Frank MacFarlane Burnet: two personal views

Frank Fenner & Gordon Ada

In honor of the fiftieth anniversary of Frank MacFarlane Burnet's presentation of the clonal selection theory, two of his former staff reminisce about their interactions with this Nobel prize–winning scientist.

There is no shortage of publications about Frank MacFarlane Burnet. His autobiography[1], Sexton's biography[2] and the biographical memoir for the Australian Academy of Science[3] all provide detailed information about his career as a scientist. Here, in honor of the fiftieth anniversary of Burnet's presentation of the clonal selection theory, we attempt to convey, in a more personal manner, an account of our interactions with and impressions of Burnet.

Burnet's early work

As a child, Burnet was an enthusiastic collector of beetles. He graduated MB BS in 1922 and MD (by examination) in 1924, and after serving as a house physician to the leading neurologist of Melbourne, Australia, Sir Richard Stawell, he was convinced that his future lay in clinical neurology. However, the Melbourne Hospital superintendent judged (correctly) that his character and personality were more compatible with laboratory medicine. In 1924, he was appointed to the position of hospital pathologist, then operated as part of the Walter and Eliza Hall Institute (WEHI). The new director of the Institute, Charles Kellaway, decided that Burnet should train overseas and sent him to the Lister Institute in the UK, where he gained a PhD working on bacteriophages at the University of London. Back in Australia in 1928, he was asked by Kellaway to carry out bacteriological investigations on children who died after immunization against diphtheria[4]. Burnet showed that these deaths were due to staphylococcal infection and carried out experiments that kindled his interest in antibody production.

In 1931, he received an offer that changed his life: two years at the National Institute of Medical Research in London, to study animal virology. There, he witnessed the first isolation of human influenza virus, an agent that was to dominate much of his subsequent scientific work, and he initiated investigations using developing chicken embryos to grow various viruses (a technique still used in 2006). Back in Melbourne, he continued this work and also published his first book, *Biological Aspects of Infectious Diseases*[5].

Frank Fenner's association with Burnet

In October 1944, while I was still serving in the Australian Army, my boss, the Director of Hygiene and Pathology, Colonel E.V. Keogh, made arrangements for me to work at WEHI for six weeks. In July 1945, I received a letter from Burnet offering me a senior position there, to work on the experimental epidemiology of ectromelia virus, which he had just shown to be closely related to the vaccinia virus. I took up the post in February 1946 and worked with Burnet's group until August 1948, when I went to the Rockefeller Institute in New York as a postdoctoral fellow.

Burnet was the most creative and imaginative scientist that I have known; and I worked for a year at the Rockefeller Institute in 1948–1949, when it was the leading medical research institute in the world, and at Cambridge University in 1961–1962. When I arrived at WEHI in 1946, Burnet and all other staff were working on influenza virus. Burnet kept tight control over their investigations, for in those days of almost nonexistent overseas travel, he thought that he had to compete with large teams studying influenza in the United States. In contrast, he allowed me complete freedom to do as I wished in my project on ectromelia. He did not like driving a car, so the laboratory manager used to pick him up and take him home. He worked at the laboratory bench from 9:30 a.m. until 4 p.m. each weekday. Although we met at the tea room, he was a reserved man and talked little. He smoked cigarettes then, although he later campaigned energetically against smoking.

Frank MacFarlane Burnet at the time of his retirement. Courtesy of the Walter and Eliza Hall Institute of Medical Research.

When I had completed an investigation and written it up, I would give the draft to Burnet. He would read it that evening, and at 4 p.m. the next day we would meet in his office to discuss its publication. He would ask about my current and ongoing work; and in contrast to the practice common in many laboratories then and now, Burnet never put his name on a paper

Frank Fenner and Gordon Ada are at the Australian National University, Canberra, Australian Capital Territory 2601, Australia.
e-mail: frank.fenner@anu.edu.au

involving bench work unless he had done some of that work himself. As a result, all 11 of the papers on mousepox (as we later called ectromelia) were published under my name, sometimes linked with that of my wife Bobbie, who was my unpaid technician.

