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Germes, 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 exchange 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.³ 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.⁴ Medawar and his team supported this argument by their transplantation experiments,⁵ which provided the first demonstration that extrinsic tissues other than cornea could be successfully tolerated within a distinct individual.⁶ 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.⁷

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.⁸ 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.⁹

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.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 *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.¹¹ Tauber has argued that Burnet, after a complex trajectory of thinking stemmed from diverse contemporary biological theories and discoveries,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 *process* and *interaction*, clearly revealed Burnet's strong commitment to dynamic and holistic philosophy.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 *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.²⁴ 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.²⁵ 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,"²⁶ 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.²⁷ 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 bacteriophage²⁸ at the Lister Institute 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.⁴⁶ 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.”⁴⁷ 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.⁴⁸ 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.⁴⁹ 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.⁵⁰ 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.⁵¹ 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.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. *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.”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.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.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.”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?⁵⁷ 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.⁵⁸

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.⁵⁹ 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.⁶⁰ 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.”⁶¹ 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.⁶² Declaring Metchnikoff’s victory over them,⁶³ however, Burnet pointed to the “greatest weakness”⁶⁴ 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.⁶⁵ 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.⁶⁶ 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.⁶⁷

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.”⁶⁸ 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.⁶⁹ The cells with these fixed

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.⁷⁶

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.”⁷⁷ 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.⁷⁸ 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.⁷⁹ 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.”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.”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 *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.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.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.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 *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.”⁹³

“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.⁹⁴ 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.⁹⁵ 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.”⁹⁶ 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.⁹⁷ 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.⁹⁸ 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.⁹⁹ 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"¹⁰⁰ 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.¹⁰¹ 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 oecological equilibrium to man's advantage" brought about "unexpected consequences."¹⁰² In the case of vaccination, he always worried about the possibility of its contamination; indeed, it had already occurred in the Bundaberg tragedy.¹⁰³ 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.¹⁰⁴ Antimalarial drugs, too, made the matter more complex by making people more susceptible to malaria by lowering their natural immunity.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.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.”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.”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.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.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.”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.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.¹¹³ In this sense, infectious diseases were merely accidental phenomena, which happened only when “some gross disturbance of normal ecological relationships” occurred.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 *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 germs¹¹⁵—he wrote:

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.¹¹⁶

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.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, *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.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.¹²⁵

But the role of the genetic factors in the host body was negligible in cases of *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 *virus* disease in man."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 viral disease.¹²⁷

In fact, Burnet had some reservations about the role of nuclear genes in infectious disease *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.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

control¹²⁹—their existence suggested a serious problem for Mendelian genetics and embarrassed many mainline geneticists like H. J. Muller and George W. Beadle.¹³⁰

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.¹³¹ 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,¹³² whose cytoplasmic inheritance revealed a definite non-Mendelian pattern.¹³³ The antibody was these adaptive enzymes’ “partial replica” that was released into the bloodstream without the self-replicating capacity of the original enzyme.¹³⁴

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.¹³⁵ 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.¹³⁶ 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.¹³⁷

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.¹³⁸ 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.¹³⁹ 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.¹⁴⁰ 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.¹⁴¹

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.¹⁴² 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.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.¹⁴⁴ Indeed, more adults in many developed countries contracted smallpox and died than infants or children did.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.”¹⁴⁶ He also pointed out that many children or infants who contracted diphtheria or herpes could recover from them without serious symptoms.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.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.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.¹⁵⁰ 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.”¹⁵¹

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.¹⁵² Infectious diseases in cattle such as Texas fever investigated by the American microbiologist Theobald Smith showed similar patterns.¹⁵³ 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.”¹⁵⁴ 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.”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.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.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.”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.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.”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.¹⁶¹ 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.¹⁶²

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.¹⁶³ 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.¹⁶⁴ 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."¹⁶⁵ 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.¹⁶⁶ Moreover, Burnet himself, using the chick embryo to culture various viruses since the early 1930s, already knew its nonresponse toward many kinds of viruses.¹⁶⁷ 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.¹⁶⁸

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

wrote,

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.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.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 *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[mouse

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.”¹⁷⁶ 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.¹⁷⁷ 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.”¹⁷⁸ 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.¹⁷⁹

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.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.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 *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.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.”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.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.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.”¹⁸⁶ Burnet thus wrote, “A very interesting field for direct experimentation is opened up.”¹⁸⁷

This “direct experimentation” was conducted by the English zoologist Peter B. Medawar and his team, in their mouse tissue transplantation experiments of 1953.¹⁸⁸ 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.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.”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.”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.¹⁹² 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.¹⁹³

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¹ Ilana Löwy, "The Strength of Loose Concepts—Boundary Concepts, Federative Strategies and Disciplinary Growth: The Case of Immunology," *Hist. Sci.*, 1992, 30, pp. 376-82.

