BIOGRAPHICAL MEMOIRS

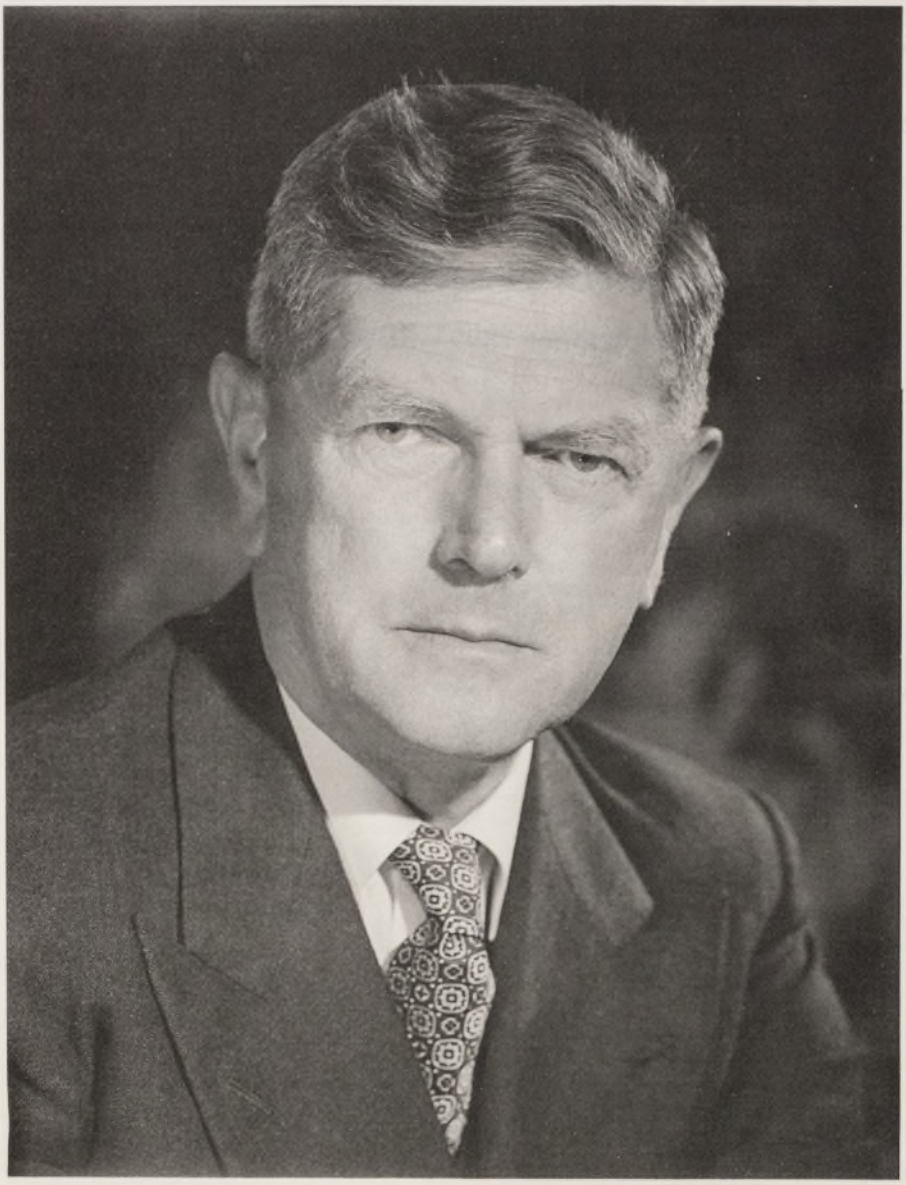
Frank Macfarlane Burnet, 3 September 1899 - 31 August 1985

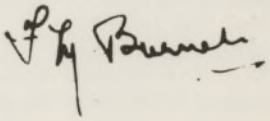
F. J. Fenner, F. R. S.

Biogr. Mems Fell. R. Soc. 1987 **33**, 99-162, published 1 December 1987

FRANK MACFARLANE BURNET

3 September 1899—31 August 1985





FRANK MACFARLANE BURNET

3 September 1899—31 August 1985

Elected F.R.S. 1942

By F. J. Fenner, F.R.S.

Frank Macfarlane Burnet was the greatest biologist that Australia has produced. He spent virtually all of a long working life in Australia. His experimental work on bacteriophages and animal viruses, especially influenza virus, resulted in major discoveries concerning their nature and replication, and he was a pioneer in the application of ecological principles to viral diseases. He proposed two concepts in immunology, acquired immunological tolerance and the clonal selection theory of antibody production, that proved to be of critical importance in stimulating research and led to a more complete understanding of immune processes. In the later stages of his life he wrote about problems of ageing and cancer.

Early life

Burnet was born in Traralgon, a country town in eastern Victoria, Australia, on 3 September 1899. His father, Frank Burnet, was born in 1856 in Langholm, Scotland, and emigrated to Australia as a young man; his paternal grandfather was an architect and factor to the Duke of Buccleuch in Dumfriesshire. His mother, *née* Hadassah Pollock Mackay, was born in Koroit, a country town in Victoria, in 1872. She also came of Scottish middle-class stock, her father being a Glasgow schoolteacher who had emigrated to Australia in the late 1850s and settled in Koroit.

Macfarlane Burnet, who from childhood and throughout his life was known as 'Mac' to his close friends, was the second of seven children. At the time of his birth, his father was manager of the local branch of the Colonial Bank in Traralgon. In 1909 he was transferred and moved with the family to Terang, a country town in western Victoria. In both places young Burnet went to the local state primary school. As related in his autobiography (212)* Burnet retained vivid memories of his life as a boy

* Numbers in this form refer to entries in the list of references at the end of the text.

in Terang, where he returned for vacations until he was in his twenties. He was a shy boy but revelled in the opportunities to wander in the nearby countryside, especially near Lake Terang, where he was greatly interested in the variety of wild life to be seen. He became a member of the Boy Scouts in 1910, soon after the movement was founded in Victoria, and enjoyed the associated camping and outdoor activities.

The first evidence of a serious interest in biology began in Terang where young Burnet became an enthusiastic collector of beetles, an interest he retained all his life. There were no books on biology in his home, and no ready access to them in Terang, but he read all the biological sections of an old *Chambers encyclopaedia* (published in the 1860s), which introduced him to Charles Darwin. His parents bought him *Harmsworth's natural history*, which appeared as a fortnightly periodical. He wrote to Melbourne for a book about beetles, and was sent an English translation of Fabre's *Souvenirs entomologique*. Later he acquired Froggatt's (1907) *Australian insects*, his copy of which shows his intense interest in the Coleoptera—these pages are covered with entries concerning his collecting and his own very creditable drawings of some of the beetles he had found. This interest in beetles led the local Presbyterian minister, the Rev. Samuel Fraser, to note that he was a bright boy and to suggest to his parents that he should have a university education. Always a person with a realistic view of his own qualities and deficiencies, Burnet notes in his autobiography that his attributes in childhood and adolescence fitted well with the picture drawn by Roe (1965) for a group of 'eminent research scientists' working in America: 'Most...were rather shy, socially late-maturing boys with strong hobbies and noticeable persistence in them. [They] were voracious if unselective readers throughout their childhood. Most regarded their fathers with great respect but felt somewhat distant from them.'

University education

Having completed his primary school education Burnet was sent to a boarding school, Geelong College, for four years, an experience that he did not greatly enjoy. In his final year he gained scholarships enabling him to proceed to the university, the most important being a residential scholarship at Ormond College in the University of Melbourne. Choice of a course was not so much because of a desire to be a doctor as a choice of the only kind of professional life that had much of an appeal of the three suggested: medicine, law or the Church. His early years at the university were accompanied by the usual wide reading and broadening of horizons, and a sorting out of his ideas on religion, during which he moved from the traditional social pattern in which he had grown up—Sunday school and later church every Sunday—to become consciously agnostic. Charles Darwin was his hero, whose writings exerted a profound influence on his

scientific work, and H. G. Wells was an important influence on his views about science and society.

At the end of a medical course that was shortened to five years because of World War I and the perceived need when he began the course to produce medical graduates quickly, Burnet graduated M.B., B.S. in April 1922, coming second in a class that contained four other persons who later achieved fame in science and medicine as Sir Roy Cameron, F.R.S., Professor R. A. Willis, Dame Jean Macnamara and Dame Kate Campbell. After graduation Burnet proceeded immediately to prepare for examination for the degree of M.D., which he acquired late in 1924. It was usual to spend one year as a resident medical officer, so as to gain experience in casualty and medical and surgical wards before going into practice. In the surgical wards he came to know two eminent surgeons, each of whom later served as a chairman of the Board of the Walter and Eliza Hall Institute when he was director: Sir Alan Newton and Sir Victor Hurley. However, his greatest satisfaction at this time was to serve as house physician to Melbourne's leading physician at the time, Dr R.R. (later Sir Richard) Stawell, a neurologist. This experience firmly convinced Burnet that his future career lay in clinical neurology, and he applied for the post of medical registrar as a stepping stone for such a career. However, the medical superintendent of the Melbourne Hospital, who was responsible for making such appointments, judged (correctly) that Burnet's character and personality were more compatible with a career associated with the laboratory than with clinical work, and instead he was appointed pathological registrar, and a few months later, senior resident pathologist.

Scientific career

The Walter and Eliza Hall Institute, 1924

At that time the pathology laboratories of the Melbourne Hospital were operated as part (then the larger part) of the Walter and Eliza Hall Institute, which had been established in 1915. As a medical resident Burnet had been interested in the attempts of Dr N. H. Fairley (later Sir Neil Hamilton Fairley, F.R.S.), then a member of the Institute staff, to treat cases of typhoid fever by intravenous injections of typhoid vaccine, an interest that led to Burnet's first scientific papers (1, 2) and subsequently to his interest in bacteriophages.

In 1924 the Institute was transformed with the arrival from University College London of Dr Charles Kellaway (later to become Sir Charles Kellaway, F.R.S., see Dale 1953), to become the second director of the Institute. Kellaway was not content with a predominantly service role for the Institute and proceeded to establish research activities in physiology, biochemistry and bacteriology.

The Lister Institute, London, 1925–27

Kellaway saw Burnet as the potential leader of the small bacteriology section, but decided that he should first have overseas training, and Burnet left for England as a ship's surgeon in June 1925. He took a position at the Lister Institute because there was a paid position available there as an assistant to the curator of the National Collection of Type Cultures, which allowed him about two-thirds of his time for research. A few months later he obtained a Beit Memorial Fellowship and was able to devote himself full time to research on bacteriophages. Under the supervision of Professor J. G. Ledingham he gained a Ph.D. degree of the University of London (1928). A measure of the respect his work had already gained is provided by the fact that he was invited to write the chapter on bacteriophages for the Medical Research Council's *System of bacteriology* (11). A copy of d'Hérelle's (1926) expanded work, *Le bacteriophage*, purchased by Burnet in Paris in July 1927, reveals how carefully he read the book and picked up aspects that prompted additional experimental work. While in London he became engaged to a fellow Australian then resident there, Edith Linda Marston Druce, whom he married on 10 July 1928, after his return to Australia.

Bacteriologist at the Walter and Eliza Hall Institute 1928–31

Shortly after his return to Australia early in 1928 an event called the 'Bundaberg disaster' occurred, in which several children died after receiving inoculations of diphtheria toxin–antitoxin. Kellaway headed the Royal Commission appointed to investigate the tragedy (Kellaway *et al.* 1928) and Burnet carried out the bacteriological investigations, leading to important studies on staphylococcal toxins (see page 116). At the same time he continued studies on bacteriophages, producing some papers later regarded as classics (see page 115).

National Institute of Medical Research, London, 1932–33

In November 1931 Burnet received an offer that changed the course of his scientific life. Sir Henry Dale, Director of the National Institute of Medical Research at Hampstead, had received a generous offer from the Rockefeller Foundation to expand the excellent work on animal virology then in progress at Hampstead, and after consultation with Kellaway he invited Burnet to participate in this work. This was a period of great activity, for with people like Sir Patrick Laidlaw, Wilson Smith, C. H. Andrewes, W. J. Elford and J. E. Barnard the Hampstead laboratories were world leaders in research on animal viruses. The excitement caused by Laidlaw's comment 'The ferrets are sneezing' remained with him all his life (212); it may even have influenced his later decision to

concentrate on influenza virus. During this period Burnet developed his work on the use of the chick embryo for the isolation and assay of animal viruses (see page 119). He also acquired a powerful friend in Sir Henry Dale, who offered him a permanent position at the National Institute. However, he decided to return to Melbourne, where he became Assistant Director of the Institute, in charge of the virus section.

FIGURE 1. Burnet in 1934, on his return from London to Melbourne, with the then Director of the Walter and Eliza Hall Institute, Dr Charles Kellaway.

