Macfarlane Burnet

The Concept of Self

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A remarkable contemporary genius, Dr. Macfarlane Burnet, the Australian immunologist, began his investigations by a poetic opposition of the self and nonself. How does the self recognize the nonself and expel it from the body?[1]

This passage appeared in a 1969 article on the nature of genius by Robert Graves.[2] The acknowledgement of Macfarlane Burnet's talents in such an article is both striking and unusual. Graves was a literary scholar, not a scientist, and the article was published in, of all places, *Playboy* magazine. Despite such exposure, Burnet has remained a relatively unknown figure outside scientific circles and beyond Australian shores.

In his article, Graves homed in on an aspect of Burnet's considerable scientific achievements, the idea of the immune self, a concept that has helped define and shape medical science as we know it today.[3] Identifying the immune self is what Graves deemed Burnet's work of genius, and it formed part of the basis on which Burnet received the 1960 Nobel Prize in Physiology or Medicine.[4] While it might be his best-known legacy, the self was neither his first nor last major contribution to science.

Burnet himself had speculated on the nature of his creativity and intellect long before Graves. In a diary he kept while a young man, he wrote:

> If there is any respect in which I have a really first class brain it is in the faculty for generalisation. Properly controlled it is the highest work of intelligence but creative imagination is liable to run far away from the bound of that which is or can be proved.[5]

Lest readers mistake this self-portrait for arrogance, it is only fair to include a second diary entry from the same period, in which the author offers an unflinching assessment of his shortcomings:

> I had a horrid experience today in the simplest of circumstance ... Just by standing near two full length mirrors. ... I never knew what an intensely undistinguished figure I cut from that aspect before ... when I saw that bashful hobbledehoy ... I really felt most vexed.[6]

Burnet was the son of a banker and a school teacher, born and raised in the small country towns of Traralgon and Terang in the southeastern Australian state of Victoria. It was to this upbringing that Burnet would attribute a lifelong interest in collecting things. He would also credit his success as a scientist to the mindset inculcated by this habit: "I am by temperament an ecologist, a naturalist, a collector of beetles, a snapper-up of unconsidered trifles. I believe that some of the best work I did ... depended on this characteristic of mine."[7]

Burnet's diaries show him to have been an avid reader, as likely to bury himself in the novels of Joseph Conrad as to grapple with the nonfiction writings of Henri Bergson. He would later admit that he opted to study medicine "for [the] weakest of reasons," more through a process of elimination than any deliberate decision on his part. At the time, the other options open to "clever boys" from country towns were "law or the church."[8] Burnet never regretted his choice. While in medical school he found the type of teachers and supervisors who steered him to his career in research; he was offered a post in pathology rather than the field he had applied for, clinical neurology. As he noted in his diary the following day:

> I was a bit nonplussed and didn't seem very keen at the time, but on thinking it over I'm sure that it's a chance not to be missed. ... I can see quite clearly that though I am an excellent hospital physician I am by no means likely to be a success as a GP. On the other hand I believe strongly in my suitability for laboratory and research work.[9]

As a pathologist dealing routinely with clinical specimens from patients, he had a steady supply of surplus raw material for microbiological research, which he evidently put to good use. Less than three months into his new position, he began a diary entry with the revelation that "the fever of scientific research is beginning to grip me."[10]

♦

> Today I'm in the best of spirits with the world. I have isolated a bacteriophage that is behaving very nicely indeed and probably today was the first occasion on which any man in Australia ever saw the curious worm eaten appearance of a bacteriophage culture on agar ... The "alone I did it" feeling is nice and it is pleasant to be tackling something new ... I have more imagination than is good for a pure scientists and at the moment rosy colored visions of the possibilities in the bacteriophage are opening before me.[11]