² Leo Leob, "The Biological Basis of Individuality," *Science*, 1937, 86, pp. 1-5; Clarence C. Little and E. E. Tyzzer, "Further Experimental Studies on the Inheritance of Susceptibility to a Transplantable Tumor, Carcinoma (J. w. A.) of the Japanese Waltzing Mouse," *J. Med. Res.*, 1916, 33, pp. 393-427.

³ Frank Macfarlane Burnet and Frank Fenner, *The Production of Antibodies* (Melbourne: Macmillan and Company Limited, 1949), p. 102.

⁴ Burnet and Fenner, *Production of Antibodies* (1949), p. 104.

⁵ Rupert E. Billingham, Leslie Brent, and Peter B. Medawar, "'Actively Acquired Tolerance' of Foreign Cells," *Nature*, 1953, 172, pp. 603-6.

⁶ Arthur M. Silverstein, *A History of Immunology* (San Diego: Academic Publishers, 1989), pp. 288-95.

⁷ Löwy, "The Strength of Loose Concepts," pp. 386-9.

⁸ Gustav J. V. Nossal, "Some Landmarks in Australian Immunology," *Immunol. Cell Biol.*, 1991, 69, p. 329; Alberto Martini and Giuseppe R. Burgio, "Tolerance and Auto-immunity: 50 years after Burnet," *Eur. J. Pediatr.*, 1999, 158, pp. 769-70; Ian R. Mackay, "The 'Burnet Era' of Immunology: Origins and Influence," *Immunol. Cell Biol.*, 1991, 69, pp. 301-2; Leslie Brent, *A History of Transplantation Immunology* (San Diego: Academic Press, 1997), p. 9.

⁹ Frank Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: William Heinemann, 1968), pp. 189-200.

¹⁰ See, for example, Paul John Eakin, *Fictions in Autobiography: Studies in the Art of Self-Invention* (Princeton: Princeton University Press, 1985); Thomas Söderqvist, "Darwinian Overtones: Niels K. Jerne and the Origin of the Selection Theory of Antibody Formation," *J. Hist. Biol.*, 1994, 27, p. 489; Ilana Löwy, "Variances in Meaning in Discovery Accounts: The Case of Contemporary Biology," *Hist. Stud. Phys. Biol. Sci.*, 1990, 21, pp. 87-121; Gerald L. Geison, *The Private Science of Louis Pasteur* (Princeton, NJ: Princeton University Press, 1995), pp. 53-89.

¹¹ Alfred I. Tauber and Scott H. Podolsky, "Frank Macfarlane Burnet and the Immune Self," *J. Hist. Biol.*, 1994, 27, pp. 546-64; Alfred I. Tauber, *The Immune Self: Theory of Metaphor?* (Cambridge: Cambridge University Press, 1994), pp. 98-113; Scott H. Podolsky and Alfred I. Tauber, *The Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology* (Cambridge, Mass.: Harvard University Press, 1997), pp. 24-37; Eileen Crist and Alfred I. Tauber, "Selfhood, Immunity, and the Biological Imagination: The Thought of Frank Macfarlane Burnet," *Biol. Philos.*, 2000, 15, pp. 511-17.

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.

¹³ Tabuer, *The Immune Self*, p. 108.

¹⁴ Louis Pasteur, "Discussion sur l'étiologie du charbon; poules rendues charbonneuses," *Bull. de l'Academ.*, 1878, 7, pp. 253-62 in *Oeuvres de Pasteur réunies*, ed. Vallery-Radot Pasteur, 7 vols. (Paris: Masson, 1933), VI, pp. 210-14; Robert Koch, "Erste Konferenz zur Erörterung der Cholerafrage," *Berl. klin. Wochenschr.*, 1884, 21, pp. 496-507. In fact, a strict causal relationship between a germ and a disease, which was assumed in "Koch's Postulates," could not be found in many cases of infectious disease. On the problem of Koch's postulate, see William Coleman, "Koch's Comma Bacillus: The First Year," *Bull. Hist. Med.*, 1997, 61, pp. 315-42; Lester S. King, "Dr. Koch's Postulates," *J. Hist. Med.*, 1952, 7, pp. 350-61; K. Codell Carter, *The Rise of Causal Concepts of Disease: Case Histories* (Aldershot: Ashgate, 2003), pp. 138-40.