Although Burnet's work focused largely on influenza, he retained a deep interest in antibody production stemming from his early work on children immunized against diphtheria. In the 1930s, the chemists Breinl and Haurowitz[6] and Mudd[7] had suggested that antibody proteins were folded in specific ways after contact with antigenically important parts of antigens, which acted as templates; this theory formed the basis for an essentially 'instructive' hypothesis about antibody production[8]. Some years earlier, Glenny and others studying antibody responses to diphtheria toxin had shown that there were profound differences between primary and secondary antibody responses[9]. In the early 1930s, Burnet repeated these experiments with staphylococcal toxoid and concluded that the exponential increase in antibody titer that occurred during the secondary response indicated that the multiplication of some entity concerned with antibody production was involved and therefore that the instructive hypothesis must be wrong.

He did not publish these results until 1941, when he produced the first WEHI monograph, *The Production of Antibodies*[10], in which he set out his reasons for discarding the instructive hypothesis. Early in 1948, he asked me to collaborate with him in producing a second edition of *The Production of Antibodies*[11]. Although I helped chase up some of the work done since 1940, notably Medawar's studies of transplantation immunity, Burnet was responsible for all the interpretation and speculation. The second edition is notable because it contains the first mention of the concept of immunological tolerance, which was the topic cited in the award of the Nobel Prize to Burnet and Medawar in 1960.

Gordon Ada's association with Burnet

Shortly after receiving a BSc Honors degree in biochemistry from Sydney University in 1943, I was invited to continue my work at the Commonwealth Serum Laboratories in Melbourne, where I achieved some success—and met Henry Holden at WEHI. I had begun to realize the need for techniques such as ultracentrifugation and moving-boundary electrophoresis for studying and separating proteins. These were unavailable in Australia, so in mid-1946 I went to the National Institute for Medical Research in Hampstead, UK, to work with them. It was there, in early 1948, that I received a letter from Burnet offering me a position at WEHI.

Burnet, internationally recognized for his work on viruses, especially influenza virus, but with a strong interest in immunology, went to Harvard University in 1943–1944 to deliver the Dunham Lectures. He was due to return to Melbourne as the new director of WEHI, but upon seeing how well-equipped the Harvard laboratories were, he was tempted to accept a professorship offered by Harvard. Nonetheless, Burnet finally decided to return to Australia, where he later received a grant of £20,000 from the Australian government to purchase equipment. The senior biochemist at WEHI, Henry Holden, told him about my experiences; hence the letter in early 1948 inviting me to come to the Institute and assist Holden in establishing a biophysical unit. I accepted.

At the time, WEHI housed about 30 institute staff, most of whom were young virologists. I spent all my time doing collaborative research, which was easy to arrange. Burnet spent most of the day in the laboratory that he shared with others. He sat at a set spot at lunch, and this was the place to catch him for a quick discussion on a serious topic. Having earlier seen the effects of the 1918–1919 pandemic influenza in Melbourne, he decided that most laboratory staff should work on influenza virus, in the hope that such studies might lead to a vaccine. Seminars were held on Saturday mornings, and though we all appreciated his attendance, Burnet was basically a shy person and could be uncomfortable when answering some questions. He would usually return later with a precise reply.

In the early 1950s, I was collaborating with Joyce Stone. One day, as we were comparing results, Burnet approached and simply asked us, "Do you think what you are working on is worthwhile?" When we had overcome our surprise, we simply replied, "Yes." He then walked away, lost in thought. Was this an indication of some looming change? Burnet was working on influenza virus genetics. The structure of DNA had just been published, and he was concerned about the surge of interest in the new area of molecular biology.

By that time, it had become clear that antibodies could be produced that recognized almost any protein, even synthetic molecules made of different oligopeptides. Thus, it was realized that the range of different antibody specificities must be very great. It was a paper by Niels Jerne[12] in 1955, claiming that the blood contained tiny amounts of free antibody to antigens that the body had never seen, that sparked a new idea for Burnet. As he later remarked about his reading of this paper, "Suddenly, the penny dropped." He now argued that when a foreign antigen entered the body, it would bind to those clones of cells that express complementary patterns (receptors having the same specificity as the secreted antibodies). This would result in the preferential proliferation of these cells, so that the response to a second dose of the same antigen would be much greater and more rapid, a phenomenon that he had described in the first and second WEHI monographs[10,11]. In contrast, Jerne discussed the interaction of antigen with the secreted antibody, and its fate. Because one of his earlier 'bright ideas' books[13] had been severely criticized, Burnet published a brief account of his concept, which he called the clonal selection theory, in a local Australian journal. Essentially, the article proposed that individual B lymphocytes produce antibodies of a single specificity[14]. There was much discussion of the theory at WEHI seminars, and although he admitted he could not guarantee that there was not more than one antibody specificity per B lymphocyte, he very much preferred one. His book on this topic was published two years later[15].