This diary entry by Burnet, written a few weeks after he had commenced a registrarship in pathology at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne, marks what was inarguably the most exciting and influential research project that he encountered during this early phase of his career. At the time "a fascinating new fairy-tale of science," bacteriophages have since secured a permanent place in the history of science as one of the most important research tools for establishing molecular biology in the mid twentieth century.[12] Their role in this development, as well as the history of their discovery and the priority dispute that ensued, have been well documented.[13] Less well-known and only recently subject to historical investigation have been the advances in bacteriophage research in the years between these two events. Burnet was one of the most prolific and prominent contributors to this era of bacteriophage research, and made crucial contributions to the understanding of their nature and uses.[14] Reciprocally, the bacteriophages became the whetstone on which he honed his scientific style and the habits of mind and laboratory practice that shaped his career.[15] They laid the foundations for his later success as an immunologist: "keeping me thinking about the nature of immunity and the antibody," and eventually in his formulation of the concept of self.[16]

Burnet's first major contributions to bacteriophage research was made as a PhD student at the Lister Institute in London, England, where he developed a technique for assaying bacteriophages and found evidence to confirm Félix d'Hérelle's idea that the entities he had discovered and named were viruses.[17] Early in his investigation of bacteriophagy, d'Hérelle had designed an experimental protocol to track the growth of bacteriophages. The results seemed to indicate that bacteriophage particles increased in a stepwise fashion synchronized with bursts of lysis from the host bacteria. D'Hérelle had considered this evidence compelling enough to conclude that bacteriophages were particulate viruses that infected bacteria and multiplied within them.[18] Most researchers interested in the phenomenon disagreed with d'Hérelle's notion of bacteriophages as viruses; they offered many and varied alternate theories, but no one had actually tested, much less refuted, his results. It was left to Burnet, a dozen years after d'Hérelle had introduced his ideas, not only to improve the original experimental design, but more significantly, through a series of measured arguments, to falsify all other extant theories for the nature of bacteriophages.[19] When Max Delbrück and Emory Ellis published their classic paper on bacteriophage growth almost a decade later, they owed their assumptions to Burnet's findings.[20]

In a second paper published in 1920, Burnet found himself at odds with d'Hérelle. Burnet was investigating a phenomenon known as lysogeny, which had been discovered by Jules Bordet.[21] Certain bacterial strains, Bordet observed, appeared to undergo lysis spontaneously and to transmit this ability to successive generations of bacteria. It seemed to him that the lytic principle came from within the bacterial cell and could not, therefore, be an external agent akin to a virus.[22] Burnet affirmed that lysogeny was an authentic phenomenon and not an artifact, as d'Hérelle had claimed. But moving beyond Bordet's findings, Burnet saw that lysogeny and d'Hérelle's classical bacteriophagy were completely different phenomena, mediated in very different ways:

> It may be useful ... to regard the phage as an independent parasite *or* [emphasis added] as a unit liberated from the hereditary constitution of some bacterium, the usage being determined wholly by its functional activity at the time.[23]

Burnet's insights into lysogeny may have been premature in light of the lack of knowledge at the time about the physicochemical nature of both viruses and genes, but they were shown to be true by André Lwoff during the 1950s. Many years later, in a commemorative volume in honor of Burnet's eightieth birthday, it would be his work on lysogeny, rather than any later achievements in immunology, that Melvin Cohn identified as a special act of creative genius.[24] Although Cohn did not allude to the earlier article by Graves, there is, in fact, a curious link between the two men's perception of Burnet's genius. The first glimmerings of the notion of organismal selfhood can be found in Burnet's description of lysogeny. By Burnet's reckoning, lysogeny was a phase in the life cycle of the bacteriophage when its autonomous viral self became indistinguishable from the self of the host bacterium by merging with its hereditary constitution.[25]

Burnet continued to work on the bacteriophages, creating a solid body of work. He published 28 papers between 1925 and 1937, including an influential review article, an invited contribution to a set of volumes on medical microbiology, and an original article later deemed a crucial contribution to microbial genetics.[26]

Although Burnet's research during the first decade or so of his career was primarily focused on bacteriophages, they were not his sole pre-

occupation. While a PhD student at the University of London, he was an assistant in the National Collection of Type Cultures (NCTC) at the Lister Institute of Preventative Medicine. This work engaged him in the daily business of bacteriological work; he maintained the NCTC's vast collection of bacterial cultures, "keeping them in order, checking that there had been no changes in character and preparing cultures for dispatch to bacteriologists who had ordered them."[27] When he revisited England as a research fellow during the early 1930s, Burnet developed what he described as a "very warm iron in the fire with the method just devised by Dr. Goodpasture of cultivation of viruses" in chick embryos.[28] His collaboration with British virologist Christopher Andrewes also piqued his curiosity about some groundbreaking work on influenza in which Andrewes was involved.[29] The melding of these two interests would result in some of Burnet's most significant achievements in the 1940s and 1950s.