Assistant Director, the Walter and Eliza Hall Institute, 1934–43

Back in Melbourne Burnet rounded off his work on bacteriophages and continued actively to study the behaviour of a variety of viruses in the developing chick embryo. Seizing opportunities as they arose, he worked on psittacosis, an experience that influenced his thinking in his first book *Biological aspects of infectious disease* (64), recognized a rickettsia to be the cause of Q fever, and carried out studies on poliovirus. However, his major interest after 1939 was influenza virus, prompted by the discovery of methods of growing the virus in the amniotic and allantoic cavities of the chick embryo (61, 66). With the onset of World War II his attention was focused on methods of immunizing against influenza, in case there should be another epidemic like that of 1918–19. In 1942 he was elected

F.R.S. and in 1944 made his first trip to America, where he delivered the Dunham Lectures at Harvard University (97) and received an attractive offer of a chair at Harvard. This tempted him greatly and was refused only after much soul-searching, principally out of a feeling of loyalty to Australian science and especially to the Hall Institute.

Director of the Walter and Eliza Hall Institute, 1944–65

In 1943 Kellaway was appointed Director of the Wellcome Foundation in London and Burnet was appointed Director of the Walter and Eliza Hall Institute in 1944. He had been greatly impressed with what he saw of medical research in the United States in 1944, especially in Harvard, and set out to achieve something of this pattern in Melbourne (89). He decided that the future activities of the Institute should be concentrated on animal virology, and of those already in the Institute (apart from the Clinical Research Unit), only Gottschalk, a biochemist, continued to work on any other topic. Work continued on influenza virus, concentrating at first on the phenomenon of haemagglutination. When the enzymic nature of influenza virus action on red blood cells became apparent, Gottschalk joined the team and unravelled the nature of the viral enzyme (neuraminidase).

Although he personally evinced no desire to become involved in experiments that used biochemical and biophysical techniques, Burnet recognized that such an approach was essential if the Institute was to contribute to a comprehensive study of animal viruses. In 1946 he sought and obtained from the Government of Australia a special grant of £20 000 (then a very considerable sum) to establish a group equipped to carry out biophysical research on viruses, including electrophoresis, ultra-centrifugation, and later electron microscopic studies. For the next decade the Institute was a mecca for overseas scientists who came to work on influenza virus under Burnet's guidance.

From 1951 to 1956 Burnet himself concentrated on studies of the genetics of influenza virus. His demonstration of high-frequency recombination was received with great scepticism by scientists overseas, because it did not accord with what was found with bacteriophages and therefore with conventional wisdom. The soundness of Burnet's experimental work in this field became apparent when it was demonstrated several years later that influenza virus had a segmented genome (Pons & Hirst 1968).

Although he was an expert and assiduous experimentalist, Burnet also found time to write books summarizing his views on animal virology (160, 177), and with W. M. Stanley acted as co-editor of a major compendium on virology (174).

In parallel with his work on virology Burnet had always been interested in the immune response, and in 1941 he had produced a monograph analysing the nature of antibody production (74). In 1948 he re-examined

this topic (121) and propounded a new hypothesis on antibody production based on analogies with adaptive enzymes. More important, however, was his enunciation in this book of the hypothesis of acquired immunological tolerance.

Honours, both scientific and civil, began to come his way (see page 148). In 1947 he received a Royal Medal and in 1959 the Copley Medal of the Royal Society; he was knighted in 1951. In 1958 he was awarded the Order of Merit and in 1960 the Nobel Prize in Physiology or Medicine.

Although never a keen committee man, as Director of the Institute Burnet accepted an increasing number of national and international obligations. Apart from board meetings and membership of committees of the (Australian) National Health and Medical Research Council that were an obligation of this position, he served as a member of the Defence Research and Development Policy Committee of the Commonwealth of Australia (1947–52), as Chairman of the Radiation Advisory Committee (1955–59), and as Chairman of the Queen Elizabeth II Fellowship Committee (1963–69). As Chairman of the Papua New Guinea Medical Research Committee (1962–69) he played a major part in the establishment of the Papua New Guinea Institute of Human Biology, a name that he preferred to 'Medical Research' in that it emphasized the importance of demography and population growth in the future of that country.

Internationally, Burnet had the unusual distinction of serving as President of both the International Association of Microbiological Societies (1953–57), and the Third International Congress of Immunology (1977). He served on several committees of the World Health Organization, including the W.H.O. (Global) Medical Research Advisory Committee (1959–63), and on retirement undertook the task of acting as foundation chairman of the Commonwealth Foundation in London (1966–69).

In 1957, at an age when most scientists are thinking of contracting their bench work, Burnet made a revolutionary change in the direction of his own work and that of the Institute. He decided that henceforth he (and all staff in the Institute) would abandon virology and concentrate instead on immunology. The reasons for this decision were complex. He saw that virology would in future demand the use of tissue culture rather than the developing chick embryo, and that it would become more and more 'molecular', and he was loathe to undertake either transition. Further, as Lederberg noted (Lederberg, pers. comm., 1986), Burnet at the time was 'remarkably uninformed with respect to modern views on the mechanism of protein synthesis, DNA coding, etc.'. More important, his long-time interest in the theory of antibody production had been stimulated by a paper by Jerne (1955) that proposed a selective model for the process, and by other advances in immunology (see page 134). A few years later this decision was vindicated by the award of the Nobel prize not for virology (for which the award would certainly have been merited),

but for an immunological discovery, acquired immunological tolerance. By 1960 Burnet had gone beyond tolerance to formulate what he himself regarded to be his major contribution to science, the clonal selection theory of antibody production (164, 175).

Burnet's increased prestige and international fame led to a change in his work pattern (see below), so that he had less and less time to spend at the bench. Nevertheless, he continued to produce papers on experimental immunology—on graft-versus-host reactions, as described by Simonsen (he was delighted to find that he could use the chorioallantoic membrane to study immunological phenomena), and on autoimmune diseases, by using New Zealand Black mice as a model.

Burnet had always kept the staff of the Walter and Eliza Hall Institute small, partly, no doubt, to maximize his opportunities for research at the bench. But by 1962 he saw that his successor, whoever he was to be, would require more space, and he devoted considerable effort to obtaining money for two more floors, which were completed in 1966 and named the 'Nuffield–Burnet Laboratories' by his successor. In 1965 he retired from directorship of the Institute, and Dr G. J. V. Nossal (now Sir Gustav Nossal, F.R.S.) was appointed as Director. To mark the occasion the Ciba Foundation organized a symposium on 'The Thymus' (Wolstenholme & Porter 1966) in Melbourne, and the Governor-General of Australia attended his Farewell in the University of Melbourne.

University of Melbourne, 1966–77

For Burnet, as for most scientists, retirement from an official position did not mean the end of active work. Professor S. D. Rubbo, who had just moved into the newly built School of Microbiology in the University of Melbourne, across the road from the Hall Institute, offered Burnet rooms and organized the provision of a secretary, and Burnet began a new career as a writer and elder statesman of science in Australia. At this time (1965) he accepted the Presidency of the Australian Academy of Science, which he had declined 8 years earlier because of his wish to devote himself primarily to his work as Director of the Hall Institute. During the 12 years that he was at the University of Melbourne Burnet produced 13 books, initially on immunology and subsequently on human biology, ageing and cancer, as well as a fourth edition of his first book (230).

He continued to receive honours, both scientific and civil. In 1969, and again in 1974, international symposia were organized by Nossal to celebrate his 70th and 75th birthdays. He received a K.B.E. in 1969 and Australia's highest award, Knight of Australia (A.K.), in 1978. However, in 1973 he suffered a grievous loss when his wife, Linda, died of lymphoid leukaemia. For a time he went to live again in Ormond College, University of Melbourne, where he had lived as a medical student, and renewed his friendship with the Principal, Dr Davis McCaughey, who was later to be

appointed Governor of Victoria. In 1976 he was married again, to Hazel Jenkin, a widow who had endowed the library in the School of Microbiology to commemorate her only daughter, who had died while still a graduate student.

Retirement, 1978–85

In 1978 Burnet decided, at the age of 78, that the time had come to slow down somewhat. He left the School of Microbiology and moved to his home, where he produced two more books, and continued to maintain an extensive correspondence and to write articles on general problems such as the future of Australia. In November 1984 he was operated on for cancer of the rectum and appeared to have made a good recovery, but secondary lesions were discovered early in August 1985 and he died on 31 August at his son's home at Port Fairy, near where he had spent his boyhood. He was given a State funeral by the Government of Australia, and was buried at Tower Hill Cemetery, near Port Fairy. He was survived by his second wife Hazel, his son Ian, his daughters Elizabeth and Deborah, and eight grandchildren.

Pattern of work

Daily and weekly routine

Before embarking upon an analysis of Burnet's scientific work it may be useful to outline the pattern of his activities during the period 1945–55. After this, his increasing fame led to many other calls on his time and increased absences overseas, which disrupted this pattern somewhat, but when at the Institute Burnet always devoted a substantial part of each day to work in the laboratory. Throughout his life at the bench he worked alone, except for one or sometimes two graduate assistants and one or two technicians. In consequence, many of his papers on experimental research show Burnet as the sole author and few list a co-author other than his current graduate assistant. He was careful in the selection of his graduate assistants, and had a succession of highly competent and devoted women help him in this capacity: Margot McKie (1928–34), Mavis Freeman (1928–40), Dora Lush (1934–39), Diana Bull (1941–43), Joyce Stone (1944–50), Patricia Lind (1944–65), Margaret Edney (1948–56), Margaret Gilpin (1948–52), Margaret Holmes (1958–65), Deborah Burnet (1960–62; 1963–64), and Susi Ernyei (1962–64).

Burnet's abiding passion was his scientific work. As Director of the Institute he decided policy, usually after consultation with the Deputy Director, Dr I.J. (later Sir Ian) Wood, and often after discussions with Dr E. V. Keogh, the *éminence grise* of medical research in Victoria in the 1950s. However, he always took absolute responsibility for all appointments of research staff, graduate students and overseas visitors, in

accordance with his policy of ensuring that the Institute should be an élite institution of world standard, small enough to be effectively controlled by one man, himself. He delegated the implementation of policy to the Manager of the Institute, Mr Arthur Hughes, and the Personnel Manager, initially Miss Fanny Williams and, after her retirement, Dr Margaret Holmes.

Burnet did not like driving a car, and over the greater part of the period during which he was Director of the Walter and Eliza Hall Institute he would be driven to work by Arthur Hughes, who lived nearby, just after the morning rush. Arriving at the Institute at about 9.15 a.m. he would work in a small office until about 10 a.m., reading incoming mail, dictating letters to one of the two secretary/typists employed by the Institute up to 1960, and writing some personal letters by hand. He would then go to a relatively large laboratory on the fourth floor where he, a graduate assistant and two laboratory technicians would spend the rest of the day at bench work, usually involving manipulations with developing chick embryos or mice, or reading haemagglutination reactions. At 4 p.m., for him but not his staff the end of the day's bench work, he would go to a small table and work over the data produced by the day's experiments, both his own and those done under his instruction by the graduate assistants. Data would be plotted in various ways; perhaps sketches would be drawn of the appearance of pocks on membranes or foci in mouse lungs, and details of the next day's experiments decided upon. Rarely, if ever, was an experiment exactly repeated; Burnet's usual practice was to accept earlier results and move on to an experiment that would fail if, for some reason, the previous results were incorrect, but that would provide him with new information if, as was usual, they were valid.

He then went again to his office, looked over the afternoon mail and signed letters, talked with the Manager and was driven home by him. Evenings followed a similar regular pattern. After dinner and discussions with his wife and children about the day's affairs, he would sit in a comfortable chair, place a cushion on his knees (like his hero, Charles Darwin), and read through the current journals or scientific papers submitted by members of staff or sent for review, or else write papers or lectures. Relevant references would be entered on cards, with a brief abstract in small, neat handwriting. As Director he read all papers that were to be submitted for publication from the Institute, invariably dealing with them within a day or so of their receipt. If he had an address, lecture or radio interview to give, he would read it aloud to his wife Linda, to elicit her judgement on its intelligibility for the proposed audience, its style and its length.

On Saturday mornings he was involved in two other activities—an hour-long round-table discussion of scientific work in which all scientific staff and research students participated, and 'Saturday morning experiments', which were usually probing experiments on new ideas that might

have little chance of success, or might provide a new lead. These were entered in a special 'blue duck' experiment book. Saturday afternoon was spent reading or writing, doing household chores, or at monthly intervals going on walks in the country with a walking club, 'The Wallabies'. His other relaxation was provided by participation in the monthly dinners of one of Melbourne's oldest dining clubs, the Boobooks, of which he eventually became 'Archboobook'. Most Sunday mornings Burnet himself drove his car to the laboratory, taking the children with him, to take down eggs if the experiment demanded it, while the children went round with the animal attendant to feed and water the rabbits, mice and ferrets. These Sunday morning visits were made as much to give Linda a few hours of freedom from the children, and himself their uninterrupted company, as for scientific reasons. The rest of the weekend was spent mainly on writing, for he always had a book, monograph or major review 'in production'. A feature of his writing, even of the most abstruse theoretical discussions, was that he rarely crossed out a word, and almost never produced a second draft; the first, neatly hand-written draft was ready for typing out as the final draft, ready for the publisher.

Burnet was very proud of being an Australian, and was determined to show that science of first-class quality could be carried out in Australia by Australians. The majority of his research papers were published in Australian journals, notably the *Australian Journal of Experimental Biology and Medical Science*, and for papers with a medical flavour, *The Medical Journal of Australia*. It was very fitting, and a source of considerable pride, that he was selected as 'Australian of the Year' in 1961.