Then came the surprise. At a special staff meeting late in 1957, he announced that henceforth all laboratory research in WEHI would focus on immunological topics; virology would be phased out. At about this time, the eminent bacterial geneticist Joshua Lederberg arrived on a quick visit to discuss viral genetics with Burnet. A recent medical graduate, G.J.V. Nossal, also arrived, intending to work on a virology topic for his PhD. Instead, using Lederberg's expertise, together the two devised a unique microscopic assay to determine whether rats, each immunized with two serologically distinct salmonella flagella, produced an individual plasma cell that secreted antibodies with two distinct specificities, each capable of recognizing one flagellum[16]. Altogether, 1,500 cells were examined, but not a single 'double producer' was found[17]. This result was the first direct evidence consistent with Burnet's hypothesis. Analyses of a similar type were performed by others, but the results were not always so clear-cut.

Burnet then began to study autoimmunity, but he traveled abroad most years until 1964, to give special lectures on clonal selection. Initially, he had to argue strongly, as the theory was not popular. However, work aimed at elucidating the structure of antibody molecules and related topics forged ahead. At a meeting in southern California in early 1965, different amino acid sequences for different antibody molecules were reported. The slides were shown for only a short time, to avoid details being copied. In 1972, Gerard Edelman and Rodney Porter shared the Nobel Prize for their discovery of the chemical structure of antibodies.

When Burnet retired as director of WEHI in 1965, attitudes toward the clonal selection

theory were changing. Burnet gave the introductory presentation[18] at the first large International Immunology Conference, which was held in Cold Spring Harbor in 1967. In summing up the meeting, Niels Jerne said, "Sir MacFarlane Burnet must have been pleased not only to witness at this symposium the vindication of his Clonal Selection Theory of Acquired Immunity, but also to see how his stimulating ideas have led to a great proliferation of immunologists and to know that the fate of immunology is deposited in so many capable hands."

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

1. Burnet, M. *Changing Patterns: An Atypical Autobiography* (Heineman, Melbourne, Australia, 1968).
2. Sexton, C. *Burnet, A Life* (Oxford University Press, Oxford, 1999).
3. Fenner, F. *Hist. Rec. Aust. Sci.* **7**, 39–77 (1987).
4. Kellaway, C.H., MacCallum, P. & Tebbutt, A.H. *Report of the Royal Commission into the Fatalities at Bundaberg* (Government printer, Canberra, Australia, 1928).
5. Burnet, F.M. *Biological Aspects of Infectious Disease* (Cambridge University Press, Cambridge, 1940).
6. Breinl, F. & Haurowitz, F. *Z. Physiol. Chem.* **192**, 45–57 (1930).
7. Mudd, S. *J. Immunol.* **23**, 423–427 (1932).
8. Pauling, L. *J. Am. Chem. Soc.* **62**, 2643–2657 (1940).
9. Glenny, A.T. in *A System of Bacteriology in Relation to Medicine* Vol. VI, 106–193 (His Majesty's Stationary Office, London, 1931).
10. Burnet, F.M., Freeman, M., Jackson, A.V. & Lush, D. *The Production of Antibodies: a Review and Theoretical Discussion* (Monograph of the Walter and Eliza Hall Institute of Research in Pathology and Medicine, No. 1) (Macmillan, Melbourne, Australia, 1941).
11. Burnet, F.M. & Fenner, F. *The Production of Antibodies* 2nd edn. (Monograph of the Walter and Eliza Hall Institute of Research in Pathology and Medicine, No. 2) (Macmillan, Melbourne, Australia, 1949).
12. Jerne, N.K. *Proc. Natl. Acad. Sci. USA* **41**, 849–857 (1955).
13. Burnet, F.M. Enzyme, Antigen and Virus: a Study of Macromolecular Pattern in Action (Cambridge University Press, Cambridge, 1956).
14. Burnet, F.M. *Aust. J. Sci.* **20**, 67–69 (1957).
15. Burnet, F.M. *The Clonal Selection Theory of Acquired Immunity* (Cambridge University Press, London, 1959).
16. Nossal, G.J.V. & Lederberg, J. *Nature* **181**, 1419–1420 (1958).
17. Nossal, G.J.V. *J. Exp. Path.* **41**, 89–96 (1960).
18. Burnet, M. *Cold Spring Harb. Symp. Quant. Biol.* **9**, 1–9 (1967).