¹⁵ J. Andrew Mendelsohn, "From Eradication to Equilibrium: How Epidemics Became Complex after World War I," in *Greater than the Parts: Holism in Biomedicine, 1920-1950*, ed. Christopher Lawrence and George Weisz (New York: Oxford University Press, 1998), pp. 303-31; "Medicine and the Making of Bodily Inequality in Twentieth Century Europe," in *Heredity and Infection: The History of Disease Transmission*, ed. Jean-Paul Gaudillière and Ilana Löwy (London: Routledge, 2001), pp. 21-79; Stephen J. Kunitz, "Explanations and Ideologies of Mortality Patterns," *Popul. Dev. Rev.*, 1987, 13, pp. 382-5; Jan Sapp, *Evolution by Association: A History of Symbiosis* (New York: Oxford University Press, 1994), pp. 76-92.

¹⁶ Mendelsohn, "From Eradication to Equilibrium," pp. 303-31; "Medicine and the Making of Bodily Inequality," pp. 21-79; Kunitz, "Explanations," pp. 382-5; Ohad Parnes, "Troubles from Within: Allergy, Autoimmunity, and Pathology in the First Half of the Twentieth Century," *Stud. Hist. Phil. Biol. Biomed. Sci.*, 2003, 34, pp. 425-54; Olga Amsterdamska, "Medical and Biological Constraints: Early Research on Variation in Bacteriology," *Soc. Stud. Sci.*, 1987, 17, 657-87. While Mendelsohn has claimed that Burnet himself "left out half the story by attributing the emergence of a new "ecological point of view" to the ascendance of other scientists over" medical bacteriologists, I show that Burnet himself was indebted to these medical researchers.

¹⁷ Burnet, *Changing Patterns*, pp. 117-18.

¹⁸ E. Ashworth Underwood described Charles Creighton's skeptical attitude on the germ theory in the context of his academic activities as a medical researcher and "natural historian" of infectious disease. For a brief biography of Creighton, see E. Ashworth Underwood, "Charles Creighton, The Man and His Work," in *A History of Epidemics in Britain with Additional Material by D. E. C. Eversley, E. Ashworth Underwood, and Lynda Ovenall*, 2 vols. (London, Frank Cass & Co.

Ltd., 1965), I, pp. 43-135.

¹⁹ Burnet, *Changing Patterns*, p. 118.

²⁰ Koch, "Erste Konferenz," pp. 496-507.

²¹ Pasteur, "Discussion sur l'étiologie du charbon," pp. 210-14.

²² For example, see Elie Metchnikoff, *Leçons sur la pathologie comparée de l'inflammation, Faites à l'Institut Pasteur in 1891* (Paris, Masson: 1892). For an excellent review on Metchnikoff's theory, see Tauber, *The Immune Self*, pp. 15-26; Leon Chernyak and Alfred I. Tauber, "The Idea of Immunity: Metchnikoff's Metaphysics and Science," *J. Hist. Biol.*, 1990, 23, pp. 187-249; Alfred I. Tauber and Leon Chernyak, *Metchnikoff and the Origins of Immunology: From Metaphor to Theory* (New York: Oxford University Press, 1991).

²³ Nancy J. Tomes and John Harley Warner, "Introduction to Special Issue on Rethinking the Reception of the Germ Theory of Disease: Comparative Perspectives," *J. Hist. Med. Allied Sci.*, 1997, 52, pp. 7-16. See other articles published in the same volume, especially, Nancy J. Tomes, "American Attitudes toward the Germ Theory of Disease: Phyllis Allen Richmond Revisited," *J. Hist. Med. Allied Sci.*, 1997, 52, pp. 17-50; Terrie M. Romano, "The Cattle Plague of 1865 and the Reception of 'The Germ Theory' in Mid-Victorian Britain," *J. Hist. Med. Allied Sci.*, 1997, 52, pp. 51-80. Also see Michael Worboys, *Spreading Germs: Disease Theories and Medical Practices in Britain, 1865-1900* (Cambridge: Cambridge University Press, 2000), pp. 2-3.