Burnet proved his mettle as an independent scientist in Australia during the investigation of the incident that came to be known as the Bundaberg tragedy, named for the northeastern Australian town where it occurred. In January 1928, what had begun as a progressive, health-conscious campaign to immunize local children against diphtheria took a tragic turn, leaving 12 dead and six others severely ill within 24 hours of receiving the vaccine. Despite the vaccine being the obvious common denominator, exactly how and why it was implicated in the illness and fatalities was not immediately evident.[30] A task force headed by the director of WEHI, Charles Kellaway, was formed in response to a public outcry.[31] Kellaway swiftly turned over the microbiological part of the investigation to Burnet, who worked with Mavis Freeman to solve the mystery. They determined that the vaccine material had been contaminated with *Staphylococcus aureus*, a fairly innocuous bacterium that causes boils and carbuncles, but which can be dangerous when introduced into the bloodstream in large numbers.[32] Besides helping to establish Burnet's reputation, the Bundaberg tragedy also proved to be a scientific opportunity:

> From the point of view of my own professional career the "staphylococcal phase" was important for a totally different reason. It was the beginning of a more serious approach to the nature of antibody production.[33]

By the late 1930s, Burnet had given himself over entirely to investigating animal viruses. Spurred by epidemics in Australia, he investigated not only viruses, but also diseases, such as psittacosis and Q fever, caused by more mysterious agents. His most significant body of work in animal virology was on the influenza virus. Between 1935 and 1958, he published some 98 papers on the subject. He developed methods for cultivating and assaying influenza viruses in chick embryos, identified techniques for isolating them from human patients, and made some of the earliest attempts to develop influenza vaccines.[34] Of the six times Burnet was nominated for a Nobel Prize prior to receiving the award, he was named twice, along with Ernest Goodpasture, for refining the techniques for growing the influenza viruses on chick embryos into a quantitative assay for these viruses.[35]

In 1944, while on a three-month tour of major research centers in the United States, Burnet was invited to deliver the prestigious Dunham lectures at Harvard University.[36] Rather than presenting details of his ongoing clinical research, he chose instead to focus on the more theoretical topic, "Virus as Organism," because, "I had an interesting story to tell of virus diseases looked at from an ecological angle."[37] This ecological viewpoint was in fact an integral element of Burnet's biological thinking. He had already begun to elaborate these views in *Biological Aspects of Infectious Disease*, a semipopular book "written from the point of view of a biologist as much interested in how the parasitic species survives as in how the host species resists it."[38] It was here that Burnet first clearly articulated his concept of selfhood. "Any organism," he wrote, "which lives by digesting the substance of other organisms must in some way be able to distinguish between 'self' and 'non-self.'"[39]

Although the first mention of the self was put forward in the context of digestion rather than immunology, it was not long before Burnet extended the argument to draw broader generalizations about the nature of biological individuality. His work on staphylococcal toxins was a major step in this direction, but he was also shaped by more philosophical influences, such as the works of Alfred North Whitehead, along with advances in cybernetics and information theory.[40] By 1949, Burnet felt he had sufficiently developed his ideas about the self in the immunological context and published *The Production of Antibodies*, coauthored with his colleague Frank Fenner. Their detailed explanation of what was meant by the self and why it was important came to define the entire discipline of immunology for generations to come:

> It is an obvious physiological necessity and a fact fully established by experiment that the body's own cells should not provoke antibody formation ... This is not due to any intrinsic absence of antigenic components ... The failure of antibody projection against autologous cells demands the postulation of an active ability ... to recognize "self" pattern from "not-self" pattern in organic material taken into their substance.[41]

Until this point, Burnet, for all his deep thinking on the subject, had not published papers in basic immunology. Despite this status as a relative newcomer to the field,

