psittacosis, poliomyelitis, influenza, Q-fever, and herpes. He also continued to investigate bacteriophages. Yet he occasionally wrote theoretical papers and monographs as well, which contained his distinctive insights on his own investigations as well as intensive reviews of the contemporary research on immunity and infectious disease. \textit{Biological Aspects of Infectious Disease} (1940), was the first among these theoretical monographs that were written for “medical practitioners and students” as well as “the one with a general interest in biology in relation to human affairs.”\textsuperscript{53}

In the first chapter of this monograph, Burnet proposed a novel understanding of infectious disease based on the predator-prey relationship and the food chain that he appreciated through Wells, Huxley, and Wells’ book as well as his own research. This new understanding began with the fact that every living organism was linked with others through predator-prey relationship and the food chain.\textsuperscript{54} Even the largest carnivores like eagles and lions were not exceptions, because they, too, were susceptible to attacks of tiny worms, which fed on these animals’ bodily components and metabolites.\textsuperscript{55} In such relationships, it seemed to be natural that the prey was destroyed and eventually digested by the actions of the predator. But what happens if the prey was not destroyed by the predator? If that prey was the microbe which could multiply inside the predator while evading the host’s defense mechanism, it was not a “prey” any more, but a pathological agent responsible for the development of infectious disease. He thus wrote that “we have an interaction between two organisms which, if it swings in favour of one, is an act of digestion, if in favour of the other, it is an attack of infectious disease.”\textsuperscript{56} Burnet was confident that this new perspective based
on ecological principles should be considered in understanding the relation of humans to infectious disease.

The ecological perspective led him to think of “self” and “not-self” distinction operating in nature. After describing the complexities of food chains, he asked a question about an important fact related to them. How could a predator capture its preys and destroy them in its digestive organs without harming its own body components? For an example, an amoeba could engulf and digest bacteria in its vacuoles without destroying its own constituents. How could this happen? His answer was that the predator could distinguish its own bodily materials from those of the prey and destroy only the latter. Since every living organism was participating in predator-prey relationships, such a distinction meant that all these organisms, including humans, could differentiate “self”—the elements of its own body—from “not-self”—all the other organic beings.

This distinction was highly important for humans’ immunity, because they had “wandering cells” or “phagocytes” that performed intracellular digestion through a process that was very similar to that of the amoeba. Citing Elie Metchnikoff, who had recognized the importance of these phagocytes and named them, Burnet emphasized their role in protecting the human body from the attacks of pathogenic microorganisms. Of course, the human’s phagocytes did not have amoeba’s nutritive function, because this capacity was transferred to the specialized feeding cells in its digestive organs. Yet the phagocyte, like the amoeba, was able to engulf and digest any foreign invaders without harming its own body. If this digestion failed to occur for some reason and the invading organisms were allowed to proliferate at the expense of the host, they could give rise to infectious disease within the host body. Since humans with active phagocytes could be “immune” from such infectious diseases, their role for the defense of the “self” against infection was vital.

This reasoning explains Burnet’s skepticism toward the “chemical immunologists.” Indeed, the mainline immunologists of the 1930s and 1940s studied immunity only in terms
of its chemical aspects and pursued the line of work established by earlier “humoralist” like Emil von Behring and Paul Ehrlich, who had been Metchnikoff’s lifelong opponents. Declaring Metchnikoff’s victory over them, however, Burnet pointed to the “greatest weakness” of the theories proposed by the younger chemical immunologists such as F. Haurowitz and S. Mudd, who argued that a specific antibody against a certain antigen was produced when an antibody molecule was physically “impressed” by the shape of the antigen. According to Haurowitz and others, the antibody thus produced could be easily reattached to the antigen when it reinvaded the host, because the antibody—whose shape had been formed through its physical contact with the antigen—already had a chemical structure complementary to that antigen. However, Burnet pointed out that this “orthodox theory” failed to explain a biological phenomenon that could not be observed in a test tube—how and why the second contact with the same antigen led to “a more rapid and large production of antitoxin” against it. He already observed this phenomenon through his research on the Bundaberg tragedy and hypothesized the replication of antibody-producing cells or their sub-cellular units after the first contact of these cells with the antigen. Definitely, a significant change seemed to occur among “the specialized antibody-producing cells” that defended the host body against extrinsic agents.

The cellular change in the host body occurring after the first infection could bring in another consequence important in biology and medicine, because the changes were not limited to the antibody producing cells. He thought that “many other cells in all parts of the body are also modified in their reactions as part of the bodily response to foreign antigenic material.” Anaphylaxis was an unfortunate byproduct of this modification occurring in the host body that had experienced an infection. Burnet wrote that when a viral antigen entered an animal for the first time, some of the antibodies that were produced against it could be fixed in the cells that directly experienced the infection as well as in more remotely located cells that did not have immediate contact with the antigen.
antibodies, on the second contact with that antigen, might liberate histamine that “brings the
defence reactions of the blood vessels and phagocytes into play much earlier than would
happen otherwise, and with the cooperation of antibody in the blood, the invading virus is
summarily dealt with before it can do any real damage.” 70 In some unfortunate cases,
however, the “relatively large amounts of a soluble antigen” might be introduced and be
“immediately carried to all parts of the body.” 71 In this situation, “the antigen unites with
antibody wherever it finds it, and the result may well be disastrous,” 72 because all those cells
with fixed antibodies united with the antigens would release too much histamine at the same
time that adversely affected the vital organs like the lung or liver, by causing asthma or liver
damage. 73 In this anaphylactic case, the host’s body was much more important than the
invading bacteria or viruses for the causation of a health problem. As historian Ohad Parnes
has noted, Burnet, in this respect, followed the increasing number of medical researchers of
the early twentieth century, who began to find the actual cause of the damages incurred from
infectious disease in the bodily reaction to the germ, rather than the germ itself. 74

Indeed, Burnet held that diverse factors influencing the host body’s state took part in
the occurrence of infectious disease. A germ could never be the sufficient cause of a disease,
although he took it for granted that it was a necessary cause—without any germs, no
infectious disease could occur. 75 He wrote:

It will be obvious that the fatal result of any infection will depend both on the
micro-organism and the host, and we can also feel certain that, except for certain
abnormally fatal epidemics, the state of the host is of far greater importance in
determining the outcome than is the virulence of the micro-organism. It is a truism
to say that a tremendous amount of death directly due to infection is really
determined by malnutrition or unhealthy environmental circumstances, in other
words, by poverty. The excessive height of the infantile and childhood death rates
in slum areas makes this perfectly clear, and it is unnecessary to do more than mention the inevitable concurrence of pestilence with famine in all primitive or semi-civilized peoples throughout history. Experimental bacteriology has not been very successful in discovering why under-nourishment should favour a fatal outcome to infections. The same holds in regard to the influence of climate, occupation and race. All may appear to have some effect on the result of infection by certain micro-organism.  

In this paragraph, we can observe that Burnet distinguished “the result of infection” from “infection.” Even though it was certain that a host was “infected” with a microorganism, the result of that infection could vary depending on diverse factors within the host and parasite. 