Intellectual processes

This account of his daily work shows that Burnet was a dedicated and hard-working scientist. Hundreds of other scientists share these traits—what made Burnet so outstanding? Nossal (1969) and Cohn (1979) have analysed this question, and some of the answers will emerge from the description of Burnet's scientific work that follows. But it may be useful to attempt a summary here.

Although perhaps better known as a theoretical biologist, Burnet was a first-class experimental scientist, who until well into his sixties spent the greater part of each day working at the laboratory bench. His name never appeared on an experimental paper unless he had participated substantially in the bench work himself. This involvement in bench work meant that he was able to notice the unexpected result that might otherwise be dismissed as a technical mistake, and follow it up. His own experiments never made use of apparatus more complex than a microscope, for like many medically trained laboratory workers of that era he overestimated the difficulties inherent in the use of biochemical and

biophysical equipment. He rarely used statistical analysis for the evaluation of his experimental results; they had to be capable of unequivocal interpretation without it. And he found that bench work was excellent 'occupational therapy' that allowed his mind to wander and wonder while his hands were occupied with pipettes and eggs.

In his experimental work Burnet was a reductionist; he designed experiments to demonstrate or disprove the 'minute particulars' of his current hypothesis. However, in discussions of his own work, and even more that of his associates, he was quick to relate any new finding to biology as a whole in a most perceptive way. As he says of himself (212), Burnet was an ecologist, and his capacity to integrate discoveries made in diverse fields of science, which is the hallmark of the ecologist, was one of his great strengths.

A remarkable feature of Burnet's career was that although he worked as a virologist until the age of 57, some 90% of his experimental papers being on virology, the two contributions to science for which he became most renowned were in the field of immunology, on aspects in which he had done little or no experimental work. Such breadth and depth of understanding, and such self-assurance as to allow him to challenge established dogma in a field not his own, is rare in the present era of scientific specialization.

In spite of the fact that he never gave a regular course of lectures to undergraduate or graduate students, Burnet was a great teacher. He had a lasting impact on the thinking of the stream of scientists who came to the Hall Institute from Australia and overseas, especially between 1944 and 1965 (*Walter and Eliza Hall Institute of Medical Research Annual Review 1978–79*). Even at this stage of his life he was shy and withdrawn, and reacted most strongly with his colleagues when he discussed a paper that they wished to submit for publication. But all who worked in the Institute had no doubt that they were privileged to be working with a man of genius. He influenced an even wider audience through his books, the majority of which were not technical monographs, but were written in '*Scientific American*' style, for the physician or biologist who was not a specialist in virology, or immunology, or gerontology.

Burnet had knowledge and intelligence in abundance. He was uncommonly broad in his interests and reading and had an excellent memory. But the great and rare qualities to which his knowledge and intelligence were harnessed were originality and creativity. Burnet had a remarkable intuitive grasp of certain fundamental biological concepts, especially Darwinian evolution. He had courage, optimism and the self-assurance and confidence in his own judgement that allowed him to address questions of fundamental importance in spite of his relative isolation in Australia. Indeed, he thought that this isolation was an advantage, because it protected scientists from being too much influenced by 'fashions' in scientific thinking. He was a lateral thinker with an unparalleled capacity

to link apparently unconnected observations. This led him to devote as much mental energy into interpreting the world literature as most people put to interpreting their own work. However, he did not have much interest in other people's theories, except in so far as they helped him to remould his own.

Of course, he had weaknesses. He was very reluctant to accept the 'ultimate reductionism' of DNA, and in both articles and books castigated molecular biology as being potentially dangerous, and unlikely to make a contribution to human health commensurate with the funds and talent that were devoted to it. Even this much-criticized shortcoming had its logic. His comment referred to medical science, not biology in general, and he argued that little could ever be done to prevent afflictions due to genetic errors (germline or somatic), and that little research in molecular biology was needed to control or prevent the diseases due to environmental influences. The major problem, he thought, was to ensure the proper distribution of known methods of preventive and curative medicine, which applied almost exclusively to extrinsic diseases, to all of the world's people.

If one had to nominate 'keywords' to describe Burnet's greatness as a biological scientist, they might include originality, creativity, biological intuition, high intelligence, discipline, persistence, excellent memory, capacity for lateral thinking, ability to write rapidly and clearly, and self-confidence.

Scientific work

Burnet's first scientific paper was published in 1924 and his last (246) in 1983; his first monograph appeared in 1936 and his 31st and last book in 1979. For over two thirds of the long period during which he was writing, he spent well over half of each working day, on average, at the bench. His work covered a wider range of subjects in biomedical research than that of most scientists, hence it is convenient to arrange it by major topics, in roughly chronological order. There are, of course, some temporal overlaps, as Burnet responded to urgent biomedical problems that occurred when he was involved in other studies, for example the Bundaberg disaster in 1928 and the poliomyelitis epidemic in 1937; and as Director of the Hall Institute, the outbreak of Murray Valley encephalitis in 1951.

Bacteriophages

Although as the pathology registrar at the Walter and Eliza Hall Institute in 1924–25 he was responsible for clinical bacteriology for the Melbourne Hospital, Burnet immediately began to carry out research. In 1924, shortly after beginning work at the Institute, he had acquired a copy

of an English translation of Félix d'Hérelle's first book on bacteriophages (d'Hérelle 1922). His fascination with this subject was heightened by the observation, soon afterwards, of bacteriophage plaques in a culture of *Escherichia coli* grown from the urine of a patient with pyelitis. The study of bacteriophages was to dominate Burnet's research for the next decade, and his 32 papers on the subject, published between 1924 and 1937, included two authoritative reviews on bacteriophages themselves (11, 19), one review on their immunological reactions (43), and several papers of seminal importance for what came to be the sciences of molecular biology and microbial genetics.

In contrast to d'Hérelle, who held that the phenomenon of transmissible bacterial lysis was caused by self-reproducing virus particles, many other scientists of the period, including such notable figures as Jules Bordet and André Gratia, maintained that the phenomenon was caused by bacterial enzymes. Burnet was convinced by the logic of d'Hérelle's view of the particulate nature of bacteriophages, but his experience with isolations from human faeces soon led him to believe that d'Hérelle was wrong in insisting that there was only a single, highly variable, species of virus—*the* bacteriophage. He thought that there were many different species of bacteriophage, and showed that different strains differed greatly in physical and physiological characteristics. To establish this point unequivocally he adopted an approach that was to characterize his later work in animal virology and reflected his childhood interest in collecting and classifying beetles. Taking advantage of the opportunity provided by his brother's dairy farm, he collected specimens from fresh excreta of pigs, cows, horses and chickens, from which he isolated many bacteriophages. Up to this time the principal method of classification was that introduced by Bail (1923), namely study of the resistance patterns of 'smooth' and 'rough' salmonellas to various bacteriophage strains. Burnet decided to employ serology (virus neutralization) for the classification of his collection, and found that with this method 50 cloned bacteriophage strains could be classified into 12 natural groups (23). All members of each serological group also produced plaques with the same general appearance and showed similar patterns when studied by Bail's method. His observations of physical differences between different strains of bacteriophage (10) were greatly strengthened by the demonstration by Elford & Andrewes (1932) that different bacteriophages, mainly from Burnet's collection, differed greatly in size, as judged by filtration through graded collodion membranes.

Although d'Hérelle had made many fundamental observations on bacteriophages and had introduced the basic techniques for their study, namely the limiting dilution method and the plaque assay, he was principally concerned with their possible use for the therapy of human diseases. As a medical bacteriologist Burnet had a similar concern and produced three papers exploring such possibilities (6, 12, 13). However,

his major interest was with the nature of bacteriophages and their interactions with bacteria. Several of his contributions were to be of lasting historical importance, notably a paper on techniques for studying bacteriophage multiplication, papers on the nature of lysogeny, and experiments on the inheritance of bacterial resistance to bacteriophages.

Bacteriophage multiplication

In 1926 d'Hérelle had demonstrated that with a highly virulent strain of bacteriophage and highly susceptible bacteria, bacteriophage multiplication caused step-wise increases in titre. However, proponents of the bacterial enzyme hypothesis of bacteriophage action regarded this as a special case. By modifying d'Hérelle's methods, Burnet (5) was able to show that the step-wise increases in titre were a general phenomenon, applicable to all bacteriophages. These experiments provided the basis of the classical experiments of Ellis & Delbrück (1939) on the one-step growth experiment, a technical manipulation that was to prove of crucial importance in the use of bacteriophages for the development of molecular biology. Shortly after I had joined the staff of the Hall Institute, in 1946, Burnet gave me reprints of the Ellis–Delbrück and subsequent Delbrück papers to read, with the remark that they were scientifically fascinating, but of no practical importance. Parenthetically, Delbrück also had a blind spot; he did not believe in lysogeny but thought that the persistence of bacteriophages in some cultures was due to cryptic infections.

Burnet also carried out important experiments on the initial stage in virus multiplication, namely the attachment of virus particles to the susceptible bacterial cell. He proposed that the initial contact between infecting virus and bacterial cell was a stereo-specific process between complementary structures on virus and cell, analogous to an antigen–antibody reaction (3, 9), and showed that bacterial extracts could specifically inactivate bacteriophage particles to which the intact cell was sensitive, but that similar extracts of bacteriophage-resistant bacteria could not (18, 23).

The significance of lysogeny

The phenomenon of lysogeny has played a central role in the formulation of ideas about bacteriophages. Excluding contamination of a partly susceptible bacterial strain with a bacteriophage ('carrier' cultures), certain bacterial strains exhibit lysogeny, i.e., during their multiplication the bacteriophage genetic material is replicated as part of the bacterial genome (prophage), but occasionally certain bacterial cells release viral particles, which can be detected by their effects on susceptible bacteria.

Lysogeny provided Bordet and other critics of d'Hérelle with their most serious objection to the notion that serially transmissible bacterial

lysis was caused by a particulate virus, because lysogenic bacteria reproduced the lytic principle during their growth without the viability of the cell being affected, a contradiction to beliefs of d'Hérelle and his contemporaries about the essential nature of viral reproduction. The problem was conclusively solved by the elegant experiments of Lwoff & Gutmann (1950), involving the cultivation of individual lysogenic bacteria in microdrops, which led to the notion of 'probacteriophage' (later called 'prophage' and ultimately generalized to 'provirus'). As these authors noted, however, Burnet & McKie (7) had already come close to this view, when they said that permanence of the lysogenic character made it necessary to assume the presence of the bacteriophage or its anlage in every cell of the culture, and drew the conclusion that it was a part of the hereditary constitution of the strain. In other experiments Burnet also recognized the difference between resistance of bacteria at the level of adsorption of bacteriophage particles (4, 18) and what came later to be called the 'immunity' of lysogenic bacteria to infection by a bacteriophage homologous to that it already carried (35).

Microbial genetics

Because so many bacteria are lysogenic, the development of bacterial genetics has been inseparable from studies on bacteriophages. To this extent Burnet's contributions to the understanding of lysogeny, just discussed, are an important part of the early history of microbial genetics. Two other papers report pioneering experiments in what came to be the science of bacterial genetics. Many years before Luria & Delbrück (1943) published their classical paper on the 'fluctuation test', showing that the occurrence of bacteriophage-resistant bacteria in a culture exposed to bacteriophages was due to the selection of bacterial mutants, Burnet (3) had reached the same conclusions, by selecting resistant mutants by their colonial morphology, without the use of phage as a selective agent. Subsequently Burnet & Lush (35) wrote the first paper on bacteriophage genetics, when they discovered a bacteriophage whose capacity for being carried in the lysogenic state had been lost, permanently, by mutation.

Staphylococcal toxin

Burnet arrived back in Australia from his first sojourn in England in December 1927, filled with enthusiasm to carry on his work with bacteriophages. On 27 January 1928, however, within 12 hours after 21 children in the country town of Bundaberg in Queensland had received injections of a diphtheria toxin–antitoxin mixture (then the accepted method of immunization against diphtheria), 18 of them had become ill, and 12 died within 25 hours. Dr Charles Kellaway, the then Director of the Walter and Eliza Hall Institute, was immediately appointed Chairman

of a Royal Commission to investigate the fatalities (Kellaway *et al.* 1928) and Burnet was deputed to carry out the laboratory part of the investigations. He soon showed that *Staphylococcus aureus* could be recovered from both the fluid in the toxin–antitoxin bottle and the pus in the abcesses of survivors. This led him into a completely new field, and over the period 1928–31 the behaviour of staphylococci and their toxins was the central theme of his research, with bacteriophages taking second place.