²⁴ Worboys, *Spreading Germs*, esp., p. 284.

²⁵ Amsterdamska, "Medical and Biological Constraints," pp. 671-6.

²⁶ J. C. G. Ledingham and J. A. Arkwright, *The Carrier Problem in Infectious Diseases* (London, Edward Arnold, 1912), p. 2.

²⁷ *Ibid.*, pp. 219, 261-63.

²⁸ Frank Macfarlane Burnet, *Bacteriophage Phenomena in Relation to the Antigenic Structure of Bacteria* (London: The University of London, Ph.D diss., 1928). His dissertation was published as F. M. Burnet, "'Smooth-Rough' Variation in Bacteria in its Relation to Bacteriophage," *J. Pathol. Bacteriol.*, 1929, 32, pp. 15-42.

²⁹ Frank Macfarlane Burnet, "Lysogenicity as a Normal Function of Certain Salmonella Strains," *J. Pathol. Bacteriol.*, 1932, 35, p. 861; "Recent Work on the Biological Nature of Bacteriophages," *Trans. R. Soc. Trop. Med. Hyg.*, 1933, 26, p. 413. Also See Tauber, *The Immune Self*, pp. 84-92.

³⁰ Frank Macfarlane Burnet, "Herpes Simplex: A New Point of View," *Med. J. Aust.*, 1939, 1, p. 642; "The Rickettsial Disease in Australia," *Med. J. Aust.*, 1942, 2, p. 130.

³¹ Sapp, *Evolution by Association*, pp. 76-92.

³² Medical historian W. F. Bynum suggested that Darwin's theory influenced many British physicians during the nineteenth century. They gradually began to consider, during their theorizations on the nature of disease, the evolution of both infectious diseases and human's constitutions that responded to germs. William F. Bynum, "Darwin and the Doctors: Evolution, Diathesis, and Germs in 19th-Century Britain," *Gesnerus*, 1983, 40, pp. 43-53.

³³ Herbert G. Wells, Julian S. Huxley, and George P. Wells, *The Science of Life: A Summary of Contemporary Knowledge about Life and Its Possibilities* (London: Amalgamated Press, 1929).

³⁴ *Ibid.*, pp. 961-1011.

³⁵ *Ibid.*, p. 303.

³⁶ *Ibid.*, p. 301.

³⁷ *Ibid.*, p. 1039.

³⁸ *Ibid.*, pp. 303-6.

³⁹ *Ibid.*, p. 931.

⁴⁰ *Ibid.*, p. 1039.

⁴¹ *Ibid.*, pp. 1037-38.