Tuberculosis was one of the best examples showing the influence of such diverse factors on the spread of infectious disease, because “[a]t least 80 per cent of those who are infected suffer no ill effects at all.” Why, then, did the remaining 20 percent of “unfortunates” suffer from severe symptoms? One factor, he pointed out, was the dangerous consequence that anaphylaxis brought about in these unfortunate patients’ body in their early adult life. Those who had been infected during their infancy or early childhood might remain as healthy carriers—if they were raised in good living conditions—until their early adulthood, when the bacteria restarted their fresh activities, which might provoke an overreaction in their body leading to anaphylaxis and death. 

In this case, the reaction of the body against the germ was as important as the germ itself. But what was more significant to Burnet than these relatively few cases of anaphylaxis was the fact that the number of tuberculosis patients in developed countries had been gradually decreasing since the late nineteenth century. What made their number decrease? His first answer to this question was found in the fact that “the average person in a civilized community now eats more and better food, is housed in greater comfort, has more opportunity for fresh air and sunlight, and is more cleanly in his habits.
than was the case 90 years ago.\textsuperscript{80} A better living environment contributed to the decrease of tuberculosis by strengthening an individual’s constitution as well as by making his or her environment cleaner. Burnet also thought that this decrease might be closely related to the continuous death of patients who were hereditarily susceptible to tubercle infection—the gradual decline of tuberculosis in the twentieth century might be due to the “weeding out” of the large number of patients “with inheritable tendency toward tuberculosis.”\textsuperscript{81} The consequence of this death was the selective survival of the people who had an inborn resistance against tuberculosis. This demonstrated the importance of the inherited constitution as another important causal factor for the development of tuberculosis.

He also discussed a few recent medical issues concerning the relationship between a microbe and the \textit{location} within the host body that was susceptible to that microbe’s infection. First, studies of puerperal fever revealed that the state of the uterus, as well as the traditional causal agent, the streptococcus, should be given due attention in explaining the occurrence of the disease.\textsuperscript{82} Burnet wrote that since the uterus after childbirth was “in rather a disorganized state” which had “not yet commenced the process of shrinking and reorganization,” it could easily succumb even to the mild and benign streptococcus which resided in the throat of healthy medical staff.\textsuperscript{83} The epidemiology of meningitis raised a similar issue concerning the location of the microbe and the occurrence of disease. Although meningitis was a fatal infection of the brain and spinal cord by various coccus-type bacteria such as meningococcus, streptococcus, staphylococcus, or pneumococcus, all these bacteria except pneumococcus were “harmless denizens of the human throat” that did not cause any problems in healthy human bodies.\textsuperscript{84} The few unfortunate patients of meningitis were thus those in whose body the bacteria—especially meningococcus—succeeded in reaching the surface of their brain. These patients demonstrated that a germ caused a disease only if it arrived at the \textit{right location} within the host body.

But how can these bacteria live in the host without doing any harm to it, if they can
cause severe problems, at least in particular locations within our body? How can they remain as “harmless denizens” in some parts of the host while becoming virulent causal agents of an infectious disease in other portions of its body? Although Burnet did not answer this question directly, he provided a clue for this question in his account of other cases of nonsymptomatic coexistence between hosts and parasites. His main source for this account was his investigations of psittacosis since 1934.85 He had begun his research on why most Australian parrots appeared healthy even though they were heavily infected with “psittacosis viruses” in their spleen or kidney.86 Pondering this problem, he concluded that these parrots did not show any symptoms of infection because they were living in an adequate natural environment, where they and the viruses in their spleen and kidneys had developed a “stabilized equilibrium” over many generations.87 “In captivity,” however, “crowded, filthy and without exercise or sunlight, a flare-up of any latent infection was only to be expected.”88 Such unnatural and undesirable environments disrupting the equilibrium led these viruses in spleen and kidney to multiply quickly and to move toward other portions of the host body that could be harmed by these viruses.89 The reason why the viruses did not harm the parrots in their spleen and kidney was thus that these organs were the places where the viruses had maintained a balanced cohabitation with their hosts that had lived and evolved in their natural environment.90 If the hosts’ condition was changed, then this balance could be disrupted as well and the viruses might leave their natural places and destroy their hosts.

Burnet’s idea of “tolerance” first appeared in his observation on this phenomenon. Burnet thought that such a balanced cohabitation was a kind of healthy carrier state that resulted from “a virtual equilibrium, a climax state in which both species would survive indefinitely.”91 This “climax state,” which could be observed in some species including the parrot and the psittacosis virus, was the result of a mutual physiological adaptation of two neighboring species that developed an ability to maximize their chance of survival during their long coevolutionary process.92 Through this process, the host and parasite could reach a
“mutual tolerance.”

“Tolerance” was significant in other respects, because it was related to the issue of “intermediate hosts” as well. At that time, the fact that some infectious diseases—such as malaria and yellow fever—were transmitted via insects was widely known, and Burnet and other researchers had been investigating Q-fever and Rocky Mountain spotted fever that spread through various intermediate hosts such as lice, ticks, mites, or rats. Based on these investigations, Burnet raised an important question about these intermediate hosts. Why did the rickettsiae and bacteria producing infectious diseases destroy the human body, while leaving that of ticks and mites apparently healthy? Burnet offered a plausible answer to this question in the papers published in 1941 and 1942: It was another case of “tolerance” between the hosts—mites, ticks, and lice—and the parasites—rickettsiae and bacteria—that had been established during their long coevolution. Through this process, the hosts and parasite had evolved physiological abilities to live peacefully together, tolerating each other as symbionts. But a serious problem could occur when these microbes were transferred to a new host such as the human “as a result of man’s accidental intrusion into that almost equilibrated biological system.” Here, the tolerance established between the old hosts and microbes could not be applied to the relationship with this novel host, and the microbes tended to provoke a severe symptom of an infectious disease. Indeed, Rocky Mountain spotted fever was the best example of this non-tolerance of rickettsiae toward a new host, the human. Even though the rickettsia did not cause a significant problem in its old hosts like rats and ticks, it definitely provoked a fatal and dangerous spotted fever in humans who were infected through their accidental contacts with rats or ticks. What humans called the “intermediate hosts” of a microbe had only been its old symbionts that had developed a mutually tolerant relationship with that microbe.

If this type of tolerance resulted from the persistent coexistence of hosts and germs for a long period, then humans could also benefit from the continuous encounter with microbes
even for a short time during childhood. Of course, it was not possible to establish in such a brief period a full symbiotic and nonsymptomatic relationship with a microbe, because such a relationship required an evolutionary process sustained over many generations. Nevertheless, Burnet was confident in his idea, because he thought that childhood was a special phase in life during which a human could enjoy the benefit of nonsymptomatic contact with diverse germs. As will be explained in the next section, he held that children’s susceptibility to infectious diseases was generally much less than that of adults. Therefore, their contact with germs could be relatively safe and eventually beneficial for their future health, because it could provide them a natural form of immunization. To do so, Burnet proposed that adults should allow their children to be exposed to the natural environments as often as possible in order to make them undergo mild subclinical infections in their early years. If these children were healthy and well-nourished and microbes were not particularly virulent at that time, this exposure would give these children plenty of opportunities to meet diverse microbes in their environments without becoming ill. The child raised in this way would “overcome without damage each of the common endemic infections” and ultimately develop a sufficient resistance against many infectious diseases.