Over the next four years Burnet published nine papers on the staphylococcal alpha toxin, which was regarded as the cause of death in these children, and some years later, a paper on staphylococcal bacteriophages (26). The Bundaberg disaster was important in the history of the Walter and Eliza Hall Institute (225) because the effective work of its Director, Charles Kellaway, and his staff on a matter of great public interest impressed the name of the Institute and the significance of medical research on the Australian public. Burnet's work on the staphylococcal exotoxin extended a field that had barely been studied before, but the most important aspect of this work for Burnet's future development was an incidental observation on the antibody response of rabbits after intravenous or subcutaneous injection of the toxoid. Despite a very small and slow response to the first intravenous injection, a second injection a few weeks later led to an immediate and rapid rise in the antitoxin level, which rose logarithmically over a period of 40–120 hours after the second injection. Burnet's interpretation of this phenomenon was that something was duplicating itself every 12 hours or so to produce the antibody. His paper on these results and their implications was rejected by the British journal to which it had been sent, but this only stimulated him to collect further information on the topic and to publish it in an Institute monograph, *The production of antibodies*, which was eventually published in 1941 (74). These data also figured prominently in the second edition of the monograph (121), for Burnet saw in this difference between the primary and secondary response, and the logarithmic rise in antibody titre during the secondary response, overwhelming evidence that the Haurowitz–Mudd–Pauling 'instructive' hypothesis of antibody production could not be correct (see page 134).

Animal virology

Although Burnet had already carried out some work with poliomyelitis virus (8, 14; see page 123), his introduction into animal virology really came with his second two-year-long visit to England in 1932–33. Before Kellaway came back to Australia in 1923 he had worked with Sir Henry Dale, the Director of the National Institute of Medical Research in Hampstead, England. Since its opening in 1919 the microbiology department of the National Institute had concentrated on virus diseases, and

by 1931 Dale had gathered together an active group of workers who had made some well-publicized discoveries and were at that time recognized as world leaders in this field. The Rockefeller Foundation offered Dale substantial support to develop work on animal viruses further and, through Kellaway, Dale asked Burnet to come to the Institute on a two-year appointment to study animal viruses. After assuring himself that there would be a post at the Hall Institute when he returned, Burnet accepted the offer and started work at Hampstead early in 1932.

At that time animal virology was in its infancy. Apart from smallpox and vaccine virus, which had been studied for many decades, the only viruses of medical importance that had been isolated were those that caused herpes simplex, poliomyelitis, rabies and yellow fever, and very little detailed study had been made of any of these, However, because all these viruses were already being studied by staff members at Hampstead, another virus had to be found for Burnet. The chance came when Kikuth, the German worker who had just discovered the first effective synthetic antimalarial drug, atebrin, asked Dale to help with the study of a virus that had caused problems in their testing of antimalarials. With the collaboration of J. E. Barnard and W. J. Elford, Burnet (16) showed that the virus was a large one and correctly identified it as canarypox virus, related to but different from fowlpox virus. The fact that it was a virus of birds suggested to Burnet that it might be a good candidate for growth on the chorioallantoic membrane, a technique described for fowlpox virus a year before by Woodruff & Goodpasture (1931) at Vanderbilt University, U.S.A. Many years later Burnet was to pay gracious tribute to Goodpasture (233). The initial experiments were successful and Burnet was introduced to the developing chick embryo, an experimental animal that was to dominate his work in virology, and even in immunology, for the rest of his life at the bench.

At the National Institute of Medical Research Burnet found a lively group of colleagues of about his own age, including C. H. (later Sir Christopher) Andrewes, with whom he continued to conduct a correspondence ('FMB' to 'CHA', and *vice versa*) for many years afterwards. Although working with animal viruses, Andrewes and Elford were also interested in bacteriophages, studying their size, as determined by gradocol filtration (Elford & Andrewes 1932) and the mechanism of neutralization by antibody (Andrewes & Elford 1933). With this example and stimulus, Burnet himself divided his time between studies of animal viruses (mainly their growth on the chorioallantoic membrane), and further work with bacteriophages, on which he published, from the National Institute of Medical Research, seven experimental papers and a major review (19).

Growth of viruses in the developing chick embryo

Although Goodpasture and his colleagues had shown that fowlpox and vaccinia viruses could be grown on the chorioallantoic membrane, they had always used large inocula and obtained confluent growth. In the work described in his paper on canarypox virus (16) Burnet also used concentrated inocula. Some time later, however, he noticed that with dilute suspensions, opaque spots of proliferating cells a few millimetres in diameter were produced. Here was a system comparable with plaque assay with bacteriophages that might be employed for the titration of animal viruses and antisera to them. However, it was not until 1936, after he had returned to Melbourne, that he was to utilize the pock-counting technique for studying the relation between canarypox virus and fowlpox virus (36).

Growth on the chorioallantoic membrane. Having found that canarypox virus grew on the chorioallantoic membrane, Burnet again followed his collecting habits. He studied all the viruses he could obtain, whether from human or animal sources, to study their growth on the chorioallantoic membrane and their effects on the developing chick embryo. In rapid succession papers appeared on the growth on the chorioallantoic membrane of infectious laryngotracheitis virus (17), fowl plague and Newcastle disease viruses (21), vesicular stomatitis virus (22), influenza virus (25), psittacosis 'virus' (27), louping ill virus (34), and ectromelia virus (38). Initially, he merely tested for growth by subinoculation into susceptible animals, and studied the macroscopic and histological changes in the membrane and elsewhere in the chick embryo.

In 1936 he published his first paper on the use of the pock-counting technique, with avian laryngotracheitis virus (30), and illustrated the potential of this method for assaying antibodies to the virus. He immediately applied the method to other viruses, and by the time he came to write his monograph on the use of the developing egg in virus research (39), he or workers in his laboratory had shown that a variety of viruses could be assayed in this way: avian poxviruses, vaccinia, ectromelia, herpes simplex, infectious laryngotracheitis and louping ill viruses and, after adaption by serial passage, influenza A virus.

Over the next four years (1936–40) he worked on a variety of viruses and with the chlamydia of psittacosis (see page 121) and the rickettsia of Q fever (see page 122). A series of eight papers (31–33, 40, 41, 44, 47, 48) utilized pock-counting of egg-adapted influenza virus for the study of various aspects of influenza; other papers illustrated the use of the pock-counting method for the analysis of the natural history of herpes simplex (see page 124) and the pathogenesis of louping ill (53). A few years later he produced a paper (82) describing in detail the methodology of the pock-counting technique, including ways of minimizing the occurrence of non-specific lesions.

Amniotic inoculation. Following a report that inoculation of meningococci into the amniotic cavity produced infection of the lung and meninges of chick embryos, Burnet demonstrated that unadapted (ferret) as well as egg-adapted strains of influenza virus could be propagated in the chick embryo by amniotic inoculation (60, 61), and that this route of inoculation could be used for titration of influenza virus and antibodies (65). It also provided a new, simpler and more sensitive method (than ferret inoculation) for the recovery of influenza virus directly from human patients (69). Until about 1968, when it was found that the Hong Kong strain would grow directly in the allantoic cavity, amniotic inoculation continued to be the method of choice for the recovery of influenza virus from human and animal sources.

Allantoic inoculation. Although he had previously observed that the allantoic fluid contained large amounts of virus after the amniotic inoculation of influenza virus (61), Burnet had regarded this as having been derived from the infected lung, and did not test whether influenza virus would grow after direct inoculation into the allantoic cavity. However, after reading that Nigg *et al.* (1940) had found that a high yield of influenza virus could be obtained from membranes of chick embryos inoculated *through* the chorioallantoic membrane, Burnet tested direct allantoic inoculation, and showed that 2–3 days later all strains tested could be recovered to high titre in the allantoic fluid (66, 67). He commented that this method might be useful for the production of large amounts of virus for use as vaccine (it is still the preferred method of preparation of influenza vaccine). He also noted that with some strains of influenza virus that multiplied to high titre, the embryo was unaffected and hatched normally, however no antibody to influenza virus was produced. It was not until 1950 that he used the chick embryo to test for acquired immunological tolerance (125).

With the discovery of haemagglutination by influenza virus by Hirst (1941), the possibility arose of using allantoic inoculation as a cheap, simple and reliable method of titrating influenza viruses and their antibodies (85, 86). Later he was to concentrate the full resources of the virus group in the Hall Institute on the elucidation of the haemagglutination–elution phenomenon (see page 128). In 1942 Burnet published his first paper on the genetics of influenza virus, based on differences between viruses that were maintained by amniotic passage (O) or passed in the allantoic sac (D) (88). This was a topic that was to become his major interest in the 1950s (see page 130).

This phase of Burnet's research was rounded off with the publication, in 1946, with his colleague W. I. B. Beveridge, of the second edition of the Medical Research Council monograph (105). In contrast to the first edition, which was concerned only with the results of inoculation on the chorioallantoic membrane, all routes of inoculation—chorioallantoic, amniotic, allantoic, intravenous, intracerebral and yolk sac—were discussed.

Psittacosis and the ecological approach to infectious diseases

Burnet did not carry out much research on psittacosis and he published only six papers, over a period of eight years, on the topic. Two of these were routine papers for a laboratory-based microbiologist: one the demonstration that the chlamydiae of psittacosis, like many viruses, multiplied on the chorioallantoic membrane, with the production of pocks when dilute suspensions were used, with characteristic Levinthal–Coles–Lillie (LCL) bodies (27), and the other with the production of focal pulmonary lesions after the intranasal inoculation of mice with dilute suspensions and the use of the method for titrating the agent (73). However, his work with psittacosis had some interesting side effects:

(i) it brought him into contact with Karl Meyer, a powerful figure in contemporary public health activities in California, leading to a lifelong friendship;

(ii) his recent use of Castaneda's strain for LCL bodies led to his early recognition of rickettsiae in Q fever material (see below); and

(iii) his studies of latent psittacosis and an outbreak of lethal disease in Australian wild parrots directly influenced his thinking about the ecology of infectious diseases.

It may be useful to elaborate somewhat on the last of these matters here. In his autobiography (212) Burnet notes that he was '...by temperament an ecologist, a naturalist...'. Until 1934 his naturalist's instincts had been largely directed to beetle collecting, bird watching, and curiosity about the ecology of the bacteriophages of intestinal bacteria. In 1934, in response to a request from the Commonwealth Director-General of Health, he demonstrated that psittacosis was present in apparently healthy parrots obtained from bird dealers in Adelaide and Melbourne (20). Following up this study he demonstrated that asymptomatic psittacosis was enzootic among Australian parrots in the wild, but could cause disease when parrots were stressed under conditions of confinement by bird dealers (24). Some years later he was able to investigate outbreaks of fatal psittacosis that occasionally occurred among wild parrots in nature (49).

Lysogeny was, of course, a perfect example of latent, inapparent infection, and experimental work during 1935–36 had impressed Burnet with the frequency with which inapparent infections occurred in laboratory animals deliberately infected with different viruses (28, 37). Psittacosis exemplified a similar situation, and he interpreted data on the epidemiology of poliomyelitis and yellow fever in man as indicating that most infected humans suffered inapparent infections with these viruses (29). Over the next year or so Burnet put these ideas about the ecology of infectious diseases and immunity together as a book, *Biological aspects of infectious disease* (64), written 'from the point of view of a biologist as much interested in how the parasite species survives as in how the host resists it'. Written before he had read the only other comparable book

at that time, Theobald Smith's *Parasitism and disease* (1934), it presented a rather similar point of view. He later acknowledged his debt to Smith, whose ideas, he said, 'filtered through the writings of others long before I read this famous exposition of the ecological approach in medicine' (233). This first semipopular book of Burnet went through four editions (1940, 1953, 1962, 1972), and was translated into German, Italian, Japanese and Spanish. From my own contacts with scientists in the United States, I know that it and his 1944 Dunham Lectures, *Virus as organism* (97), had a considerable impact on many biochemists and microbiologists by showing the value of thinking of infectious diseases from the point of view of the survival in nature of the parasite, rather than just as diseases of the vertebrate host.

Burnet was to come back time and again to this ecological point of view (131, 132, 144; Fenner 1979), hence his great interest in myxomatosis and Murray Valley encephalitis in Australia (138, 139, 212), two diseases on which he did not carry out any investigations himself, although the work on Murray Valley encephalitis was carried out under his direction.

Q fever

In 1935 physicians in Brisbane, Queensland, became concerned with the sporadic occurrence of a typhoid-like disease among abattoir workers, from which no bacteria could be recovered. Guinea-pigs were susceptible, but again no organisms could be recovered (Derrick 1937). It was reasonable to assume that the disease was due to a virus, hence organs from an infected guinea-pig were sent for investigation to Burnet, late in 1936. Burnet subjected the material to the usual series of tests in experimental animals, making inoculations in guinea-pigs, monkeys, mice, rats and on the chorioallantoic membrane, but soon concentrated on studies in mice, using normal and immune guinea-pigs to determine the specificity of the findings (42). In all his studies of the growth of viruses in experimental animals Burnet used to examine infected organs histologically. Sections of the enlarged mouse spleens showed no inclusion bodies, but under high-power magnification Burnet noticed a 'vague herringbone pattern', which recalled what he had seen in psittacosis and had read about for rickettsias. Using Castaneda's stain, he decided that there was no doubt but that the agent was a rickettsia. In an addendum to his first paper on Q fever, Burnet reported that he had been able to recover the organism from the blood of a patient, and that acute and convalescent sera of another patient showed a substantial rise in agglutinating titre against a rickettsial suspension, thus establishing that it was the cause of Q fever.

The next step was the development of a serological test. Mouse spleens contained very high concentrations of the rickettsiae, which could be substantially purified by differential centrifugation and provided a satisfactory agglutinogen (46). Having confirmed by serological tests that the

rickettsia that they had isolated was without question the cause of the human disease, further work with the agglutination test devolved on Derrick, who used the method with good effect to unravel the epidemiology of Q fever in Queensland (Derrick 1944).