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- ⁴² Tabuer and Podolsky, "Frank Macfarlane Burnet," p. 540-45.
- ⁴³ Frank Macfarlane Burnet, *Biological Aspects of Infectious Disease* (Cambridge: Cambridge University, 1940), p. ix.
- ⁴⁴ For the details of Bundaberg tragedy, see Christopher Sexton, *Seeds of Time: The Life of Sir Macfarlane Burnet* (Oxford: Oxford University Press, 1991), p. 65.
- ⁴⁵ Burnet, *Biological Aspects*, p. 138.
- ⁴⁶ *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.
- ⁴⁷ *Ibid.*, p. 140.
- ⁴⁸ "Toxoid," which was named by Paul Ehrlich, is an antigen that does not have toxicity without losing its antibody-binding ability. Paul Ehrlich, "Über die Giftcomponenten des Diphtherie-Toxins," *Berl. klin. Wochenschr.* (1903), reprinted in F. Himmelweit, Martha Marquardt, and Henry Dale (eds.), *The Collected Papers of Paul Ehrlich*, 3 vols. (London: Pergamon Press, 1957), II, p. 351.
- ⁴⁹ 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.
- ⁵⁰ Burnet, *Biological Aspects*, pp. 117-18; F. M. Burnet, Mavis Freeman, A. V. Jackson, and Dora Lush, *The Production of Antibodies: A Review and a Theoretical Discussion* (Melbourne: Macmillan and Company Limited, 1941), pp. 9-16, 22-4. Also see Frank Fenner, *Sir Macfarlane Burnet: Scientist and Thinker* (St. Lucia: The University of Queensland Press, 1988), pp. 9-10; Gordon L. Ada, "Frank Macfarlane Burnet: Virologist, Immunologist, and Nobel Prize Winner," *Med. J. Aust.*, 1939, 1, p. 259.
- ⁵¹ Burnet, Freeman, Jackson, and Lush, *Production of Antibodies* (1941), pp. 23-4.
- ⁵² Burnet, *Biological Aspects*, p. 118.
- ⁵³ *Ibid.*, p. ix.
- ⁵⁴ *Ibid.*, p. 7.
- ⁵⁵ *Ibid.*, p. 8.
- ⁵⁶ *Ibid.*, p. 31.
- ⁵⁷ *Ibid.*, pp. 7-8, 27-30. Also see Crist and Tabuer, "Selfhood," pp. 519-20.
- ⁵⁸ *Ibid.*, pp. 29-30.
- ⁵⁹ *Ibid.*, pp. 31-6.
- ⁶⁰ *Ibid.*, p. 36.
- ⁶¹ *Ibid.*, pp. 117-18. For Burnet's skeptical attitude toward chemical immunology, see Silverstein, *A History of Immunology*, pp. 288-95.
- ⁶² Tauber, *Immune Self*, pp. 69-73.
- ⁶³ Burnet, *Biological Aspects*, p. 36. See also, Tauber and Podolsky, "Frank Macfarlane Burnet," pp. 545-46.
- ⁶⁴ *Ibid.*, p. 118.
- ⁶⁵ Friedrich Breinl and Felix Haurowitz, "Chemische Untersuchungen des Präzipitates aus Hämoglobin und anti-Hämoglobin-Serum und Bemerkungen über die Natur der Antikörper," *Hoppe Seylers Z. Physiol. Chem.*, 1930, 192, pp. 45-57; Stuart Mudd, "A Hypothetical Mechanism of Antibody Formation," *J. Immunol.*, 1932, 23, pp. 423-27.
- ⁶⁶ Burnet, *Biological Aspects*, pp. 117-18.
- ⁶⁷ *Ibid.*, p. 118.
- ⁶⁸ *Ibid.*, p. 118.

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- ⁶⁹ 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.
- ⁷⁵ Frank Macfarlane Burnet, "The Natural History of Tuberculosis," *Med. J. Aust.*, 1948, 1, p. 62.
- ⁷⁶ Burnet, *Biological Aspects*, pp. 135-36.
- ⁷⁷ Ibid., p. 257.
- ⁷⁸ Ibid., pp. 257-58.
- ⁷⁹ Burnet's explanation on the cause of this decrease precedes McKeown's famous thesis on the reduction of mortality rate in England and Wales. See Thomas McKeown, *The Role of Medicine: Dream, Mirage or Nemesis?* (Princeton, NJ: Princeton University Press, 1979).
- ⁸⁰ Burnet, *Biological Aspects*, p. 260.
- ⁸¹ Ibid., p. 260.
- ⁸² Ignaz Semmelweis' argument that "decaying matter" was the sole cause of puerperal fever was received by the later advocate of the germ theory who replaced "decaying matter" by "germs." On Semmelweis' causal concept of puerperal fever, see K. Codell Carter, "Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory," *Med. His.*, 1985, 29, pp. 33-53; *The Rise of Causal Concepts*, pp. 38-61.
- ⁸³ Burnet, *Biological Aspects*, pp. 137-38.
- ⁸⁴ Ibid., p. 141.
- ⁸⁵ Frank Macfarlane Burnet, "Psittacosis in Australian Parrots," *Med. J. Aust.*, 1934, 2, pp. 743-46; Frank Macfarlane Burnet and Phyllis M. Rountree, "Psittacosis in the Developing Egg," *J. Pathol. Bacteriol.*, 1935, 40, pp. 471-81; Frank Macfarlane Burnet and Jean MacNarama, "Human Psittacosis in Australia," *Med. J. Aust.*, 1936, 2, pp. 84-8.
- ⁸⁶ From the modern standpoint, the microbial agent responsible for psittacosis is a chlamydae rather than a virus.
- ⁸⁷ Frank Macfarlane Burnet, "Inapparent Virus Infections, with Special Reference to Australian Examples," *Br. Med. J.*, 1936, 1, p. 101. Also see Frank Macfarlane Burnet, "Changes of Twenty-Five Years in the Outlook on Infectious Disease," *Med. J. Aust.*, 1939, 2, p. 25; *Biological Aspects*, pp. 20-3.
- ⁸⁸ Burnet, *Biological Aspects*, p. 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.
- ⁹² Burnet, "Changes of Twenty-Five Years," p. 25; Burnet, "Inapparent Virus Infection," p. 102.
- ⁹³ Burnet, *Biological Aspects*, pp. 19, 24.
- ⁹⁴ See, for example, R. Y. Mathew, "Endemic Typhus in North Queensland," *Med. J. Aust.*, 1938, 2, pp. 371-77; E. H. Derrick, "'Q' Fever, a New Fever Entity: Clinical Features, Diagnosis and Laboratory Investigation," *Med. J. Aust.*, 1937, 2, pp. 281-99; Frank Macfarlane Burnet and Mavis Freeman, "Experimental Studies of the Virus of 'Q' Fever," *Med. J. Aust.*, 1937, 2, pp. 299-305.
- ⁹⁵ Burnet, "The Rickettsial Diseases," pp. 130-31. Also see Frank Macfarlane Burnet, "The Biological Approach to Infectious Disease," *Med. J. Aust.*, 1941, 2, p. 611. He arrived at the same conclusion on sleeping sickness. See, Burnet, *Biological Aspects*, p. 174.
- ⁹⁶ Ibid., p. 131.
- ⁹⁷ Burnet, "The Biological Approach," p. 611.