But isn’t this measure basically similar to vaccination? If vaccination was an effective way of producing immunity, why should this unpredictable method be employed? Admittedly, Burnet, as a regular medical doctor, did not deny the efficacy of standard medical or public health measures such as vaccination, chemotherapy, or quarantine. Yet he was not satisfied with these artificial health programs. As early as 1936, he argued that the best way of improving health was to imitate “the natural source of protection” since all attempts to “disturb this ecological equilibrium to man’s advantage” brought about “unexpected consequences.” In the case of vaccination, he always worried about the possibility of its contamination; indeed, it had already occurred in the Bundaberg tragedy. Excessive use of artificial drugs, such as sulphonamides, also worsened the problems, because it could
engender a new sort of germs that were resistant to those drugs.\textsuperscript{104} Antimalarial drugs, too, made the matter more complex by making people more susceptible to malaria by lowering their natural immunity.\textsuperscript{105} Burnet thus pointed out that an artificial interference in the natural course of malaria would disturb “balanced interaction” that had been established between “man, mosquito and the malarial parasite” over the course of centuries.\textsuperscript{106}

Such an interest in the “balanced interaction” between distinct species was the basis of the “ecological point of view,” by which, Burnet argued in his 1941 article, “the germ theory of disease as formulated by Koch had been gradually superseded.”\textsuperscript{107} In this article, Burnet divided medical history into four phases: The first was the age of “supernatural causes,” the second was the era of “miasmatic theory of infectious disease,” and the third was the age of the germ theory, which was subsequently superseded by the fourth period—the age of “the biological approach to infectious disease.”\textsuperscript{108} According to this approach, he argued, microbes should be seen as scavengers that took part in the final step in the food chain—the decomposition of the dead. Because of this capacity, it was easy for microbes to become the parasites of living animals whose debris could be used by them for feeding.\textsuperscript{109} But most of these parasitic microbes were not pathogens, because they allowed their host animals to survive in healthy conditions in order to get a continuous supply of food from their wastes. Only some of these microbes “have on occasion become capable of obtaining their food requirements from living cells in the immediate neighborhood of their normal habitat” and make the host sick.\textsuperscript{110} Yet even these microbes were not very harmful to humans in many cases, since most men had “considerable inborn powers to resist infection of any type.”\textsuperscript{111} Moreover, parasitic microbes tended to evolve toward a “standard virulence” that guaranteed the survival of the host—if they were too virulent and eventually killed the host, their chance of spreading to other hosts would be significantly diminished.\textsuperscript{112} Because of this tendency, humans and germs would reach a state of “balanced equilibrium” in which a severe infectious disease was only “a rare occurrence representing one of the extremes in the range of possible
interactions between” humans and microbes.\textsuperscript{113} In this sense, infectious diseases were merely accidental phenomena, which happened only when “some gross disturbance of normal ecological relationships” occurred.\textsuperscript{114}

Of course, we do not need to accept this grand but simplistic historical generalization as a meaningful account. Burnet’s argument could be accepted only as a caricature that grossly simplified the complexities of the actual past events. Moreover, he exaggerated the novelty and sophistication of his own idea in medical history by omitting more comprehensive aspects of his predecessors’ thoughts and approaches.

From the above account, however, we still can appreciate the point he wanted to emphasize, which was articulated once again in \textit{Virus as Organism} (1946). Criticizing the popular metaphor—that often designated the germ as “the enemy” of humans, and the purpose of new medicine as the “conquest” of pathogenic germs\textsuperscript{115}—he wrote:

\begin{quote}
It was once easy to think of the interaction between man and some pathogenic micro-organism as a simple antagonism, success for the pathogen being measured by its own overwhelming multiplication with death of the host, success for the patient by recovery with annihilation of the invaders. But once the pathogen began to be thought of as a living organism dependent for its existence on a means of continuous survival, such a point of view became obviously untenable.\textsuperscript{116}
\end{quote}

Therefore, the popular metaphors that postulated direct antagonism between humans and germs could be very misleading. Although some viruses were engaged in infectious diseases that damaged the host’s body, most were not enemies but innocuous organisms living in and adapting to their changing environments, especially in their host’s body.\textsuperscript{117}

The herpes infection was a very good case for this picture of human-virus relationship. As a benign microbe many people contacted in their infancy or early childhood, \textit{Herpes}
simplex tended to persist for life in a latent state. This state of existence, which had resulted from the virus’ long coevolutionary process with humans, was quite optimal for its living and proliferation because this harmlessness guaranteed an indefinite survival of the host through which the virus could multiply and spread its descendents to other hosts.118

But the herpes virus was not always benign, because the result of its infection could vary in accordance with the state of the host. Burnet thought that the nutrition of the host body was particularly important factor in this respect. He wrote that “poorly nourished children” would suffer from “a fairly severe vesicular stomatitis, that is, a local infection with blisters in the lining of the mouth and on the lips which break down into shallow ulcers.”119 Inadequate nutrition was thus closely related to the severity of symptoms infected humans experienced during their childhood, although the virulence of the virus even in this case was still not very high. Since such poor nutrition usually resulted from poverty, he concluded that “poverty and what it implies is a dominant factor in determining the incidence of infection.”120

However, Burnet knew that “the internal situation in an animal invaded by a virus which it has not previously encountered is probably more complex than is usually thought,”121 and there were other factors than poor nutrition and poverty that influenced the consequence of infections. Indeed, the development of a disease within an infected host depended upon the diverse variables that determined its condition, such as race, sex, occupation, age, and genes.122

Burnet believed that the genetic constitution of the host’s body ranked fairly high among these diverse factors. As historian J. Andrew Mendelsohn put it, the medical interest in patients’ genetic constitution as a causal factor for the occurrence of infectious disease led to the development of medical genetics after the 1920s,123 and Burnet also shared such interest. He noticed and accepted the new discoveries in genetics and biochemistry including Oswald T. Avery’s isolation of DNA as the bacterial transforming factor and George W.
Beadle’s neurospora experiment supporting his one-gene-one-enzyme theory.\textsuperscript{124} For Burnet, these discoveries indicated that the host’s genetic constitution could deeply affect the initiation and development of some bacterial diseases like tuberculosis.\textsuperscript{125}