Burnet's subsequent investigations on Q fever were concerned mainly with determining the relation of the Q fever organism to other microorganisms. In a rare excursion into tissue culture he showed that it behaved like the typhus rickettsiae and unlike viruses or chlamydiae in its capacity to continue to multiply in damaged cells (45). Subsequent studies involved direct comparisons with other known rickettsiae, the upshot of which was to show that there was no serological relation between the Q fever rickettsia and other known pathogenic rickettsiae (52). However, early experiments (53) suggested, and later investigations (71, 72) conclusively demonstrated, that it was identical with a rickettsia isolated from ticks in Montana, U.S.A., by Cox (1938), except that the American strain was much more virulent for guinea-pigs.

Apart from being the first of many laboratory workers to be infected with Q fever (51), the only other feature of note in Burnet's association with Q fever is that it was named after him—first, by Derrick, as *Rickettsia burneti* and subsequently, when taxonomists split the genus, as *Coxiella burnetii*. As noted in a recent review (Baca & Paretsky 1983), 'The papers of Derrick and of Burnet and Freeman remain models of careful investigations, critical analyses, and conclusions.'

Poliomyelitis

During the 1920s and 1930s epidemics of poliomyelitis were common in Melbourne, and as a medical virologist Burnet inevitably became involved in the experimental study of polioviruses. An early study (14) provided the first inkling that there was more than one serotype of poliovirus; monkeys that had recovered from intracerebral inoculation with either the Rockefeller Institute 'MV' strain (now known to be poliovirus type 2) or the local strain (probably type 1) were immune to reinfection with the homologous strain but susceptible to the heterologous strain. A severe epidemic of poliomyelitis occurred in Victoria in 1937–38, with over 1900 paralytic cases, and Burnet was appointed by the State Government to the local Advisory Council on the outbreak, and had his first experience of public affairs when he acted as its spokesman.

He was also asked to undertake experimental investigations into the disease, and over the period 1938–40 he and his colleagues produced seven research papers on poliomyelitis in monkeys. After isolation of the virus causing the epidemic in rhesus monkeys, Burnet and his colleagues (54) developed intraocular inoculation as a preferable alternative to intracerebral inoculation in tests for neutralizing antibodies. Then the supply of rhesus monkeys ran out, because of a six-months-long closed season in India. As an alternative, cynomolgus monkeys were obtained from

Singapore. Although some earlier workers had reported that cynomolgus monkeys, unlike rhesus, could be infected by the oral route, Flexner (1936), in extensive experiments with the 'MV' strain, had been unable to confirm this result. Burnet and his colleagues (55) found that cynomolgus monkeys were readily infected by all routes of inoculation, including feeding, swabbing the pharynx and, after laparotomy, inoculation directly into the stomach or small intestine. The orthodox view at the time was that, apart from cases after recent tonsillectomy, the only 'natural' route of human infection was via the olfactory bulbs (Flexner 1936). However, the results obtained with cynomolgus monkeys suggested to Burnet that infection of humans with poliovirus might normally occur by oral or pharyngeal routes. Extending this study (63), he found that poliovirus could be recovered from pharyngeal tissue, certain local nerves (vagus, coeliac plexus), and mesenteric lymph nodes of cynomolgus monkeys infected by the oral or intestinal routes, and then went on to carry out the second and last experiment of his career employing tissue culture. Lung, intestine and buccal tissues of a 12-weeks-old human foetus were used to set up 'Rivers-type' tissue cultures and each culture was inoculated with poliovirus. After incubation for three days the centrifuged supernatant fluids were inoculated intracerebrally into monkeys; those from the intestinal and buccal tissues, but not from the lung tissues, yielded virus. Confirmation of this experiment, the first demonstration of the cultivation of poliovirus in non-nervous tissues, was not possible because 'we have been unable to obtain any other suitable human embryos...so that its implications must be accepted with great reserve'. That paper reported the last of Burnet's experimental work with poliovirus. In a review article (119) published, ironically, in 1949, Burnet 'adopted a wholely defeatist attitude towards the problem of poliomyelitis and ...[hoped] that further developments [would] prove [him] wrong'. Yet his last unconfirmed experiments ten years before had left him poised on the edge of the discovery reported in the classical paper of Enders *et al.* (1949), which was to make possible the effective control of the disease.

Herpes simplex

Burnet and his co-workers wrote only six papers on herpes simplex, all of which were published in 1939. They provided him with confirmatory evidence of the value of the ecological approach in virus research. The studies began with the demonstration that herpes simplex virus of man, B virus of monkeys and pseudorabies virus of swine, which Sabin (1934) had shown shared many characteristics, grew well on the chorioallantoic membrane (56), which provided an accurate and sensitive method for the titration of antibodies to them (57). Burnet confirmed Sabin's opinion that these three viruses were members of a natural group (now designated as the subfamily *Alphaherpesvirinae*).

Burnet's principal contribution lay in describing, for the first time, what is now the accepted view of the epidemiology of this ubiquitous human disease (58). After confirming that aphthous stomatitis in infants was usually due to herpes simplex virus, he and his colleagues showed by serial antibody assays that these were primary infections. They suggested that non-specific resistance to primary infection developed in later childhood, except when there was intimate exposure. In adults there was a sharp distinction between persons with high titre antibody and those without any antibody; intermediate levels of antibody were not found. Further, the presence of antibody was correlated with socioeconomic status, being lowest among university graduates and highest among public hospital patients. It was clear from the occurrence of recurrent herpes that virus persisted somewhere in the body but, like others, Burnet failed in efforts to demonstrate it directly by cultivation of fragments of skin or of Gasserian ganglion. Recurrent herpes simplex occurred in the presence of high levels of antibody and was due to reactivation of the latent virus, by mechanisms then unknown. The epidemiology of pseudorabies in swine and B virus in monkeys, Burnet concluded, was very similar to that of herpes simplex in man, namely asymptomatic infection, usually in very young animals, with lifelong persistence of both virus and antibody. In animals other than their natural hosts all three viruses could produce severe disease.

Poxviruses

Burnet's first paper on animal virology was the demonstration that the causative agent of a disease of canaries was a poxvirus (16), a study that led to his lifelong devotion to the use of the developing egg as a laboratory animal. His early studies with infectious ectromelia virus, which had been discovered at the National Institute of Medical Research a few years earlier (Marchal 1930), established that pock-counting was a feasible method for assaying this poxvirus (38), a technique that I was to use extensively a decade later. It was in studies with ectromelia virus in the developing chick embryo that Burnet introduced into virology the concept that the temperature of incubation influenced viral replication, later to be extensively developed in poxvirus research by Bedson & Dumbell (1961) under the designation of 'ceiling temperature'.

Following the chance observation by Burnet that a suspension of vaccinia virus agglutinated fowl red blood cells (cited in reference 99), Nagler (1942), working at the Walter and Eliza Hall Institute, demonstrated that vaccinia virus agglutinated the red cells of certain fowls only, and that this haemagglutination could be inhibited by anti-vaccinial antibodies. Recalling his experiments with ectromelia virus a decade earlier, Burnet then showed that ectromelia virus would agglutinate cells agglutinable by vaccinia virus and that ectromelia haemagglutination was inhibited by vaccinia-immune serum (92, 100). When he had been

working in Hampstead in 1932–33 Burnet had been interested in Topley's studies in experimental epidemiology, especially in those involving ectromelia virus (Greenwood *et al.* 1936). Now that he had shown that ectromelia virus was an *Orthopoxvirus* (as the genus was later designated), he decided to develop further work in the experimental epidemiology of viral diseases in the Walter and Eliza Hall Institute, based on studies with ectromelia, and in 1946 he appointed me to do this. Burnet himself continued with laboratory studies of vaccinia haemagglutinin and showed that, unlike haemagglutination by influenza virus and arboviruses, the haemagglutinin of vaccinia and ectromelia virus, as found in extracts of infected egg membranes or rabbit skin, was separable from the virions (99, 102, 103), and that non-specific tissue lipids also agglutinated only those red blood cells susceptible to agglutination by the orthopoxvirus haemagglutinins.

Virus classification

In contrast to his friend, C. H. Andrewes, and the famous French virologist, André Lwoff, Burnet was not deeply interested in the classification and nomenclature of viruses. However, because of eminence as a virologist and his position as President-elect and then President of the International Association of Microbiological Societies, he unavoidably became involved in discussions about viral taxonomy. His first contribution came at an international conference of which he was chairman, 'Virus and Rickettsial Classification and Nomenclature', held at the New York Academy of Sciences in 1952. In his introductory address (145) he outlined his ideas on criteria for allocation to a genus ('...approximately the same size and appearance in electron micrographs and, at least, one common functional characteristic'), and concluded by suggesting that '...we should go all out to make a start on virus classification...'. This initiative was followed up at the International Congress of Microbiology in Rome in 1953, where Burnet played an important role in developing a compromise between those who wished to introduce a Linnaean binomial nomenclature forthwith, and those who opposed this. He also suggested that for animal viruses the group names should carry the suffix '-virus', an idea that eventually developed into the present system for viral families (*-viridae*), subfamilies (*-virinae*), and genera (*-virus*).

Subsequently he was a member of the subcommittees that prepared reports on two virus groups: the myxoviruses (159), later to be divided into two families, *Orthomyxoviridae* and *Paramyxoviridae*, and the poxviruses (166).

Influenza

Between 1934 and 1939, after his return from Hampstead, Burnet's investigations ranged over a wide variety of different animal viruses, and included also the non-viral causative agents of psittacosis and Q fever.

Influenza virus was among the viruses for which he was able, with a suitably adapted strain, to develop a pock-counting method of assay. However, this technique was never used by other investigators, and his major contributions to the study of influenza virus began in 1940 with the demonstration that amniotic inoculation of the developing chick embryo (60, 61) provided a method for isolating virus directly from human patients, a method that quickly supplanted intranasal inoculation of ferrets. Continuing his exploration of routes of inoculation of the developing egg, he showed that the allantoic route, although not suitable for isolation of virus from human subjects, could be used for large-scale production of virus that had initially been isolated in the amniotic sac.

By the time World War II had begun, the then Director of the Walter and Eliza Hall Institute, Kellaway, was heavily involved as Director of Pathology for the Australian Army, and Burnet had to serve as Acting Director. With memories of the devastation caused by the influenza pandemic that followed World War I revived by a review of the literature of that disaster (83), Burnet decided that his war effort should be the development of a method of immunization against influenza. In fact, the study of influenza virus became the major focus of his work, and that of the Walter and Eliza Hall Institute, of which he became Director in 1944, until 1957, when he made a historic shift to immunology (see page 133). It took some two years after that change before papers on virology ceased to appear, and over the period 1942–59 Burnet's name was attached to some 114 papers on influenza virus. Because almost every other independent worker in the Hall Institute at that time, apart from the Clinical Research Unit, was working on influenza virus, the volume of investigations on this topic that came under his influence was perhaps three times greater than this. A description of the work on influenza virus carried out at this time by his colleagues and students in the Hall Institute can be found in the annual reports of the Walter and Eliza Hall Institute over the relevant period, or more conveniently in Burnet's history of the Institute (225). All of this work was strongly influenced by Burnet's ideas and perceptions, and often by his advice.

Although his own work covered almost every aspect of the biology of influenza and influenza virus, his major contributions fall into four fields: (i) methods of isolation of influenza virus from human subjects; (ii) immunization against influenza; (iii) the phenomena of haemagglutination and elution; and (iv) influenza virus genetics. His discovery and development of the amniotic and allantoic routes of inoculation have already been discussed (see page 120); the next few pages outline in turn Burnet's work on immunization against influenza, haemagglutination and influenza virus genetics.

Immunization. As early as 1937 Burnet had found that egg-passaged influenza virus (after 65 passages on the chorioallantoic membrane) was

non-pathogenic for ferrets and mice, but produced an immune response and conferred protection against challenge with virulent virus (40). Taking the view that only a live virus vaccine administered by the natural route was likely to be of any use if there was an influenza epidemic during or after World War II that was anything like that experienced in 1918–19, Burnet concentrated his efforts on trying to produce an effective attenuated live virus vaccine. In 1940 he reported the results of spraying various strains of influenza A virus, some attenuated by passage on the chorioallantoic membrane and others fully virulent, into the nose and throat of human volunteers (62). The attenuated strains had no protective effect, whereas the virulent strains caused typical influenza in most subjects who were previously seronegative, but had no effect or produced subclinical infection (as evidenced by antibody rises) in those who had high antibody levels at the time of challenge.

Having recovered influenza virus B by amniotic inoculation from human subjects in an epidemic in Melbourne (76), Burnet proceeded to test the efficacy as a vaccine of influenza B virus attentuated by amniotic passage, inoculated in human volunteers by the intranasal route (77, 87). Antibody responses were observed only in those with low initial titres, and second inoculations produced a much lower proportion of antibody responses and virus reisolations than the first series of inoculations, suggesting that the vaccine might be protective.