The Production of Antibodies had an enormous impact on immunologists.[42] Peter Medawar claimed that the book helped him and Rupert Billingham to evaluate the results of certain transplant experiments, which had appeared nonsensical without the context that Burnet and Fenner provided.[43]

As for its impact on Burnet, it is not a stretch to credit this publication as the most important milestone on the "road that led eventually to Stockholm."[44] When he was awarded the Nobel, *The Production of Antibodies* had been Burnet's only publication that dealt explicitly with the notion of the immunological self. The concept of immunological tolerance, for which he was recognized by the committee, did not in fact appear in the book, but rather in a report by Medawar and Billingham.[45] But, as Medawar remarked in homage to Burnet, "the notion of acquired tolerance was a natural inference" of the concept of the self.[46] Medawar and Burnet shared the 1960 Nobel Prize.

Despite all the attention it drew from different quarters, Burnet saw his work on immunological tolerance as "essentially only a way-station on the road to [a] broader conception" of the nature of immunity.[47] He believed that the most important contribution of his scientific career was the formulation and explication of the clonal selection theory of antibody production.[48] This theory explained how a finite population of cells in a body could be responsible for the vast repertoire of exquisitely specific antibodies produced against the myriad of challenges that an organism was likely to face, such as infectious organisms and allergens. Burnet's proposal was that upon its first encounter with a new antigen, a single clone from a population of antibody-producing cells would react by producing two distinct lineages of clones: one to multiply into an army to fight off the invading antigen, and a second held in reserve to reproduce rapidly as the specific antibody when the organism was exposed again to the same pathogen. Burnet's theoretical framework was later backed up by others with experimental evidence.[49] Published in 1957, the clonal selection theory was likely too recent for the 1960 Nobel Prize committee to properly analyze and assimilate into their evaluation of Burnet; they avoided mentioning it altogether. Burnet, though, made up for this oversight during his Nobel lecture, in which he explained the nature of immunity and the immune self against the context of his theory.[50]

Burnet was just a few years away from retirement when he published his first paper on clonal selection. Although he maintained an active publication record until nearly the end of his life, in his own assessment, "I knew that I had done the most important thing I would ever do in science. From December 1960, my personal ambition waned and science seemed less important than the social predicament of man."[51] His later publications reflected this shift as he began publishing books, articles, and reviews ruminating on subjects such as cancer and aging.

Although Burnet is undoubtedly best known for his contributions to biomedical research, his activities were not solely confined to that sphere. "Biological science," he wrote in his autobiography, "studied in the laboratory has *not* [emphasis original] been the whole of my life ... I have not always lived in an ivory tower."[52] Indeed, Burnet made prominent contributions by advising the Commonwealth government on scientific policy pertaining to ionizing radiation and biological warfare, chairing a committee to address the health issues of indigenous populations in Papua New Guinea, and communicating the hazards of cigarette smoking to the public. Gustav Nossal, Burnet's protégé and successor as director of WEHI, characterized his larger role as "the scientist as citizen." Throughout his career, according to Nossal, Burnet

> displayed unusual zeal in communicating to the public his deeply held conviction that an appreciation of scientific principles could impact on many facets of life. He used public lectures, media appearances and the written word in many articles and books to expound his views on diverse subjects of general interest.[53]

The most obvious place where Burnet wielded influence was at WEHI, one of the oldest institutes dedicated to medical research in Australia. He first entered its doors as a first-year medical student in 1923 and remained associated with it for the rest of his career. In 1928, as its assistant director, he led a newly established bacteriology unit. He took over the director's position from Kellaway in 1944. Reflecting on his career, Burnet acknowledged the importance of WEHI: "It is certain [that] if you take away from my life the [WEHI] and what it implies, there is just nothing left."[54]