But the role of the genetic factors in the host body was negligible in cases of \textit{viral} diseases. Although some bacterial diseases revealed that nuclear genes were important causal elements in determining the occurrence of infection, “there is very little evidence that inheritable variation in resistance play any part in relation to \textit{virus} disease in man.”\textsuperscript{126} Of course, “genetic factors undoubtedly play a limited role in determining the susceptibility or resistance of a mammalian host to a given infection, and particularly in small rapidly multiplying rodents the elimination of susceptible and the survival of genetically resistant strains may be important part of the ecological process.” But in humans, such feature could not be seen very often, and “the relative insusceptibility of Negroes to yellow fever is the only example,” for which the host’s genetic factors primarily determined the occurrence of \textit{viral} disease.\textsuperscript{127}

In fact, Burnet had some reservations about the role of nuclear genes in infectious disease \textit{in general}, and this attitude was closely related to the state of genetics in the 1940s when he composed his theoretical works. At that time, cytoplasmic inheritance received renewed attention with the rise of research on eukaryotic microorganism’s heredity pursued by several American scientists including Sol Spiegelman, Carl and Gertrude Lindegren, and Tracy Sonneborn.\textsuperscript{128} They argued that the study of the heredity of unicellular eukaryotes like yeast and paramecium demonstrated the existence of cytoplasmic hereditary factors that did not follow the Mendelian laws established through research on nuclear genes in multicellular organisms: Cytoplasmic factors could replicate themselves and change their characteristics in accordance with environmental conditions and were inherited by descendent cells only through the cytoplasm where they resided. Although these factors could not be called independent “genes”—because they were not completely free from the influence of nuclear
control—their existence suggested a serious problem for Mendelian genetics and embarrassed many mainline geneticists like H. J. Muller and George W. Beadle.

Burnet was immensely impressed by cytoplasmic inheritance theories and attempted to apply them to account for antibody production. According to Burnet, the antibody was made by self-replicating adaptive enzymes in the immune cell cytoplasm, which could change their structures and replicate in response to “environmental rather than nuclear stimuli”—in this case, the environmental agent was the antigen contacting immune cells. Since these adaptive enzymes with changed structures were inherited by their descendent cells only through the cytoplasm, these enzymes closely resembled Spiegelman and Lindegrens’ melibiozymase in yeasts, whose cytoplasmic inheritance revealed a definite non-Mendelian pattern. The antibody was these adaptive enzymes’ “partial replica” that was released into the bloodstream without the self-replicating capacity of the original enzyme.

Admittedly, Burnet first proposed his self-replicating adaptive enzyme theory of antibody production in 1941 when the cytoplasmic inheritance of microorganism was not yet an important issue among biologists. At that time, Burnet’s theory was inspired by a few American researchers who hypothesized self-replicating adaptive enzymes in bacteria that did not have a visible nucleus-cytoplasm distinction. With these hypotheses in mind, Burnet postulated in 1941 that the antibody was also produced by similar enzymes that had a capacity for self-replication and adaptation within the immune cell, although he did not specify their intracellular location.

After employing cytoplasmic inheritance theories during the mid-1940s, Burnet began to place these adaptive enzymes within the cytoplasm of antibody-producing cells. But the consequence of employing this theory was more than just determining the location of the enzymes within the cell: The cytoplasmic inheritance theory conferred a developmental dimension to the workings of his adaptive enzymes. In contrast to the self-replicating
adaptive enzyme in 1941 whose modification by antigens occurred only in the adult body, the
modification of his later enzymes, which were now located in the cytoplasm, occurred during
the embryo developmental process as well, through their contacts with diverse molecules and
cells within the embryo. In his second edition of *The Production of Antibodies* (1949), Burnet
stated that as the embryo grew, his self-replicating enzyme was gradually modified by these
numerous entities within an embryo and was inherited through the cytoplasm of the immune
cells undergoing differentiation.  

In fact, many advocates of cytoplasmic inheritance argued that all the cells of an
embryo underwent a similar differentiation process involving cytoplasmic inheritance during
its development. The type of each cell was determined through this process which occurred
during embryogenesis, rather than through nuclear genes’ direct influence. Indeed, such a
relation of cytoplasmic inheritance to developmental process was linked to a paradoxical fact
concerning the role of the nuclear gene in cell differentiation—the nuclear gene sets were
identical in almost every differentiated somatic cell of a multicellular organism. If there were
no differences in the nucleus, what then made a hepatocyte differ from a nerve cell? Although
geneticists asserted that the nuclear gene ultimately controlled cell differentiation, this
paradox suggested that their assertion could not be easily demonstrated without attributing an
inherent intellectual capacity to the nuclear gene. Thus, during the mid-1940s, many
advocates of cytoplasmic inheritance pointed to this paradox to argue for the role and
importance of cytoplasmic inheritance in differentiation and development. According to
them, it was the inheritance of cytoplasmic material in accordance with the changing
environmental conditions during embryo development that was responsible for somatic cell
differentiation. Sonneborn, Spiegelman, and Lindegrens argued that cytoplasmic heredity
observed in simple unicellular eukaryotes could be employed as a useful model to study this
complex differentiation process occurring in multicellular species. Since this argument
was very persuasive in the 1940s when few other explanations were as convincing, even
some mainline geneticists began to consider its possibility. Burnet was also persuaded by this argument and started to conceive a hypothesis on the function of his self-replicating adaptive enzyme based on cytoplasmic inheritance theories. What, then, did this new function of the adaptive enzyme mean for Burnet’s conception of “the biological approach to infectious disease”? It meant two things. First, the role of nuclear genes in determining the host’s response toward germs was substantially circumscribed, because the antibodies attacking these germs were produced by the self-replicating adaptive enzyme, which was a kind of cytoplasmic hereditary entity rather than a nuclear gene. Second, the age of the host became a highly important factor in determining the outcome of infection; from bacteriological and virological perspective, the developing embryo was none other than a very young host into which diverse bacteria and viruses could enter. Indeed, since the Bundaberg tragedy had revealed that older children survived the incident better than the younger, Burnet had been considering the age of the host one of the most significant factors for the occurrence of infectious disease. The next section will review how this consideration developed into his theory of “self” and “tolerance” in 1949.

Age, Embryogenesis, Self, and Tolerance

Burnet’s appropriation of cytoplasmic inheritance theories and its developmental implication for his account on antibody production suggests that he seriously considered the importance of the temporal variation in organisms’ responses toward germs. This consideration can also be seen in his study of the relation of an organism’s age to the occurrence of infectious disease. Since a human or animal’s response toward a germ could change as it grew old, the age of the host was a significant variable determining whether the host would develop diseases after contacting viruses or bacteria. In fact, he always regarded the host’s age as an essential factor in the occurrence of infectious diseases along with other factors such as sex, nutrition, race, occupation, and genetic constitution. In his 1940 book,
Biological Aspects of Infectious Disease, Burnet called the relation of this age factor to disease causation “the age-incidence of infectious disease.”