However, any pandemic was likely to be caused by influenza A, and in February 1942 Burnet received permission to test, on Australian Army volunteers, influenza A virus that had been grown in the allantoic cavity of the chick embryo. Initial experiments were satisfactory, but by the time vaccination got under way on a large scale (20000 men by June 1942), a natural epidemic of influenza A had already occurred (81); the immunization programme had been launched just too late to test its efficacy adequately (211). By 1943 experiments in the U.S.A. with inactivated vaccine (produced by Burnet's method in the allantoic cavity) had shown good enough results to convince the Australian Army that further experiments with live virus vaccine were not justified. Almost half a century later the position remains unchanged; inactivated influenza vaccines are not very effective, but a satisfactory live virus vaccine has still to be produced.

Haemagglutination. The agglutination of chicken red blood cells by influenza virus was reported independently by Hirst (1941) and McClelland & Hare (1941). It was a discovery that Burnet conceded that he should have made, for he had been working with influenza virus in developing chick embryos for much longer, and much more intensively, than anyone else, but he did not follow up his observation that such clumping occurred. However, immediately after reading Hirst's paper, he saw the value of the method for assaying influenza viruses, and realized that the phenomena of haemagglutination and elution had the makings

of a first-class scientific problem. As the Institute staff built up after the end of World War II he deployed almost all of them on the study of haemagglutination. This work reached its peak in the period that I worked at the Hall Institute (1946–48); I was the only virologist there at that time who was not working on influenza virus and in one way or another on the phenomenon of haemagglutination–elution. Burnet believed that intensive teamwork was essential if the Institute was to be competitive with what were assumed to be the large teams working on the problem in the U.S.A. In fact McClelland & Hare did not follow up the discovery, and Hirst, who did, preferred to work alone, and was very conscious of the size and power of the group of scientists that Burnet had assembled.

A practical result of the availability of the haemagglutination test was to make all other methods of assay of influenza virus and antibodies to it obsolete (79, 86), especially as it was directly applicable to untreated allantoic and amniotic fluids. Following his usual practice of testing new discoveries with all available viruses, Burnet soon showed that Newcastle disease virus also exhibited haemagglutination and elution (75). He seized on the demonstration by Levens & Enders (1945) that mumps virus also agglutinated fowl red cells to point out its similarity to Newcastle disease virus (93), and demonstrated that vaccinia and ectromelia viruses produced a different kind of haemagglutination (see page 125).

However, the major focus of interest was the phenomenon of elution. It was shown that cells from which a particular 'myxovirus' (influenza, Newcastle disease virus or mumps virus) had eluted were inagglutinable by that virus but agglutinable by others further down a 'receptor gradient' (93, 94, 101). Then came one of those feats of biological intuition that were the hallmark of Burnet's genius. Having observed that fowl or human erythrocytes from which myxoviruses had eluted became susceptible to agglutination by normal sera that were without action on normal cells, Burnet recalled the phenomenon of 'panagglutinability' of human red cells described by Thomsen (1926) and Friedenrich (1928). This was ascribed by them to the action of bacterial enzymes, and Burnet (101) showed that enzymes of *Vibrio cholerae*, one of the bacterial species that produced panagglutinability, would remove viral receptors from red cells in almost the order of the receptor gradient. Further studies showed that *V. cholerae* filtrates contained other enzymes of interest—a mucinase and a 'tissue disintegrating enzyme' (108, 110); however his main interest was in what was described as the 'receptor-destroying-enzyme' (109). At the same time Burnet seized on the discovery of Francis (1947) that mucins would inhibit influenza virus haemagglutination to show that mucins were a substrate for both bacterial and viral receptor-destroying-enzymes (107, 114–117, 129). These two discoveries opened the way for Gottschalk, a skilled carbohydrate biochemist who until then had been outside of the 'virus group', to join it (Trikojus 1975), an event that changed Gottschalk's subsequent career and led to his pioneering work

on sialic acid and the glycoproteins (Gottschalk 1957*b*, 1966). The immediate result was the definition of receptor-destroying-enzyme as a neuraminidase (Gottschalk 1957*a*); since then the influenza virus neuraminidase has been crystallized and its sequence and three-dimensional structure determined (Varghese *et al.* 1983).

Leaving the biochemical work to others Burnet's interest in haemagglutination and elution was principally in relation to what light it might shed on the initiation of infection by influenza virus, a topic that he reviewed (129, 130, 135) and chose for his Croonian Lecture to the Royal Society (128).

Influenza virus genetics. (i) *Mutation.* Like other virologists Burnet had always been interested in the changes in virus virulence, for particular hosts, that occur after serial passage of a virus in another host—the classical method of 'adaptation' for laboratory use and attenuation for use as a vaccine. With influenza virus he had observed such changes after passage on the chorioallantoic membrane (40) and after amniotic passage (70). However, his first explicit discussion of genetic changes in influenza virus came with observations of changes in the haemagglutination behaviour of strains of influenza virus newly isolated in the amniotic sac, and after serial passage (80, 88). Newly isolated virus (O; original) differed from passaged virus (D; derived) in a number of characteristics, notably O virus showed a much higher haemagglutination titre with guinea-pig cells than with fowl cells and would not multiply in the allantoic cavity; with D virus the haemagglutination titre was much the same in guinea-pig and fowl cells and the virus multiplied readily in the allantoic cavity. Further, because passage in the amniotic cavity at high dilutions maintained the O characteristics, whereas passage at low dilutions produced D virus, Burnet concluded that the change from O to D was a 'discontinuous mutation'.

He returned to this problem in 1945 (95, 96), and showed that virus could be maintained in the O form if the inoculum was obtained from embryo lung emulsion purified by adsorption with fowl cells, to which such O form virus does not attach. Further observations of sporadic and epidemic cases of influenza (106) supported the concept that in human infections influenza virus always occurred in the O form, and clarified anomalies apparent in earlier work (120). The molecular explanation of the difference between O and D forms emerged 40 years later. They differ in a specific amino-acid residue in the cell-binding site at the distal tip of the haemagglutinin molecule, which alters the binding preferences of the virus for glycoprotein receptors with one kind of sialic acid linkage to those with another. The mutation also produces an antigenic change that may explain the ineffectiveness of inactivated influenza virus vaccines, all of which are produced from allantoic fluid (Robertson *et al.* 1985).

At the time, however, others had not been able to confirm Burnet's

ideas about the mutational nature of the O–D change, partly, he believed, because of the difficulty inherent in the system. He therefore used a simpler system to establish the same principle, namely the maintenance of the neurotropic character of the NWS variant of influenza A virus by serial passage in the allantoic sac at limit dilution, and the loss of the neurotropic character when passage was made at low dilutions (127).

(ii) *Recombination*. Having established to his satisfaction that mutations occurred in influenza virus similar to those observed in bacteriophages, bacteria and higher organisms Burnet set out to determine whether recombination would occur with mixed infections. He first defined two variants of the original WS strain of influenza A virus, WSM and NWS, by a number of very simple 'marker' characteristics—virulence for mouse lung and neurotropism (126). Taking advantage of the phenomenon of viral interference, he found that when a mixture of varying larger amounts of non-neurotropic WSM were mixed with a constant small amount of neurotropic NWS and inoculated intracerebrally in mice, recombinants occurred at the level at which interference with NWS by WSM was just being overcome (133). Subsequently he extended the system by demonstrating recombination between two strains with different serological characteristics (134).

However, mouse brain inoculation, followed by limiting dilution analysis of the progeny of mixed infections, was a laborious process, and it was natural for Burnet to try to demonstrate recombination after inoculation of viral mixtures into developing eggs. In the first of three papers describing recombination between strains of influenza A virus in the developing egg (141), Burnet observed and described a novel kind of interference. He mentioned the possibility that the observed interference was due to some product of the virus–cell interaction that might modify the susceptibility of the target cells (vascular endothelium)—what would now be interpreted as interferon—but preferred the 'negative' interpretation, namely that the continuing viral multiplication in the allantoic membrane led to a deficiency in some plasma component that was needed if the virus was to multiply in and damage the vascular endothelium. Like his failure to discover haemagglutination, this was another 'near miss'; Isaacs, who was later to describe interferon and open a new field in cell biology (Isaacs & Lindenmann 1957), was working on interference between heat-inactivated and active influenza viruses in Burnet's laboratory at this time.

Subsequent papers (142, 143) demonstrated that reciprocal recombination occurred between two different strains of influenza A virus in first-cycle viral multiplication in the allantoic cavity; back-cross experiments were also positive (148) and provided suggestive evidence for the production of 'heterozygotes', a matter that was subsequently elaborated (153, 157). He also showed that recombination would occur between two different strains of influenza B, but not between strains of influenza A and

influenza B virus (149), and obtained recombinants with a wide range of virulence for the mouse lung, a result that led him to postulate the possibility that the genome of influenza virus 'may fracture and the fragments themselves replicate independently'.

In his earlier writings on influenza virus genetics Burnet noted with regret that single-cell experiments of the type used in bacteriophage genetics were not then feasible with animal viruses, a deficiency made good a few years later by Lwoff *et al.* (1955). However, he tried to simplify the system as much as possible, and turned to the use of de-embryonated eggs (147, 152, 153). Some of the progeny obtained in such experiments were doubly neutralizable, partly as a result of phenotypic mixing, partly, he thought, because some of them were heterozygous (153).

Over the next three years Burnet explored a number of unusual features of influenza virus multiplication by means of this approach, including the production of 'incomplete' virus (155), which he showed could contribute genetic information in recombination experiments (158), and the reactivation of inactivated influenza virus (154, 169), which he interpreted, correctly, as being due to genetic recombination. He also reinvestigated the significance of heterozygosis (167) and probed further into the genetic control of viral virulence (165, 168, 171). By this time, however, Burnet realized that he had exploited the purely biological approach to influenza virus genetics as far as it would go. Ada, working in the Hall Institute, had shown that the genome of influenza virus was RNA (Ada & Perry 1954) and that 'incomplete' virus contained less RNA than infectious virus (Ada & Perry 1956). However, it was not until the demonstration by Pons & Hirst (1968) that the genome of influenza virus was segmented that Burnet's results, and those of Hirst, fell into place. Until then many virologists had regarded the 'high-frequency recombination' demonstrated by these two workers with great suspicion, because it was so unlike the results obtained with bacteriophages.

Later, long after Burnet had abandoned the field, genetic reassortment, as the process has come to be called, was taken up as a method of producing vaccine strains (Kilbourne 1969), although in the process the occurrence of the O–D change rendered the vaccine less than ideal (see page 130). It is now widely accepted, also, that new pandemic strains of influenza A virus arose, and may arise again, by reassortment between animal and human strains of influenza virus (Murphy & Webster 1985).

Mumps and Newcastle disease viruses

During his wide ranging examination of other viruses for evidence of haemagglutination, Burnet (75) noticed that Newcastle disease virus behaved very like influenza virus, producing haemagglutination and then eluting from the red cells, although there was no serological relation between the two viruses. He suggested that influenza, Newcastle disease, and mumps viruses (93) belonged to the same group, and used all three

species in experiments with the receptor gradient. However, unlike influenza viruses, mumps and Newcastle disease viruses also lysed red blood cells (118, 123, 124). His only other contribution with these viruses was that he himself was the subject of first reported case of human conjunctivitis due to Newcastle disease virus (84).

In 1955 he was one of the three members of a subcommittee that proposed the name 'Myxovirus' group for the influenza, mumps and Newcastle disease viruses (159), a taxonomic view based on particle morphology and the property of haemagglutination and elution, which had to be discarded when the properties of the genomes of these viruses were discovered (Waterson 1962).

Immunology

Apart from the relatively small speciality of human blood group serology, immunology remained largely the province of the microbiologist until transplantation became a practical measure in the 1950s. Like other microbiologists, Burnet employed serological techniques from the time of his entry into the laboratory (1, 2), and he was an early exponent of serology as a method of bacteriophage classification (15). His interest in the immune response *per se* was stimulated by observations on the antibody response to staphylococcus toxoid, which led to an abiding interest in the production of antibodies and the publication of his first monograph on this topic (74).

After starting work on influenza virus in 1935 Burnet had, by 1956, 'worked out' what could be done with influenza virus genetics without adopting a molecular biological approach (which still lay some years in the future). Tissue culture methods were essential for the study of all other viruses, and he was reluctant to use this technique. On the other hand, his latent interest in immunology had been restimulated by Jerne's (1955) paper describing a 'selective' hypothesis for antibody production. At about the same time Dr Carleton Gajdusek, working in the Hall Institute, had found very high levels of autoantibodies in a patient with an immunoproliferative disease (Gajdusek & Mackay 1958), and Simonsen (1957) had shown that graft-versus-host reactions could be demonstrated on the chorioallantoic membrane, producing pocks caused by cellular proliferation that could be regarded as clonal.

This combination of circumstances led, in 1957, to a decision by Burnet to reorient work at the Hall Institute from virology to immunology, although it took until about 1960 before publications on virology ceased to appear. From 1957 onwards, however, new students, staff and visitors to the Institute worked on immunological problems, Burnet himself being involved in bench work relating to autoimmune diseases and the graft-versus-host reaction, and increasingly in theoretical studies of immunology, immunological surveillance and cancer.