Despite his long association with the institute, Burnet's appointment as its director was not a straightforward promotion. Although he had been a mentor throughout Burnet's early career, Kellaway advised him against making a bid for the position. The advice was prompted, at least in part, by a belief that Burnet's shy and introverted temperament was ill-suited to the nonscientific demands of the role.[55] Burnet did not entirely disagree with Kellaway, but he felt he had earned the position, for which he had the "fundamental vision and drive." Having "acted as [Kellaway's] deputy competently enough during his rather long wartime absence," Burnet felt that he could do the job without sacrificing his own research or scientific reputation.[56] Whatever his private advice to Burnet may have been, Kellaway did not thwart his ambitions. As it turned out, Burnet's stewardship of WEHI was certainly more than adequate. He found what Nossal described as "a superb administrative formula without ever seeming to be an administrator" and steered the institute to international prominence.[57]

Burnet's directorial decisions were not always uniformly applauded. On more than one occasion he acted unilaterally, assuming the sole responsibility for significant decisions. Likely the biggest surprise was his directive, announced at a special meeting late in 1957, that "henceforth all laboratory research in WEHI would focus on immunological topics; virology would be phased out."[58] Nossal recalls at first being dismayed by the decision: "Little did I realise that he had climbed onto a huge wave that was just about to break, propelling us younger workers into a glorious future."[59]

A decision of this magnitude, rendered almost overnight, must have undoubtedly meant major upheaval for many long-standing non-immunologists on staff. Among those affected were Fenner, who despite coauthoring *The Production of Antibodies* would remain a virologist to the end of his career, and Gordon Ada, a microbial biochemist. Both had to relocate in order to continue working, yet they maintained cordial relations with Burnet and continued to speak of him with admiration long after his death.[60] Burnet's vision appears to have paid off. Nearly 50 years after the switch, WEHI still enjoyed a reputation as "probably the world's best known research center devoted to the study of immunology."[61]

Burnet was deeply committed to promoting Australian science and would have surely been pleased by such an assessment.

> In a curiously illogical fashion I have a deep emotional attachment to Australia ... I have been treated with extraordinary generosity by the academic worlds of England and America but I am an Australian and through all my work there was a little extra drive which might be expressed in our idiom "that I'd bloody well show them that we can do as well in this country as anywhere else!"[62]

On more than one occasion, he turned down opportunities to work abroad in England and the United States at more established institutions with bigger, better-funded laboratories and better salaries. Following his Dunham lectures, Harvard University offered him a position. Although it was a flattering and undoubtedly tempting offer, Burnet, whose directorship at WEHI was still in question, turned it down. His decision so impressed Cecil Drinker, former dean of the Harvard School of Public Health, that he wrote to the chairman of the board at WEHI, praising Burnet's conduct:

> I really believe he evinced a degree of loyalty to your Institute and to his country in this matter which men of lesser character might well have given up, since we were prepared to do a great deal for him and he knew it.[63]

It is inevitable that when recognition falls upon an individual, the surroundings are also illuminated. As the recipient of numerous international awards, Burnet's glory was reflected onto both his institute and country. He found his induction into the Fellowship of the Royal Society (FRS) of London in 1942 especially gratifying.

> There is a special magic attaching to the letters FRS, and nothing I have experienced really quite equaled the elation that came with a cable from London in March 1942, telling that I had been elected a Fellow.[64]

Burnet subsequently received the Society's highest awards: the Royal Medal in 1947 and the Copley Medal in 1959. He was knighted in 1951 and received honorary doctorates from Cambridge, Harvard, and Oxford. But he expressed particular pride in being the first Australian to receive the Nobel Prize for research conducted in his home country. The sense of pride was reciprocal. In 1960, the same year he won the Nobel, Burnet was announced as the inaugural winner of the Australian of the Year award.[65]

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1. Robert Graves, "Genius," *Playboy* (December 1969): 276.
2. Graves saw genius as "an incommunicable power of inventive thought" distinctly different from "mere talent," which was the "intelligent exploitation" of said genius. Robert Graves, "Genius," *Playboy* (1969): 127.
3. The immune self was first described in F. Macfarlane Burnet and Frank Fenner, *The Production of Antibodies* (Melbourne: Macmillan, 1949), and explained further by Burnet in "Immunological Recognition of Self," *Nobel Lecture*, Stockholm, December 12, 1960.
   For more recent discussions about Burnet's formulation of this theory and its evolution over time, see Alfred Tauber and Scott Podolsky, "Frank Macfarlane Burnet and the Immune Self," *Journal of the History of Biology* 27, no. 3 (1994): 531–73; Neeraja Sankaran, "The Bacteriophage, Its Role in Immunology: How Macfarlane Burnet's Phage Research Shaped His Scientific Style," *Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 4 (2012): 367–75; Warwick Anderson and Ian Mackay, "Fashioning the Immunological Self: The Biological Individuality of F. Macfarlane Burnet," *Journal of the History of Biology* 47 no.1 (2014): 147–75.
4. He shared the prize with Peter Medawar. "The Nobel Prize in Physiology or Medicine 1960," *NobelPrize.org*.
5. F. Macfarlane Burnet, February 4, 1924, personal diary.
6. F. Macfarlane Burnet, June 1, 1922, personal diary.
7. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 54.

8. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 25.
9. F. Macfarlane Burnet, December 9, 1922, personal diary.
10. F. Macfarlane Burnet, March 20, 1923, personal diary.
11. F. Macfarlane Burnet, January 30, 1924, personal diary.
12. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 52.
13. For an overview of the molecular biology story, see John Cairns, Gunther Stent, and James Watson, eds., *Phage and the Origins of Molecular Biology* (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory of Quantitative Biology, 1966). Primary and historical writings about the discovery include Frederick Twort, "An Investigation on the Nature of Ultra-Microscopic Viruses," *The Lancet* 186 (1915): 1,241–43; Félix d'Hérelle, "*Sur un microbe invisible antagoniste des bacilles dysentériques*," *Comptes rendus de l'Académie des Sciences* 145 (1917): 373–75; Donna Duckworth, "Who Discovered Bacteriophage?" *Microbiology and Molecular Biology Reviews* 40 (1976): 793–802; William Summers, *Félix d'Hérelle and the Origins of Molecular Biology* (New Haven, CT: Yale University Press, 1999).
14. Alan Varley, "Early Bacteriophage Research: The Contribution of Frank Macfarlane Burnet" (MA thesis, University of Kansas, 1981); Neeraja Sankaran, "Frank Macfarlane Burnet and the Nature of the Bacteriophage, 1924–1937" (PhD diss., Yale University, 2006); Neeraja Sankaran, "Stepping-Stones to One-Step Growth: Frank Macfarlane Burnet's Role in Elucidating the Viral Nature of the Bacteriophages," *Historical Records of Australian Science* 19 (2008): 83–100; Neeraja Sankaran, "Mutant Bacteriophages, Frank Macfarlane Burnet, and the Changing Nature of 'Genespeak' in the 1930s," *Journal of the History of Biology* 43, no. 3 (2010): 571–99.
15. Neeraja Sankaran, "The Bacteriophage, Its Role in Immunology: How Macfarlane Burnet's Phage Research Shaped His Scientific Style," *Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 4 (2010): 367–75.
16. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 62.
17. F. Macfarlane Burnet, "A Method for the Study of Bacteriophage Multiplication in Broth," *British Journal of Experimental Pathology* 10 (1929): 109–15.
18. See Félix d'Hérelle, *The Bacteriophage and Its Behavior*, trans. George Smith (Baltimore: Williams and Wilkins Company, 1926), 116.
19. F. Macfarlane Burnet, "A Method for the Study of Bacteriophage Multiplication in Broth," *British Journal of Experimental Pathology* 10 (1929): 114, 109–10.
20. Emory Ellis and Max Delbrück, "The Growth of Bacteriophage," *The Journal of General Physiology* 22, no. 3 (1939): 365–84. For a full treatment of this argument, see Neeraja Sankaran, "Stepping-Stones to One-Step Growth: Frank Macfarlane Burnet's Role in Elucidating the Viral Nature of the Bacteriophages," *Historical Records of Australian Science* 19 (2008): 92–93.
21. F. Macfarlane Burnet and Margot McKie, "Observations on a Permanently Lysogenic Strain of *B. Enteritidis Gaertner*," *The Australian Journal for Experimental Biology and Medical Science* 6 (1920): 277–84. The phenomenon of lysogeny was first described in Jules Bordet and Mihai Ciuca, "*Le Bactériophage de d'Hérelle, sa production et son interprétation*," *Comptes rendus de l'Académie des Sciences* 83 (1920): 1,296–98.
22. Jules Bordet, "Concerning the Theories of the So-Called Bacteriophage," *British Medical Journal* 2 (1922): 296.
23. F. Macfarlane Burnet and Margot McKie, "Observations on a Permanently Lysogenic Strain of *B. Enteritidis Gaertner*," *The Australian Journal for Experimental Biology and Medical Science* 6 (1920): 282.
24. Melvin Cohn, "Burnet, Lysogeny and Creativity," *The Walter and Eliza Hall Institute of Medical Research Annual Review: A Tribute to Sir Macfarlane Burnet* (1979): 9–13.
25. Neeraja Sankaran, "The Bacteriophage, Its Role in Immunology: How Macfarlane Burnet's Phage Research Shaped His Scientific Style," *Studies in History and Philosophy of Biological and Biomedical Sciences* 41, no. 4 (2010): 374.
26. F. Macfarlane Burnet, "The Bacteriophages," *Biological Reviews* 9 (1934): 332–50; F. Macfarlane Burnet, "Bacteriophage and Cognate Phenomena," in *A System of Bacteriology in Relation to Medicine*, VII (London: His Majesty's Stationery Office, 1930); F. Macfarlane Burnet and Dora Lush, "Induced Lysogenicity and Mutation of Bacteriophage within Lysogenic Bacteria," *Australian Journal for Experimental Biology and Medicine Sciences* 14 (1936): 27–38. See also Neeraja Sankaran, "Frank Macfarlane Burnet and the Nature of the Bacteriophage, 1924–1937" (PhD diss., Yale University, 2006), 270–71, for a complete list of Burnet's publications on bacteriophage.
27. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 38.
28. F. Macfarlane Burnet, "From Bacteriophage to Influenza Virus," in *Immunity and Virus Infection*, ed. Victor Najjar (New York: Wiley, 1959), 164; Alice Woodruff and Ernest Goodpasture, "The Susceptibility of the Chorio-Allantoic Membrane of Chick Embryos to Infection with the Fowl-Pox Virus," *The American Journal of Pathology* 7, no. 3 (1931): 209–22.
29. Wilson Smith, Christopher Andrewes, and Patrick Laidlaw, "A Virus Obtained from Influenza Patients," *Lancet* (1933): 66–68.
30. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 64–69.
31. Peter Hobbins, "'Immunisation is as Popular as a Death Adder': The Bundaberg Tragedy and the Politics of Medical Science in Interwar Australia," *Social History of Medicine* 24 (2011): 426–44.
32. F. Macfarlane Burnet and Mavis Freeman, "A Comparative Study of the Inactivation of a Bacteriophage by Immune Serum and by Bacterial Polysaccharide," *Australian Journal of Experimental Biology and Medical Science* 15 (1937): 49–61. This paper was published much later than the actual