Burnet declared in 1940 that a close investigation of this age-incidence of infectious disease showed that the relationship between hosts’ age and infection was more complex than an “average person” might think.\textsuperscript{143} Contrary to the widespread assumption that “children are more prone to the common infections than adults because they are weaker,” he pointed to the recent epidemiological studies demonstrating that the reverse was true in many cases: Children were more resistant to many infectious diseases.\textsuperscript{144} Indeed, more adults in many developed countries contracted smallpox and died than infants or children did.\textsuperscript{145} Yellow fever, human psittacosis, influenza, and tuberculosis showed a similar pattern: the number of the children who were killed by these infectious diseases was “negligible in comparison with the high mortality in young adults.”\textsuperscript{146} He also pointed out that many children or infants who contracted diphtheria or herpes could recover from them without serious symptoms.\textsuperscript{147} The only difference after recovery was that the herpes virus usually remained in a latent state in some parts of the body while the diphtheria bacillus was completely eliminated.

Poliomyelitis showed more complex pattern in Europe, America, and Australia. In a paper published in 1940, Burnet wrote that the age of polio patients in these countries had been rising along with the increasing virulence of the virus since the early twentieth century.\textsuperscript{148} Whereas it had been in the nineteenth century a mild disturbance of human pharyngeal region whose primary infection occurred usually among infants, it became a severe neurotropic infection of school age children and young adults in many developed countries. Why and how did this change happen? Burnet thought that during the nineteenth century the polio virus had been an organism that could maintain an “equilibrium” with the humans who had been infected with it during their infancy.\textsuperscript{149} This equilibrium was beneficial for the humans as well as for the viruses, since it could keep the former alive while securing an indefinite reproduction and spread of the latter. Moreover, many people infected
in this way could possess a lifelong immunity against more virulent strains, and many of
them became permanent carriers of the benign viruses without showing any serious illness.
But a “relatively large group of susceptible children of school age may accumulate,” as the
improved hygiene in the developed countries led to the decrease of infection of young infants
from adult carriers. If a virus was accidentally introduced into this group, it could rapidly
evolve toward more virulent neurotropic strain through its numerous passages among these
susceptible children, many of whom would ultimately be paralyzed or died after severe
neuronal damages. But this epidemic of the virulent virus was “a simple biological accident”
that did little to promote the survival of the poliovirus itself. To him, “all the indications are
that in the pre-epidemic era the virus had developed a satisfactory mode of existence as a
mild parasite of the human pharyngeal region, its latent neurotropism becoming manifest
only on rare occasions.”

In this example, the increased virulence of the virus, rather than the condition of the
host body, was the major factor determining the outcome of poliomyelitis infection. But in
many other cases of disease, the varying condition of the host body according to its age was a
more important factor influencing the outcome of infection. In general, the infection of young
human hosts—including children and infants—was milder and safer than that of older ones in
the cases of yellow fever, human psittacosis, or influenza. Infectious diseases in cattle
such as Texas fever investigated by the American microbiologist Theobald Smith showed
similar patterns. According to Burnet, Smith’s study revealed that “adult cattle infected for
the first time with any of the pathogenic protozoa suffer more severely than calves.” This
phenomenon, along with many human cases, revealed that young hosts—regardless of
whether they were humans or cattle—were better in surviving their infectious diseases.

How, then, can we explain this phenomenon? In his 1940 book, *Biological Aspects
of Infectious Disease*, Burnet proposed a hypothesis based on the physiology and
evolutionary biology of the host body. This hypothesis held that adults could be more
adversely affected by a microbial infection because they reacted “too effectively against any infection which involves the whole body.”\textsuperscript{155} The large number of the adults who died of infectious diseases could be ascribed to adverse bodily responses such as anaphylaxis that children and infants, who had less effective immune system, did not normally experience.\textsuperscript{156} Burnet hypothesized that such a strong and effective immune system had gradually evolved throughout humans’ long prehistory to deal with the local traumatic infections resulting from vigorous adulthood activities such as fighting and hunting.\textsuperscript{157} Although adults’ strong response enhanced their survival rate after being injured at a specific body part, it also raised their chance of death due to infectious diseases, because their excessive immunological reactivity could occasionally overwhelm their whole body.

Children, who did not yet have such a strong immune response, were thus safer from the risks than adults. While an adult’s immunity was “too active for general infections,” children’s response was “at its best.”\textsuperscript{158} Burnet wrote that their adequate level of immune response was also a product of the human evolution.

…for the last two or three thousand years man has evolved in an environment saturated with infection. An intense selection of those best fitted to resist disease has been constantly in progress….Ever since man became gregarious, he must have been the subject of endemic disease which, as always, attacked predominantly children. If the species was to survive, it was necessary that children should be able to overcome these diseases and develop immunity against them.\textsuperscript{159}

But early infants and embryos, who were younger than children, could not always avoid being overwhelmed by invading agents, because of their “diminished reactivity” to “toxic and infectious agents.”\textsuperscript{160} However, even for the diseases that killed more infants than older children such as smallpox and tuberculosis, the number of infants who died of such
diseases was still smaller than that of young adults. Moreover, many infectious diseases including herpes and the milder forms of polio attacked many infants without inflicting much damage on them. Nevertheless, it was obvious that embryos and early infants with insufficient immunity could be harmed more severely than older children. It was well-known among surgeons that *Staphylococcus* infection of infants’ bones might result in a severe osteomyelitis in them without any warning symptoms or inflammatory responses.

To understand this phenomenon, he turned to the experimental results obtained from laboratory animals. In a chapter titled, “Immunological Behaviour of Young Animals,” in his 1941 book *The Production of Antibodies*, Burnet pointed out that infantile animals and embryos had a weak immune reactivity to extraneous agents including viruses, toxins, and tumor cells. He cited many researchers including James Murphy of the Rockefeller Institute, who first discovered the nonresponse of the chick embryos on which mammalian tumor tissue had been grafted. Murphy’s experiment revealed that “the foreign tissue becomes vascularized from the chorioallantoic vessels and grows freely without any of the leucocytic reaction that it would provoke in an adult alien host.” Other researchers also showed that rabbits, guinea pigs, and chick embryo in their early infancy or embryonic stages experienced almost no antibody response to the viruses, bacteria, and toxoids that had been injected into their bodies. Moreover, Burnet himself, using the chick embryo to culture various viruses since the early 1930s, already knew its nonresponse toward many kinds of viruses. These experimental results were definitely relevant to a “notorious” clinical fact—“the highest mortality from the common infectious diseases” was observed “in the first two years of life” due to this low immune reactivity of infants.