The production of antibodies

During the 1930s Breinl & Haurowitz (1930) and Mudd (1932) proposed a hypothesis to account for antibody production, which was clarified and reformulated by Pauling (1940); namely that antibody protein was synthesized, or according to Pauling, folded, in specific ways in spatial contact with the antigenically significant (determinant) parts of the antigen, which acted as a template—an 'instructive' hypothesis. Burnet could not accept this 'chemical' picture of antibody production, for a number of biological aspects of antibody production were incompatible with it. In 1941 he summarized his views in a monograph (74), in which he reviewed the known facts and developed some ideas on antibody production. Because of the apparently almost infinite variety of antibodies he accepted an instructive hypothesis, but suggested that the antigen impressed a complementary pattern not on the globulin muscle, but on some cellular component, for 'antibody-producing cells must be capable of giving rise to descendant cells with the same faculty'. The same point of view was developed more forcefully in the second edition of the monograph (121), with a new hypothesis for the process of antibody production itself based on an analogy with adaptive enzymes.

The more important feature of the second edition, however, was the exposition of a hypothesis concerning the manner in which the body normally failed to make antibodies to its own components—the 'self-marker' concept. In the course of the discussion of this concept Burnet noted reports in the literature to the effect that mice and calves exposed continuously to antigens during embryonic life (congenital lymphocytic choriomeningitis virus and red cell antigens in some twin births respectively) failed to produce antibodies if exposed to these antigens in adult life. He made the comment: 'If in embryonic life expendable cells from a genetically distinct race are implanted and established, no antibody response should develop against the foreign cell antigen when the animal takes on independent existence.' This prediction was to form the basis for the award of the 1960 Nobel Prize for Physiology or Medicine to Burnet, jointly with Sir Peter Medawar, who had developed an experimental system demonstrating the generality of this phenomenon (Medawar 1961), something that Burnet (125) had attempted to do without success. However, even in 1955 Burnet (161) saw no alternative to an instructive theory to account for the great multiplicity of antibodies that all animals can produce, although on this occasion he invoked the concept of an RNA 'genocopy' to serve as the template.

The revolution in his thinking came in 1956 after reading a paper by Jerne (1955), which developed a 'selective' hypothesis, in which it was postulated that every animal had a large set of natural globulins that had become diversified in some unknown fashion. According to Jerne, the function of an antigen was to combine with those globulins with which it made a chance fit and to transport the selected globulins to antibody-

producing cells, which would then make many identical copies of the globulin presented to them. Burnet turned this idea over in his mind for several months, and '... It gradually dawned on me that Jerne's selection theory would make real sense if cells produced a characteristic pattern of globulin for genetic reasons and were stimulated to proliferate by contact with the corresponding antigenic determinant. This would demand a receptor on the cell with the same pattern as antibody...' (209). Under appropriate conditions such cells would either liberate antibodies or give rise to descendant cells that would do so.

Just before writing a short paper setting out this hypothesis he saw Talmage's (1957) review, in which somewhat the same idea was suggested. Essentially, Burnet envisaged the problem in terms of the population genetics of mesenchymal cells, with the variety of surface receptors and antibody globulins arising as a result of somatic mutation or 'by some other obscure process occurring during differentiation and development'. He published his paper on the subject (164) in an Australian journal, for reasons that reveal some aspects of his personality. One was his Australian nationalism; he knew that it was a good idea and he wanted it to see first light in Australia. On the other hand, he had received adverse criticism of theories he had elaborated in a recent book (161), and he thought that by publishing the paper in this way he would have established priority, if it was eventually going to be recognized as important, and if there was something very wrong with it, very few scientists in America or England would have seen it (212). In fact, this short paper, in which he acknowledged Talmage's contribution, still provides an excellent summary of the theory. Within two years he had elaborated the concept and published it as a book entitled *The clonal selection theory of acquired immunity* (175). He regarded the elaboration of this hypothesis as his most important scientific achievement (212), a view with which many biomedical scientists concur. Two immunologists who were working at the Hall Institute during the 1950s have recently summarized the history of the clonal selection theory. Over the last 30 years it has led to a vast amount of experimental work, which has provided 'a rich insight into the biologic basis of immunity, and the central, unifying framework underlying this understanding is the clonal selection theory of antibody production' (Ada & Nossal 1987).

In 1957 Nossal (Burnet's successor as Director, now Sir Gustav Nossal, F.R.S.) was working as a Ph.D. student in Burnet's laboratory and he set out to test the clonal selection theory by determining whether one antibody-producing cell could make more than one kind of antibody. None of the 456 single cells challenged with two antigens produced two antibodies, although 33 were active against one antigen and 29 against the other (Nossal & Lederberg 1958). Further experiments from the Hall Institute (Ada & Byrt 1969; Nossal & Pike 1976), with other evidence, finally provided formal proof of the validity of the clonal selection theory.

As he was increasingly called upon to give honorific lectures or to participate in symposia, Burnet used the clonal selection theory as the central point of his contributions, and it formed the theoretical basis of the major books on cellular immunology that were produced after his retirement (214, 215). As new discoveries in immunology were made, for example the immunological functions of the thymus and the bursa of Fabricius, they were incorporated within the framework of the theory (183, 188). However, his experimental work, which went on until his retirement in 1965, was principally concerned with two other aspects of immunology: graft-versus-host reactions and autoimmune disease.

Graft-versus-host reactions

In 1957 Simonsen showed that when a chick embryo was inoculated intravenously with adult fowl blood, a graft-versus-host reaction occurred. Here was an immunological phenomenon demonstrable in the chick embryo, Burnet's favourite experimental animal. Further, it was amenable to quantitative study by the pock-counting technique (176, 187). Over the three years 1960–62 the 'Simonsen phenomenon' was the major focus of Burnet's personal laboratory work. He studied the role of major histocompatibility antigens (178) and the effects of corticosteroids on the reaction (181), and showed that chickens could be rendered tolerant by prenatal administration of embryonic spleen cells (186). He and his colleagues also continued to explore the roles of the thymus and bursa of Fabricius in the immune responses of the chicken (180, 188, 190). In a review of the history of the graft-versus-host reaction, Simonsen (1985) commented that: '...the most significant use to which Burnet's group put their CAM assay was in their investigations of bursectomized chicks....That work marked the beginning of our understanding of the T and B cell dichotomy in lymphocytes.' By the end of 1962, however, Burnet felt that investigation of the graft-versus-host reaction on the chorioallantoic membrane had yielded as much as it was likely to in his hands, although a few years later it was to form the basis of experimental work that helped to re-establish the 'passenger leukocyte' concept in tissue transplantation (Lafferty & Jones 1969; Lafferty *et al.* 1983).

Autoimmune disease

Burnet became interested in autoimmune disease in about 1955, partly because staff of the Clinical Research Unit of the Hall Institute suspected that some aspects of chronic hepatitis appeared to have an autoimmune basis. At that time the laboratory findings on which ideas about autoimmune disease rested were the Coombs antiglobulin test, the antinuclear antibody basis of the lupus erythematosus (LE) cell effect, and autoimmune thyroiditis. The demonstration of LE cells in a patient with active chronic hepatitis (Joske & King 1955), and the subsequent observation that such patients, and patients with macroglobulinaemia, had very high levels of antibody to extracts of normal human liver (Gajdusek & Mackay

1958), forced Burnet to face up to the problem of autoimmune disease in the formulation of the clonal selection theory of antibody production (Mackay 1979).

One important aspect of Burnet's elaboration of the clonal selection theory was the notion of 'forbidden clones', which he suggested would provide an explanation for the 'self' 'not-self' conundrum. Autoimmune diseases were seen as aberrations of this mechanism. At 63 Burnet was still a keen experimenter, and he therefore turned to an experimental model that promised to provide an opportunity for the study of autoimmune disease. The model he chose was a strain of mice, 'New Zealand Black' (NZB), of which he heard by chance (189, 212). With Dr Margaret Holmes he devoted the last few years of his life at the bench to exploring various aspects of the biology and immunopathology of these mice, which spontaneously develop a high incidence of haemolytic anaemia of an autoimmune type, at an early age, and other signs recalling human systemic lupus erythematosus (Bielchowsky *et al.* 1959; 191). Having shown that the anaemia could be transferred to young isologous mice by transfer of spleen cells from older mice (179), Burnet and Holmes showed that the affected mice developed characteristic thymic lesions (185, 195). Over the next few years they studied the inheritance of autoimmune disease and thymic lesions (196, 197, 199, 203, 204), emphasizing the importance of a genetic factor and dismissing the influence of a virus (as suggested by others). The clearcut effect of cyclophosphamide in enhancing survival and abrogating renal disease (205) influenced clinical thinking on the use of immunosuppressive drugs in human autoimmune diseases. However, when Burnet abandoned laboratory work at the end of 1965 he was unsatisfied with the results of these experimental studies: '...without [a] break, the whole field may be deserted within a year or two', he wrote in 1967 (212). In fact, the discovery of other inbred strains of mice that also developed autoimmune disease showed that the phenomenon was not just an idiosyncracy of the NZB mouse, and murine models of systemic lupus erythematosus continue to be extensively exploited (Theofilopoulos & Dixon 1985). However, mouse models have not proved to be very useful for studying the basic mechanisms of autoimmune disease.

After his retirement from the Hall Institute Burnet continued to lecture and write on autoimmune diseases (206, 208, 210), and in 1972 he followed up the earlier technical book on the subject (193), written mainly by Mackay, with a second more general book of which he was sole author (231), designed for the 'physician or biologist' rather than the immunologist. Later he became more and more interested in ageing and diseases associated with it, such as cancer, which he approached as he had approached the biological basis of immunity, i.e. as a biologist interested in the population genetics of the cells of the body. Looking at cancer as an immunologist he developed the concept of 'immunological surveillance'.

Immunological surveillance

In 1957 Burnet suggested that 'small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence' (162), a concept for which he later coined the term 'immunological surveillance'. However, he has said that he really developed this concept only after hearing of remarks by Lewis Thomas (1959), suggesting that 'perhaps, in short, the phenomenon of homograft rejection will turn out to represent a primary mechanism for natural defence against neoplasia'. This happened after he had abandoned virology and was reorienting his interests, ranging widely over other kinds of human disease in which immune mechanisms might play a role, notably autoimmune diseases and cancer. He did not carry out any experimental work on surveillance, but discussed it in lectures (207, 213) and reviews (194, 217, 219) over the succeeding years, ascribing a major responsibility to cellular immunity, mediated by T lymphocytes. In 1970 his views on the topic were elaborated in a book entitled *Immunological surveillance* (221), and the same year saw the first international congress on the topic, which Burnet was unable to attend, but for which he provided a final comment (218). Over the next decade he further refined his views on surveillance in books and lectures, expounding the idea that a self-monitoring system was of major importance in cancers of the lymphoid cells, but accepting the widely held view that immune surveillance was probably much less effective in affecting the development of epithelial tumours (243). Inevitably, Burnet's views on surveillance now look dated because, since 1970, new immunological mechanisms that bear directly on the phenomenon have been discovered, such as suppressor cells, natural killer cells, and major histocompatibility (MHC) restriction of the activity of T lymphocytes. However, it is still regarded by tumour immunologists as a useful concept (see Doherty *et al.* 1984).

Cancer

Burnet's experience on the Australian Radiation Advisory Committee (1955–59) had made him think about the relation between ionizing radiation and cancers, especially leukaemia, and he spoke about this problem at some length to both Australian and overseas audiences (163, 170). In 1957, in the process of looking at other fields of biomedical science as he moved out of virology, he undertook a survey of cancer as a biological problem (162), much as he had reviewed the 1918–19 pandemic of influenza in 1941 (83) before embarking on attempts to produce an influenza vaccine. In these articles, and subsequently (240), he was highly critical of research in tumour virology, holding that the conditions under which experiments in this field were carried out were

so highly selected and artificial that they had no relevance for the understanding of human cancer, its prevention or its cure. Burnet did not foresee how the 'oncogene' hypothesis, proposed in 1969 as a direct outcome of research in tumour virology (Huebner & Todaro 1969), would change and develop so that by the late 1980s, in a radically different form, it promised to provide 'the final common pathway to tumorigenesis' (Bishop 1984).

His approach to cancer was profoundly influenced by the observation that in all mammals that have been adequately studied, the incidence of cancers increases with increasing age, reaching much the same levels towards the end of the life span, whether this was 2 years, as in the mouse, or 70 years, as in man. He looked for random processes in the renewable cells of the body, the likelihood of which would increase with the passage of time, as the key to the development of the malignant cell and, therefore, espoused the somatic mutation hypothesis of cancer causation. As advances in molecular biology revealed the complexity of DNA replication and the role played by various enzymes in 'error repair', Burnet emphasized the importance of random somatic mutations in the genes for such enzymes in relation to both carcinogenesis and ageing. He found support for this concept in certain 'experiments of nature', such as the high frequency of skin cancers in patients suffering xeroderma pigmentosum, in which there are congenital defects in these enzymes (243).

He thought that environmental causes of cancer, cigarette smoke, irradiation, etc., might greatly enhance the likelihood that relevant sequential mutations might occur, but that even without such influences the error-proneness in the DNA replication process was subject to random mutation, a process that he called 'intrinsic mutagenesis' (221). In parallel with the increased likelihood with time of the emergence of a series of somatic mutations that might result in the production of a clone of tumour cells, Burnet envisaged that immunological surveillance (see above) diminished in efficiency with increasing age (223). As a corollary, tumours would be likely to develop earlier in individuals with genetic or acquired immunodeficiencies. His concept of cancer was thus a logical extension of the application of Darwinian principles to the phenomena of disease and the interactions of cells within the body, just as was the clonal selection theory of antibody production (172, 173, 235, 240, 242, 245).