problem was resolved. For a more comprehensive account and analysis of the Bundaberg tragedy, see Claire Hooker, "Diphtheria, Immunisation and the Bundaberg Tragedy: A Study of Public Health in Australia," *Health and History* 2, no. 1 (2000): 52–78.

33. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 70.
34. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 5; F. Macfarlane Burnet, *The Use of the Developing Egg in Virus Research* (*Medical Research Council Special Reports* no. 220, Medical Research Council, 1936).
35. "Sir Frank Macfarlane Burnet – Nominations," *Nobelprize.org*, Nobel Media AB 2014. Australian immunologist Peter Doherty believes that "It would not have surprised anyone if [Burnet] had shared a Nobel Prize for his influenza work." Peter Doherty, "Living in the Burnet Lineage," *Immunology and Cell Biology* 77 no. 2 (1999): 168.
36. This tour left such an impression that he devoted an entire chapter of his autobiography to its personal and wider significance. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 73–87.
37. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 79. The lectures were published in book form: F. MacFarlane Burnet, *Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases* (Cambridge, MA: Harvard University Press, 1945).
38. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 23.
39. F. Macfarlane Burnet, *Biological Aspects of Infectious Disease* (New York: Macmillan, 1940), 117.
40. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 79. Warwick Anderson and Ian Mackay, "Fashioning the Immunological Self: The Biological Individuality of F. Macfarlane Burnet," *Journal of the History of Biology* 47, no. 1 (2014): 49.
41. F. Macfarlane Burnet and Frank Fenner, *The Production of Antibodies* (Melbourne: Macmillan, 1949), 85–86.
42. The American immunologist David Talmage, for example, would later recall,

> [T]he little book played a large role in changing the conceptual framework through which antibody formation was viewed. I know it made a large impression on me, because it was published just as I was starting out in immunology.