In other respects, however, the infant’s and the embryo’s low immunity resulted in a phenomenon in which he had been very interested. He asserted that Murphy’s and other researchers’ investigations revealed that the immature tissue could “tolerate” foreign cells and molecules that had not been its intrinsic parts, whereas mature organisms rejected them. He
A particularly striking incidence of the tolerance of immature tissues for foreign material is seen in the chick embryo on which fragments of a mammalian tumour, the Jensen rat sarcoma, have been grafted. In some way the embryonic cells seem to be unable to recognize and resent contact with foreign material in the way adult cells do. It is therefore not unexpected that no antibody response takes place.\textsuperscript{169}

Burnet thought that this inability to recognize foreign materials was due to the lack of “training” of immature animals. Since “all biological activities tend to improve with practice,” embryos and early infants could gradually develop a capacity to recognize extrinsic entities as they had more experience and training in dealing with them.\textsuperscript{170}

However, this type of “tolerance” was very different from other cases of tolerant relationship he had studied since the 1930s. While the peaceful coexistence he investigated—such as the relationship between parrots and the psittacosis viruses, or that between ticks and rickettsiae—was established through their long coevolution over many generations, the above example was a temporary phenomenon occurring only in an animal’s early phase of life. Furthermore, in contrast to the mutual benefit the psittacosis virus and the parrots could share from their cohabitation, extrinsic organisms or tumor tissues in Murphy’s experiment could inflict a severe damage to young animals that could not yet recognize and react to them.

Nevertheless, Burnet was able to find an interesting example of “tolerance” that resembled the cases of the parrot and psittacosis virus. In the second edition of \textit{The Production of Antibodies} (1949), Burnet wrote,

In work extending over several years, Traub (1936, 1938 and 1939) carried out a comprehensive series of studies of the natural history of this disease.
lymphocytic choriomeningitis] in an infected stock. At the close of his studies the infected community of mice appeared to have reached a virtual state of symbiosis with the virus. All mice were carriers for the greater part of their lives and all young mice were infected in utero. No clinical evidence of illness was apparent and the mice were quite resistant to intracerebral challenge with virus. No neutralizing antibody could be detected in the blood nor any complement fixing antibody…These phenomena are obviously complex but there is the development of a tolerance to the foreign microorganism during embryonic life which is in line with the present hypothesis.171

While Murphy’s chick embryo had been damaged by the proliferation of foreign cells, Traub’s mice never became ill with the attack of the choriomeningitis virus.172 Furthermore, his mice “tolerated” this virus even after they had become adults, in contrast to Murphy’s chicks that rejected tumor tissues after their embryonic life. The development of permanent tolerance between Traub’s mice and the viruses, which Burnet called “a virtual state of symbiosis,” was thus quite similar to the relationship between the parrot and psittacosis virus, or the rickettsia and tick, which Burnet also called a “mutual symbiosis.”

In the same book, Burnet discussed the importance of a similar observation by Ray Owen at the University of Wisconsin.173 It is noteworthy that Burnet introduced Owen’s studies in a chapter whose title is the same as the one in the first edition of The Production of Antibodies, where he discussed “tolerance” with respect to the age of the host body— “Immunological Behaviour of Young Animals.”

In cows, twin young often develop a common placental circulation, and hormones interchanged between male and female twins may result in the production of “freemartins” or sterile heifers. Owen found that the common placental circulation
of twin foetuses might also result in two antigenic types of red blood cell being found in both of the twins for life. One corresponds genetically to its own cells, the other to its twin’s cells. The important implication of this work is that cells “foreign” to the host may be tolerated indefinitely provided that they are implanted early in embryonic life.\(^{174}\)

Like the phenomenon observed by Traub, Owen discovered that an entity of extrinsic origin could be indefinitely “tolerated” in an animal body if it had been introduced during the embryogenesis of the host. Burnet’s response toward Owen’s discovery of this phenomenon was thus highly enthusiastic. He wrote that it was “[a] particularly interesting example of the tolerance of foetal tissues for foreign material.”\(^{175}\)

What, then, happened in the host body during its “foetal” stage? To answer this question, Burnet in his 1949 book brought forth the issue of “self” and “not-self” distinction which he had introduced in 1940. The theory of the self-replicating adaptive enzyme and cytoplasmic inheritance, which he had been developing during the 1940s, were also employed to account for this distinction: He hypothesized that each somatic cell in the host body had a peculiar set of “self-markers” whose structure had been determined by nuclear genes. The antigenic molecule on the surface of a red blood cell determining humans’ ABO blood type could be a typical self-marker, because a normal human always rejected transfused blood cells that had different antigenic molecules on their surface. Yet what was more important in this process was that the “self-marker” had to be recognized during the host’s embryonic stages to function as a “valid” marker that could be used to distinguish “self” from “not-self.” To do so, the embryonic phagocytes which had self-replicating adaptive enzymes in their cytoplasm had to modify the structures of their enzymes according to the shapes of the “self-markers” of all the other cells during the embryonic life. This modification occurred during the process to make the adaptive enzyme “deal effectively with
those components which need to be broken down for reintegration into the metabolic activities of the body.” Burnet wrote that this modification became “stabilized as part of the inheritable structure of these cells and is transmitted indefinitely to their descendents” through the self-replication of the modified enzymes in the cytoplasm. Therefore, after embryo development had been completed, all the phagocytes would possess these cytoplasmic adaptive enzymes matching the structures of the self-markers within the organism. From then on, the “liability of intracellular enzyme is lost, the patterns engraved during embryonic life harden as it were and become permanent possessions.” He summarized this theory as follows.

The nuclear complement of genes is constant for every somatic cell of the body, the cytoplasmic components, derived in the last analysis from genic pattern, change qualitatively and quantitatively in the course of embryonic development according to their temporal and spatial distribution. The functional cytoplasmic entities (which may be termed plasmagenes, enzymes or living protein) are self-replicating but subject to modification by the circumstances of the changing intracellular environment and particularly according to the concentration and qualitative character of their appropriate substrates. In warm blooded vertebrates at least, and probably to some extent throughout the Metazoa, there are functional units concerned with the breakdown of complex molecules which form part of the expendable cells of the body. In embryonic life these units become specifically adapted to the characteristic patterns of a number of the molecules concerned. This can be expressed as the implantation in the “scavenger” cells of the body of a means of recognizing “self-marker” components of expendable body cells.

After this developmental process had ended, “a foreign red cell or an invading
pneumococcus” could enter the host and encounter the immune cells that already had cytoplasmic enzymes adapted to the shapes of the self-markers of the host body. But this “new substrate”—foreign red cells or invading germs—“does not quite fit the specific adsorptive pattern of the enzyme,” and subsequently “the process leading to antibody production set in train” to eliminate them.\textsuperscript{180} In contrast, the host body could not develop any antibody responses against the “expendable cells from a genetically distinct race” that had been introduced during its embryonic stages.\textsuperscript{181} This nonresponse was possible, because the structures of some adaptive enzymes in the embryonic host’s phagocytes had already been modified according to the shapes of the genetically distinct cells. The shapes of those cells came to “fit” with the molecular structures of the adaptive enzymes.