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- ⁹⁸ Burnet, *Biological Aspects*, p. 199.
- ⁹⁹ *Ibid.*, p. 222.
- ¹⁰⁰ *Ibid.*, p. 222.
- ¹⁰¹ Burnet, *Biological Aspects*, pp. 219-20, 224; "Changes of Twenty-five Years," p. 27.
- ¹⁰² Burnet, "Inapparent Infection," p. 103.
- ¹⁰³ Burnet, *Biological Aspects*, p. 225; "Epidemiology Today," *Med. J. Aust.*, 1946, 2, p. 828.
- ¹⁰⁴ Burnet, "Epidemiology Today," p. 829. In fact, the increasing resistance of bacteria against artificial drugs has recently begun to be considered a serious threat to man's health. See Laurie Garrett, *The Coming Plague: Newly Emerging Diseases in a World Out of Balance* (New York: Penguin Books, 1994).
- ¹⁰⁵ Burnet, *Biological Aspects*, p. 288.
- ¹⁰⁶ *Ibid.*, pp. 282-83.
- ¹⁰⁷ Burnet, "The Biological Approach," p. 611.
- ¹⁰⁸ *Ibid.*, pp. 607-8.
- ¹⁰⁹ *Ibid.*, p. 609.
- ¹¹⁰ *Ibid.*, p. 609.
- ¹¹¹ *Ibid.*, p. 610.
- ¹¹² *Ibid.*, p. 611.
- ¹¹³ *Ibid.*, pp. 610, 612.
- ¹¹⁴ *Ibid.*, p. 612.
- ¹¹⁵ On the popular metaphor, see, for example, Christoph Gradmann, "Invisible Enemies: Bacteriology and the Language of Politics in Imperial Germany," *Sci. Context*, 2000, 13, pp. 9-30; Nancy J. Tomes, *The Gospel of Germs: Men, Women, and the Microbe in American Life* (Cambridge, Mass.: Harvard University Press, 1998), p. 124. Perhaps, the title of Winslow's classical monograph also represents the popular notion of germs and infectious diseases. See Charles-Edward Amory Winslow, *The Conquest of Epidemic Disease: A Chapter in the History of Ideas* (Princeton: Princeton University Press, 1943).
- ¹¹⁶ Frank Macfarlane Burnet, *Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases* (Cambridge, Mass: Harvard University Press, 1946), pp. 25-6.
- ¹¹⁷ Burnet, *Virus as Organism*, pp. 19-25. Burnet cited Robert Green and Patrick Laidlaw's "retrograde evolution theory of the virus," for this argument. For the meaning of this theory in contemporary debates on the nature of the virus, see Scott Podolsky, "The Role of Virus in Origin-of-Life Theorizing," *J. Hist. Biol.*, 1996, 29, pp. 79-126.
- ¹¹⁸ Burnet, *Virus as Organism*, p. 53.
- ¹¹⁹ Burnet, "Epidemiology Today," p. 826.
- ¹²⁰ *Ibid.*, p. 826.
- ¹²¹ Burnet, *Virus as Organism*, p. 37.
- ¹²² Burnet, "The Natural History of Tuberculosis," p. 62; "The Biological Approach," p. 610; "Epidemiology Today," p. 829.
- ¹²³ Mendelsohn, "Medicine and the Making of Bodily Inequality," pp. 55-66.
- ¹²⁴ Frank Macfarlane Burnet, "Some Borderlands of Microbiology, Genetics and Biochemistry," *Aust. J. Sci.*, 1944, 7, pp. 2-4; *Virus as Organism*, pp. 9-16.
- ¹²⁵ Burnet, "Epidemiology Today," p. 829; "The Natural History of Tuberculosis," pp. 60-61.
- ¹²⁶ 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.
- ¹²⁷ *Ibid.*, p. 36.
- ¹²⁸ Tracy M. Sonneborn, "Gene and Cytoplasm. I. The Determination and Inheritance of the Killer Character in Variety