David Talmage, "The Acceptance and Rejection of Immunological Concepts," *Annual Review of Immunology* 4, no. 1 (1986): 4.

43. "Light dawned when we read ... *The Production of Antibodies*[, which] formed the principal basis of Burnet's audacious theory of the biology of self recognition." Peter Medawar, "Burnet and Immunological Tolerance," *Walter and Eliza Hall Institute of Medical Research Annual Review: A Tribute to Sir Macfarlane Burnet* (1978): 31–33.
44. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 72.
45. David Anderson et al., "The Use of Skin Grafting to Distinguish between Monozygotic and Dizygotic Twins in Cattle," *Heredity* 5, no. 3 (1951): 379–97.
46. Peter Medawar, "Burnet and Immunological Tolerance," *Walter and Eliza Hall Institute of Medical Research Annual Review: A Tribute to Sir Macfarlane Burnet* (1978): 32.
47. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 190.
48. F. Macfarlane Burnet, "A Modification of Jerne's Theory of Antibody Production Using the Concept of Clonal Selection," *Australian Journal of Science* 20, no. 3 (1957): 67–69.
49. Gustav Nossal and Joshua Lederberg, "Antibody Production by Single Cells," *Nature* 181 (1958): 1,419–20.
50. F. Macfarlane Burnet, "Nobel Lecture: Immunological Recognition of Self," Stockholm, Sweden, December 12, 1960.
51. F. Macfarlane Burnet, *Walter and Eliza Hall Institute, 1915–1965* (Melbourne: Melbourne University Press, 1971), 77.
52. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 246.
53. Gustav Nossal, "The Burnetian Legacy: Scientists as Citizens," *Immunology and Cell Biology* 65 (1987): 1.
54. F. Macfarlane Burnet, *Walter and Eliza Hall Institute, 1915–1965*, (Melbourne: Melbourne University Press, 1971), v.
55. Burnet wrote,

> His view was that I was probably near my peak as an investigator and that I should go on at the bench and [thus] remain shielded by someone else from the administrative responsibilities from the administrative responsibilities which I would obviously find difficult and frustrating.

Macfarlane Burnet, *Walter and Eliza Hall Institute, 1915–1965* (Melbourne: Melbourne University Press, 1971), 55.

56. Christopher Sexton, *Burnet: A Life* (Melbourne: Oxford University Press, 1999), 113; F. Macfarlane Burnet, *Walter and Eliza Hall Institute*, 1915–1965 (Melbourne: Melbourne University Press, 1971), 55.
57. Gustav Nossal, "Burnet and Science—An Appreciation," *Australasian Annals of Medicine* 18, no. 4 (1969): 314.
58. Frank Fenner and Gordon Ada, "Frank MacFarlane Burnet: Two Personal Views," *Nature Immunology* 8, no. 2 (February 2007): 111–13.
59. *Water and Eliza Hall Institute of Medical Research*, "Past Directors: Sir Frank Macfarlane Burnet."
60. Gordon Ada and Frank Fenner, conversation with author, August 2003.
61. John Marchalonis, "Burnet and Nossal: The Impact on Immunology of the Walter and Eliza Hall Institute," *The Quarterly Review of Biology* 69, no. 1 (1994): 53.

62. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 43.
63. Quoted in F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 44; and Christopher Sexton, *Burnet: A Life* (Melbourne: Oxford University Press, 1999), 109.
64. F. Macfarlane Burnet, *Changing Patterns: An Atypical Autobiography* (Melbourne: Heinemann, 1968), 234.
65. *Australian of the Year Awards*, "Honour Roll: 1960 Australian of the Year."

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