Burnet thought that the “self” of an organism was formed through this process. If foreign entities that had entered the embryonic host could be indefinitely tolerated through the above mechanism, what was the boundary of the “self” of the host? As described in the previous section, he already stated his view on “self” and “not-self” in \textit{Biological Aspects of Infectious Disease}. In this book, this distinction was an established biological fact observed in all living individuals in the food chain. Since the boundary of “self” in this book was clearly demarcated according to the genetically given boundary of an individual, there was no need for further theorization. But in 1949, the situation became more complex, due to the discoveries made by Traub and Owen, and Burnet’s own theories based on cytoplasmic inheritance. How could he explain “self” without neglecting these new complexities? Burnet’s answer was brief but ingenious. He wrote,

It is of considerable interest that foetal mammals and chick embryos are incapable of producing antibody…and the full capacity to do so develops only slowly in the young free-living animal…This raises the suggestion that the process by which self-pattern becomes recognizable takes place during the embryonic or
immediately post-embryonic stages. The hypothesis of antibody production that we have developed can readily be adapted to such a possibility.\textsuperscript{182}

In other words, “self” was defined during embryonic development rather than genetically determined. He stated this idea more clearly in 1956 by writing that “the recognition of self is something ‘learnt’ during embryonic life and not genetically ingrained.”\textsuperscript{183} Even though the genetic constitution of bacteria or viruses was very different from that of an animal, they could be recognized during embryogenesis as if they had been a part of that animal’s “self,” provided that they had been residing in the animal since its embryonic stages.\textsuperscript{184}

Burnet, with this new idea of “self,” declared that “tolerance” could be observed through the experimental inoculation of “a wider range of antigens” into an embryo of distinct genetic constitution.\textsuperscript{185} He thought that even though the host was genetically different from them, it would still show “the persisting tolerance of foreign cells found by Owen in his studies on multiple births in cattle.”\textsuperscript{186} Burnet thus wrote, “A very interesting field for direct experimentation is opened up.”\textsuperscript{187}

This “direct experimentation” was conducted by the English zoologist Peter B. Medawar and his team, in their mouse tissue transplantation experiments of 1953.\textsuperscript{188} They inoculated a suspension of living cells from an adult mouse of an inbred strain into a fetal mouse of another strain. As Burnet predicted, these cells became a permanent part of its recipient mouse even after the end of that mouse’ fetal stages. Moreover, the mouse was also tolerant of the tissue graft transplanted from any mouse that belonged to the original donor strain.\textsuperscript{189} This was the strong evidence of Burnet’s theory that “the process by which self-pattern becomes recognizable takes place during the embryonic or immediately post-embryonic stages.”\textsuperscript{190} That is, the “self-marker” of the previous graft was already recognized as a permanent part of the “self” of the recipient during its embryonic phases, although that marker was “a pseudo one.”\textsuperscript{191} Once the cells carrying these self-markers had been classified
as a part of “self,” later grafts with the same markers could also be regarded as belonging to
the “self.” This theoretical explanation and its experimental demonstration became the basis
for awarding Burnet and Medawar the Nobel Prize in Physiology and Medicine in 1960.

Conclusion

But a Nobel Prize may not be enough to acknowledge Burnet’s contribution to
modern medical practice and research. His theorization of “self” and “not-self” distinction
was crucial for the development of the investigation and treatment of diverse health problems
that have arisen as major medical issues since the early twentieth century—cancer, allergy,
autoimmune disease, immune deficiency syndrome, and so on. It is quite noticeable that
these “new” diseases are substantially different from those that killed innumerable people
before that time, such as typhoid fever, tuberculosis, malaria, and cholera. In a sense, the
difference between these “traditional” diseases that prompted nineteenth century doctors to
develop germ theories and the “new” disease like cancer and AIDS may reflect the trajectory
of Burnet’s ideas: He began with the complex issues concerning the role of germs in the
causation of diseases and ended up by proposing a novel conceptual tool for the study of new
diseases such as cancer and acquired immune deficiency syndrome.

In this essay, I have followed this trajectory and showed how Burnet arrived at his
innovative idea of “self” and “tolerance” in 1949. As Burnet recognized the complexities
involved in the occurrence of infectious diseases, he came to realize that the condition of the
host body and its interaction with evolving microorganisms should be considered from an
evolutionary and ecological perspective. Yet among the diverse factors that influenced a host
body’s condition, its age was a particularly important variable, because humans and animals
with different age substantially differed in their responses toward an extrinsic microbe.
Burnet’s acceptance of cytoplasmic inheritance theories reinforced in his mind the
importance of age, since these theories, with a strong embryological implication, led him to
study the changing state of the embryonic host body according to its age. As he recognized the importance of age and cytoplasmic inheritance, Burnet could notice the significance of Owen’s and Traub’s observations, and argued that the “self” of the host body was defined during embryonic and early infantile stages. Extrinsic cells or germs that had been introduced into the host during these stages could be “tolerated,” even after its embryonic life had ended, as if they had been a part of the host’s “self.”

This theory of “self” and “tolerance” offered a critical insight on the novel diseases emerging in a new age. Perhaps, Burnet’s argument that “the germ theory had gradually been superseded” was right in this respect, because the threats of traditional diseases that had inspired Pasteur and Koch became substantially weakened in this age, at least in developed countries.  

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12 Among these diverse issues, Tauber mentioned the influence of genetics on Burnet’s conception of “self-marker” theory. However, Tauber wrote that the existence of this self-marker itself became less important than the enzymes that recognized these markers during embryonic development. The structure of these enzymes were made according to the environmental influences during the development rather than genetically determined. See Tabuer, *The Immune Self*, pp. 105-13; Tauber and Podolsky, “Frank Macfarlane Burnet,” 556-64.


27 Ibid, pp. 219, 261-63.

Frank Macfarlane Burnet, Biological Aspects of Infectious Disease (Cambridge: Cambridge University, 1940), p. ix.


Burnet, Biological Aspects, p. 138.

Ibid., p. 139. Indeed, Burnet emphasized that the number of bacterium should be sufficient to replicate the human disease in experimental animals. See Ibid., p. 143.

Ibid., p. 140.


Booster effect, which was often neglected by chemical immunologists, was first observed and investigated by clinicians who used antisera for therapeutic purposes. We can trace Burnet’s interest on booster effect to his clinical experience at Melbourne Hospital. On “affinity/avidity controversy,” see Peter Keating, Alberto Cambrosio, and Michael Mackenzie, "The Tools of the Discipline: Standards, Models, and Measures in the Affinity/Avidity Controversy in Immunology," in The Right Tools For the Job: At work in Twentieth-Century Life Sciences, ed. Adele E. Clarke and Joan H. Fujimura (Princeton, N. J.: Princeton University Press, 1992), pp. 312-54.


Burnet, Freeman, Jackson, and Lush, Production of Antibodies (1941), pp. 23-4.

Burnet, Biological Aspects, p. 118.

Ibid., p. ix.

Ibid., p. 7.

Ibid., p. 8.

Ibid., p. 31.


Ibid., pp. 29-30.

Ibid., pp. 31-6.

Ibid., p. 36.

Ibid., pp. 117-18. For Burnet’s skeptical attitude toward chemical immunology, see Silverstein, A History of Immunology, pp. 288-95.

Tauben, Immune Self, pp. 69-73.

Burnet, Biological Aspects, p. 36. See also, Tauber and Podolsky, “Frank Macfarlane Burnet,” pp. 545-46.

Ibid., p. 118.