4 of *Paramecium Aurelia*," *Proc. Natl. Acad. Sci. USA*, 1943, 29, pp. 329-38; "Genes and Cytoplasm. II. The Bearing of the Determination and Inheritance of Characters in *Paramecium Aurelia* on the Problems of Cytoplasmic Inheritance, Pneumococcus Transformations, Mutations and Development," *Proc. Natl. Acad. Sci. USA*, 1943, 29, pp. 338-43; Sol Spiegelman, Carl C. Lindegren, and Gertrude Lindegren, "Maintenance and Increase of a Genetic Character by a Substrate-Cytoplasmic Interaction in the Absence of the Specific Gene," *Proc. Natl. Acad. Sci. USA*, 1945, 31, pp. 95-102. For a general discussion of the cytoplasmic inheritance theory in the 1940s, see Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (Oxford: Oxford University Press, 1987), pp. 87-115.

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 Lindegren's melibiozymase 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, Lindegren, 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.

¹³⁰ For example, see "Discussion," *Annals of the Missouri Botanical Garden*, 1945, 32, pp. 251-63. For Muller's later criticism on cytoplasmic inheritance, see Hermann J. Muller, "The Development of Gene Theory," in *Genetics in the 20th Century: Essays on the Progress of Genetics during Its First 50 Years*, ed. Leslie C. Dunn (New York: The Macmillan Company, 1951), pp. 82-3. Beadle also pointed out that cytoplasmic factors had only a limited degree of autonomy, and ultimately was controlled by nuclear genes. See Beadle, "Genes and Biological Enigmas," in *Science in Progress, Sixth Series*, ed. George Baitsell (New Haven: Yale University Press, 1949), p. 232.

¹³¹ Frank Macfarlane Burnet and Frank Fenner, "Genetics and Immunology," *Heredity*, 1948, 2, p. 290.

¹³² Frank Macfarlane Burnet, "Antibody Production in the Light of Recent Genetic Theory," *Aust. J. Sci.*, 1946, 8, p. 145.

¹³³ Sol Spiegelman, "The Physiology and Genetic Significance of Enzymatic Adaptation," *Ann. Mo. Bot. Garden*, 1945, 32, p. 160.

¹³⁴ Frank Macfarlane Burnet, "The Basis of Allergic Disease," *Med. J. Aust.*, 1948, 1, p. 31.

¹³⁵ Burnet, Freeman, Jackson, and Lush, *Production of Antibodies* (1941), pp. 58-64.

¹³⁶ See the papers written by Dubos, Avery, Bergmann and Niemann. René Dubos and Oswald T. Avery, "Decomposition of the Capsular Polysaccharide of Pneumococcus Type III by a Bacterial Enzyme," *J. Exp. Med.*, 1931, 54, pp. 51-71; Max Bergmann and Carl Niemann, "Newer Biological Aspects of Protein Chemistry," *Science*, 1937, 86, pp. 187-90.

¹³⁷ Burnet and Fenner, *Production of Antibodies* (1949), pp. 105-6. Also see, Burnet, "Antibody Production," pp. 143, 146; Burnet, "The Basis of Allergic Disease," p. 31.