Ibid., pp. 119-21.

70 Ibid., p. 122.

71 Ibid., p. 122.

72 Ibid., p. 122.

73 Ibid., pp. 119-20.

74 Parnes, “‘Troubles from Within’,” p. 447.


76 Burnet, Biological Aspects, pp. 135-36.

77 Ibid., p. 257.

78 Ibid., pp. 257-58.


80 Burnet, Biological Aspects, p. 260.

81 Ibid., p. 260.


83 Burnet, Biological Aspects, pp. 137-38

84 Ibid., p. 141.


86 From the modern standpoint, the microbial agent responsible for psittacosis is a chlamydiae rather than a virus.

87 Burnet, Biological Aspects, pp. 21, 23.


89 Ibid., p. 23.

90 Curiously, Burnet never attempted to offer any mechanism to explain the relationship of the environmental conditions to the development of symptoms. Burnet, Biological Aspects, p. 23; “Inapparent Virus Infections,” p. 101.

91 Burnet, Biological Aspects, pp. 21, 23.


93 Burnet, Biological Aspects, pp. 19, 24.


96 Ibid., p. 131.


Ibid., p. 222.

Burnet, *Biological Aspects*, pp. 219-20, 224; “Changes of Twenty-five Years,” p. 27.


Ibid., pp. 282-83.


Ibid., pp. 607-8.

Ibid., p. 609.

Ibid., p. 609.

Ibid., p. 610.

Ibid., p. 611.

Ibid., pp. 610, 612.

Ibid., p. 612.


Burnet, *Virus as Organism*, p. 53.


Ibid., p. 826.

Burnet, *Virus as Organism*, p. 37.


Burnet, *Virus as Organism*, p. 36. Italic is my emphasis. But Burnet did not explain why the occurrence of virus diseases was rarely related to the genetic constitution of the host.

Ibid., p. 36.

Tracy M. Sonneborn, “Gene and Cytoplasm. I. The Determination and Inheritance of the Killer Character in Variety

129 Sonneborn’s “killer trait” of paramecium, which had been regarded as a cytoplasmic hereditary entity, required the presence of the nuclear gene “K” to replicate itself in the cytoplasm. Likewise, Spiegelman and Lindegrens’ melibiozynase had to be made initially from nucleus to function as self-replicating element in the cytoplasm. See Sonneborn, “Gene and Cytoplasm. II,” p. 340; Spiegelman, Lidegren, and Lindegren, “Maintenance and Increase of a Genetic Character,” p. 100. Therefore, the supporters of cytoplasmic inheritance usually did not call their cytoplasmic entities “genes.” Whenever they did, they always used quotation marks around it. See, for example, Rupert E. Billingham and Peter B. Medawar, “The ‘Cytogenetics’ of Black and White Guinea Pig Skin,” *Nature,* 1947, 159, p. 116. Also see Sonneborn, “Genes, Cytoplasm, and Environment in Paramecium,” *Sci. Mon.*, 1948, 67, p. 156.


139 Sapp, *Beyond the Gene,* pp. 87-90.


143 Burnet, Biological Aspects, p. 199.

144 Ibid. Strangely, Burnet did not mention the Bundaberg tragedy where older children were more resistant to infection.

145 Burnet, Biological Aspects, pp. 200-1.

146 Burnet, Virus as Organism, p. 42. In the case of tuberculosis, see Burnet, “The Natural History of Tuberculosis,” pp. 59-60. Here, Burnet was not very specific about the distinction between “morbidity” and “case fatality.” I suspect that Burnet could not make this distinction because of the “healthy carrier” problem. If there were many healthy carriers of an infectious disease who were not sick, or showed only mild symptoms, how then could one measure the morbidity/case fatality of that disease?


149 Ibid., p. 332.

150 Ibid., p. 332.

151 Ibid., p. 332.

152 Burnet, Virus as Organism, p. 42.


154 Burnet, Biological Aspects, p. 207.


157 Ibid., p. 211; Virus as Organism, p. 45.


159 Ibid., pp. 210-11.

160 Burnet, Freeman, Jackson, and Lush, Production of Antibodies (1941), p. 45.

161 See the graphs in Burnet, Biological Aspects, pp. 201, 206; “The Natural History of Tuberculosis,” p. 60.


163 Burnet, Freeman, Jackson, and Lush, Production of Antibodies (1941), p. 45.


165 Burnet, Freeman, Jackson, and Lush, Production of Antibodies (1941), p. 45.

166 Ibid.


168 Burnet, Freeman, Jackson, and Lush, Production of Antibodies (1941), p. 45.

169 Ibid., p. 45.

170 Ibid., p. 46.


172 Erich Traub, “The Epidemiology of Lymphocytic Choriomeningitis in White Mice,” J. Exp. Med., 1936, 64, pp. 183-


174 Burnet and Fenner, Production of Antibodies (1949), p. 76.

175 Ibid., p. 76.

176 Ibid., p. 102.

177 Ibid., p. 103.

178 Ibid., p. 103.

179 Ibid., pp. 105-6.

180 But he did not specify “the process leading to antibody production.” Ibid., p. 101.

181 Ibid., p. 103.

182 Ibid., p. 102.


184 Of course, the virus and bacterium should not be very virulent to the host body, as could be seen in the example of the choriomeningitis virus or psittacosis virus.

185 Burnet and Fenner, Production of Antibodies (1949), p. 129.

186 Ibid., p. 129.

187 Ibid., p. 103.

188 Billingham, Brent, and Medawar, “‘Actively Acquired Tolerance’ of Foreign Cells,” pp. 603-6. In this article, they clearly declared that their results verified Burnet’s 1949 predictions.

189 Yet the organism did not tolerate the tissue graft from any other strains. Billingham, Brent, and Medawar, “‘Actively Acquired Tolerance’ of Foreign Cells,” p. 605.

190 Burnet and Fenner, Production of Antibodies (1949), p. 102.

191 Frank Macfarlane Burnet, “How Antibodies Are Made,” Sci. Am., 1954, 191, p. 76. This sentence might mean that Burnet did not really believe that the cells of extrinsic origin could be a genuine part of the host’s “self.” But he did not call them explicitly as “foreign,” either. We can see his ambivalence from the sentences in which he used quotation marks around the word, “foreign.” See. Burnet and Fenner, Production of Antibodies (1949), p. 76; Burnet, “How Antibodies Are Made,” p. 75.

192 Although these diseases had existed since the immemorial times, they emerged as the major health problems only after the twentieth century. In case of cancer, see James T. Patterson, The Dread Disease: Cancer and Modern American Culture (Cambridge, Mass.: Harvard University Press, 1987).

193 Although some people warned that many traditional infectious diseases, which became more powerful due to mutation and natural selection, will soon return to the Western World, there have been few instances of such diseases after the mid-twentieth century. Even SARS, which received widespread media attention as a highly serious threat to the modern world, killed less than 50 people in developed countries. See http://www.who.int/csr/sars/country/table2004_04_21/en/index.html