¹³⁸ Sapp, *Beyond the Gene*, pp. 7-16; "Concepts of Organization: The Leverage of Ciliate Protozoa," in *A Conceptual History of Embryology*, ed. Scott F. Gilbert (Baltimore: The Johns Hopkins University Press, 1991), pp. 237-44. Also see Viktor Hamburger, "Embryology and the Modern Synthesis in Evolutionary Theory," in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, ed. Ernst Mayr and William B. Provine (Cambridge, Mass.: Harvard University Press, 1980), pp. 100-3. Evelyn Fox Keller argued that nuclear genes were tacitly endowed a "foresight that would enable them to direct some cells of the embryo in one way, some in another," although a direct proof of this "foresight" was not possible. Evelyn Fox Keller, *Making Sense of Life: Explaining Biological Development with Models, Metaphors, and Machines* (Cambridge, Mass.: Harvard University Press, 2002), pp. 133-34.

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

¹⁴⁰ Tracy M. Sonneborn, "Genes, Cytoplasm, and Environment in Paramecium," *Sci. Mon.*, 1948, 67, pp. 154, 160; Sol

Spiegelman, "The Physiological and Genetic Significance," p. 161; Sol Spiegelman and M. D. Kamen, "Genes and Nucleoproteins in the Synthesis of Enzymes," *Science*, 1946, 104, p. 584.

¹⁴¹ "Discussion," p. 256; Beadle, "Biochemical Genetics," *Chem. Rev.*, 1945, 37, p. 84. Also see Sapp, *Beyond the Gene*, pp. 101-2.

¹⁴² Burnet, "The Natural History of Tuberculosis," p. 62; "The Biological Approach," p. 610; "Epidemiology Today," p. 829.

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?

¹⁴⁷ Burnet, "Inapparent Virus Infection," pp. 99-100; "Herpes Simplex," pp. 641-42; *Biological Aspects*, pp. 228-40.

¹⁴⁸ Frank Macfarlane Burnet, "The Epidemiology of Poliomyelitis, with Special Reference to the Victorian Epidemic of 1397-38," *Med. J. Aust.*, 1940, 1, pp. 328-29.

¹⁴⁹ *Ibid.*, p. 332.

¹⁵⁰ *Ibid.*, p. 332.

¹⁵¹ *Ibid.*, p. 332.

¹⁵² Burnet, *Virus as Organism*, p. 42.

¹⁵³ Theobald Smith and F. L. Kilborne, *Investigations into the Nature, Causation, and Prevention of Texas or Southern Cattle Fever* (Washington: Government Printing Office, 1893), pp. 132, 148.

¹⁵⁴ Burnet, *Biological Aspects*, p. 207.

¹⁵⁵ *Ibid.*, p. 210. Also see *Virus as Organism*, pp. 43-4.

¹⁵⁶ Burnet, *Biological Aspects*, p. 210.

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

¹⁵⁸ Burnet, *Biological Aspects*, p. 210.

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.

¹⁶² Burnet, *Biological Aspects*, p. 210.

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

¹⁶⁴ James B. Murphy, "Transplantability of Tissues to the Embryo of Foreign Species: Its Bearing on Questions of Tissue Specificity and Tumor Immunity," *J. Exp. Med.*, 1913, 17, pp. 482-92.

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

¹⁶⁶ *Ibid.*

¹⁶⁷ His first experiment using chick embryo was published in 1934. Burnet, "The Propagation of the Virus of Infectious Laryngo-tracheitis on the Chorio-allantoic Membrane of the Developing Egg," *Br. J. Exp. Pathol.*, 1934, 15, pp. 52-5.

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

¹⁶⁹ *Ibid.*, p. 45.

¹⁷⁰ *Ibid.*, p. 46.

¹⁷¹ Burnet and Fenner, *Production of Antibodies* (1949), p. 104.

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

200; "Factors Influencing the Persistence of Choriomeningitis Virus in the Blood of Mice after Clinical Recovery," *J. Exp. Med.*, 1938, 68, pp. 229-50; "Epidemiology of Lymphocytic Choriomeningitis in a Mouse Stock Observed for Four Years," *J. Exp. Med.*, 1939, 69, pp. 801-17.

¹⁷³ Ray D. Owen, "Immunogenetic Consequences of Vascular Anastomoses between Bovine Twins," *Science*, 1945, 102, pp. 400-1.

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.

¹⁸³ Frank Macfarlane Burnet, *Enzyme, Antigen, and Virus: A Study of Macromolecular Pattern in Action* (Cambridge: Cambridge University Press, 1956), p. 67.

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