Compared with the impact of the concepts of clonal selection and immunological tolerance on the field of immunology, Burnet's hypothesis of intrinsic mutagenesis has had little influence on cancer research. However, it illustrates Burnet's penchant for looking at specific problems from a broad biological and evolutionary point of view.

Public health

It was inevitable that as a medically qualified scientist interested in microbiology, Burnet should have been actively interested in public health and preventive medicine. Even in his early days of bacteriophage research he explored the possibility that bacteriophages might have a role in the treatment of bacillary dysentery (6, 12), and his major virological work, on influenza virus, was always done with one eye on the risks of another pandemic of influenza like that of 1918–19 and the need to develop a satisfactory method of protection against it (see page 127). Later, when poliovirus vaccines became available, he was active both in Australia (156) and in the World Health Organization in advising on their use.

Perhaps his major contributions to public health, however, were in lucid addresses on the application of science to public health. Many of these were given to Australian audiences and most of them were published. Between 1939 and 1955, when he was still working on viruses at the bench, they dealt with infectious diseases in general (50, 68, 98, 113, 131, 136, 146), poliomyelitis (59, 91, 119, 137, 151, 156), rickettsial diseases (78), influenza (90), allergic diseases (111), tuberculosis (112), staphylococcal infections (122), and Murray valley encephalitis (138). In a more general analysis of infectious diseases (140), he took recent data on mortality statistics in childhood and, by using a log–log scale, gave a good graphical illustration of the interactions of changes caused by three factors; the inexperience and development of the immune system in early childhood, its over-reaction in early adult life and its decline in old age.

After moving away from virology be lectured on cancer (162, 207, 241) and leukaemia (170), always with the possibilities of prevention in mind, and in his Presidential Address to the Australian and New Zealand Association for the Advancement of Science (163), he made a strong and well-publicized attack on the danger of undue exposure to medical and dental ionizing radiation, and on the relation between cigarette smoking and lung cancer. Other lectures with public health importance covered such topics as autoimmune disease (182, 184, 202), diseases of old age (198, 216), kuru (224), and the risks of radiation (238).

Human biology

'Human biology' receives special though brief mention in this memoir because of Burnet's view of himself primarily as a human biologist (228, 229, 243) who, from about 1940, had repeatedly tried to apply an understanding of biology to human diseases, and subsequently to human affairs. Initially his interest was in the ecology of the infectious diseases of man. His laboratory experience with the population genetics of bacteriophages and later of influenza virus was then applied to the populations of lymphocytes that make up the immune system, leading to

the enunciation of the clonal selection theory of acquired immunity. Later, he applied a similar approach to his interpretation of the nature of cancer.

However, it was his experiences just after World War II when, as the newly appointed Director of the Walter and Eliza Hall Institute, he was asked to serve on a number of official committees concerned with scientific research, that led him to take a serious interest in the major problems confronting the human species, notably war and overpopulation. A naive newcomer to official committees, he was shocked by their lack of interest in anything except short-term approaches to the problems with which they dealt. In an attempt to draw attention to the long-term problems of man as a mammal, in 1947 he wrote a book with the title *Dominant mammal*. However, at that time it was rejected by both an English and an Australian publisher, and Burnet forgot about it until after his retirement from the Institute. He then went back to his original manuscript, reduced its formerly over-ambitious coverage, and rewrote the book in conformity with scientific knowledge in the late 1960s. It was published, with the title *Dominant mammal : the biology of human destiny*, in 1970 (222). This time, perhaps reflecting Burnet's status as an elder statesman of science, it was a success, being reprinted by Penguin Books and translated into Danish, Japanese and Spanish. *Dominant mammal* expresses most clearly Burnet's philosophy of life. He returned to the same subject again in his last two books (243, 244), in which, among other things, he examined human aggression as the expression of the genetic make-up of man, selected for during his long evolution as a hunter–gatherer, but totally inappropriate for civilized life.

Burnet's deep concern with human biology, encompassing particularly problems of population growth, was expressed again in his choice of these words, rather than 'medical research', for the title of the research institute established in Papua New Guinea in 1968, when he was chairman of the Papua New Guinea Medical Research Advisory Committee. It is ironic that in 1973, reflecting the greater popular and political interest in short-term medical research than in longer-term demographic problems, the name of the institute was changed to the Papua New Guinea Institute of Medical Research.

Ageing

It was perhaps inevitable that a human biologist with as wide a spectrum of interests as Burnet, who continued to read and write well into his eighties, would become interested in the ageing process. It had been implicit in his earlier writings about immunological surveillance and the origin of cancers that both of these processes had a secular component—with increasing age both surveillance and error-correcting mechanisms became less efficient, whereas the likelihood of the occurrence of sequential mutations that might lead to cancer increased with age. In 1970 he

specifically examined immunological surveillance in relation to problems of ageing (216, 220, 221), and a few years later wrote his first paper that dealt explicity with the concept that the characteristic life span of man and other mammals was genetically determined, and that much of the process of ageing was due to somatic mutations in clonally proliferating cells in the body (232). He suggested that quite apart from the effects of extrinsic mutagens, somatic mutation depended on random errors in copying the DNA message, and that mutations in the 'editing' enzymes might increase (or, rarely, decrease) the rate of 'intrinsic mutagenesis'. This was followed, in 1974, by his last referenced 'technical' book, *Intrinsic mutagenesis: a genetic approach to ageing* (235), in which he discussed all aspects of senescence, including ageing of the post-mitotic cells of the brain and the social implications of the biological approach to ageing that he espoused. He accepted the biological necessity for death and was impatient with proposals designed to prolong the human life span. However, he saw '...wide scope for research on the best means of minimizing the depression and misery of pre-death...'. Happily, he and his relatives were spared a long period of dependent pre-death—he died, mentally acute until he lost consciousness, shortly after the onset of his last illness.

Books

This account of Burnet's scientific career mentions incidentally most of the books that he wrote, but this does not give adequate emphasis to his extraordinary productivity. He wrote no fewer than 31 books and monographs, a few of which went through second and subsequent editions, and many of which were translated into other languages. All are lucid, and his many semipopular books are very readable. His first book, as distinct from a long technical report, was written for the non-specialist, to provide a general account of the infectious diseases of man looked at from an ecological point of view (see page 121). Entitled *Biological aspects of infectious disease* (64), it was written in 1937–38 but was not published until 1940. With the title *The natural history of infectious disease* it went through three further editions (1953, 1962 and 1972) and was translated into Italian, Spanish, German and Japanese.

His output of books is all the more remarkable when it is remembered that many of them were produced while he was making major contributions as an experimental biologist. They were of two types: technical overviews of some facet of virology or immunology on which he had been working or was interested, and more or less 'popular' books, written for the physician and biologist who was not a specialist in the field concerned. Early in his life, while he was still working at the bench, his books fell equally into the two categories; of 16 books published after retirement, all except 3 (214, 221, 235) fell into the second.

He began writing major reviews early in life, after being asked to

prepare the chapter on bacteriophages for the Medical Research Council's *System of bacteriology* (11) while still doing his Ph.D. degree in the University of London. The habit of reviewing a field in which he was interested, or had recently carried out extensive experimental work, persisted throughout his life at the bench. As well as writing a classical review on bacteriophages in 1934 (19), he produced a monograph on the growth of viruses in the chick embryo in 1936 (39), which was rewritten and greatly expanded ten years later (105).

Virtually all Burnet's experimental work before 1957 was concerned with microbiology, mainly virology, but his interest in theoretical aspects of immunology was evident from early in his career, and was first expounded in a major review of the immunological reactions of viruses (43). In 1941 he used the device of a monograph, *The production of antibodies* (74), to publish some data on the antibody response of rabbits to staphylococcal toxoid, which had been rejected by a journal, as well as to review the subject in general. In 1949 he published a second edition of this monograph (121), in which he introduced to science the concept of immunological tolerance. Between the publication of these two editions of *The production of antibodies*, he wrote a monograph on influenza (83), as a prelude to his wartime work on influenza virus, and published the Dunham Lectures, *Virus as organism* (97), and another popular book on human infectious diseases (104). The lastmentioned was updated and published as a Penguin paperback in 1953 (150), with a second edition two years later.

Over the period 1955–60 he summarized his great experience in virology as a book, *Principles of animal virology* (160), which was published in 1955. A second edition, his last book on a virological subject, was published in 1960 (177), and was translated into Polish and Japanese. By 1964, when he was asked to prepare a third edition of this book, he had moved over completely to immunology and suggested to the publishers that I should be asked to do it, a request that I declined as such, but responded to by writing *The biology of animal viruses* (Fenner 1968). Burnet always preferred to be sole author of any book that he was involved with, and he had no taste at all for the task of planning and acting as editor of a multi-author book. Nevertheless, at the request of the publishers of the *Principles*, he agreed to act as an editor, with Wendell Stanley, of a multi-author three-volume book, *The viruses* (174), which was published in 1959 and contained five chapters written by Burnet. He undertook editorship, under very different conditions, on only one other occasion when he acted as editor, many years later (1976), of a number of *Scientific American* articles on immunology (239).

By 1958 he was moving out of virology, and after a rather unsuccessful book that attempted to integrate biochemistry, immunology and virology (161) and the production of the second edition of *Principles of animal virology*, he embarked upon purely immunological books. The first of

these was a classic, *The clonal selection theory of acquired immunity* (175). The material of this book was updated and enlarged in 1963 as *The integrity of the body* (192), which was translated into Italian, Japanese, Polish and Russian. His first book on autoimmune disease (193), to which Mackay made a major clinical contribution, was translated into Spanish and Japanese. In 1972, as sole author, he produced another more general book on this subject (231), for 'physicians and biologists'.

After his retirement from the directorship of the Hall Institute, in 1965, he worked full-time as a writer and lecturer, and produced 16 books, a few of which have already been mentioned. They covered a wide range of subjects. *Cellular immunology* (214), a technical, fully referenced book, was the largest book he ever wrote. Ever an innovator he carried out the interesting experiment with this book of preparing simultaneously a shortened version, without references, as a popular book (215). The large book was translated into Russian; the smaller one into Italian, Japanese and German. A year earlier, in 1968, his Boyer Lectures (the Australian equivalent of the Reith Lectures) were published (211), as well as an autobiography (212). In 1970 he produced a book, *Dominant mammal* (222), that he had been thinking about for some 20 years (see page 141). This was translated into Danish, Spanish and Japanese. The same year saw the publication of his first book on problems of ageing, cancer and the immune response, *Immunological surveillance* (221). He was to return to his theme again, with more emphasis on ageing, in 1974 (235, 236) and 1976 (240), but in the mean time he published a history of the Walter and Eliza Hall Institute (225) and another book on human biology (226), which was also published by Penguin Books and translated into Italian and French. His last books were written as he approached his 80th year and were appropriately philosophical in tone: *Endurance of life* (243) and *Credo and comment* (244).

Because of these books Burnet is thought of by many scientists throughout the world as essentially a writer and theoretician. He was this, but he was as well a superb experimenter, as all who worked with him can testify, and as the survey of his personal experimental work (pp. 113–136) illustrates.

Public policy

Burnet was an innately shy person, and until 1937 he had never served on a committee that dealt with matters of public policy. In that year he was deputed to act as spokesman for the Advisory Council set up by the Victorian Government to advise it on measures to be taken in the face of a large outbreak of poliomyelitis. In the existing state of ignorance there was little of value that could be done, but he got a sense of the difference between model infections in the laboratory and a worrying human situation. In 1944, when he was appointed Director of the Walter and

Eliza Hall Institute, he was already a greatly respected authority on infectious diseases, and as Director of what was then the major medical research centre in Australia, he now became a public figure. To fulfil his obligations he schooled himself to overcome his shyness, and in time became a lucid public speaker, and even came to enjoy the limelight. As well as serving as a member or chairman of scientific committees, both in Australia and overseas, he recognized the importance of cooperation with the media if the general public was to understand science and scientists. While ensuring that his bench work was interrupted only for cogent reasons, from the time he became Director of the Institute he always responded to enquiries from the press. In later life he gave a number of radio addresses and occasionally appeared on television but he was rarely comfortable with interviewers, either on radio or television, and he did not seek such confrontations.

Inevitably he received many invitations to participate in activities that were not directly related to his scientific interests. Because all would make demands on his available time he never accepted an invitation without careful thought. As Director of the Walter and Eliza Hall Institute he gave priority to those that would benefit the Institute and his own research activities, but he also accepted some as a matter of duty and a few that he thought might be of particular personal interest.

As a Fellow of the Royal Society resident in Australia, Burnet was a Petitioner for the Charter and a Foundation Fellow of the Australian Academy of Science. He was a member of its Council and Vice-President (1961–63), but did not become seriously involved in its affairs until just before he retired from the Hall Institute, when he accepted an invitation to become President. For the period 1965–69 he thus became 'in one sense the official spokesman for science in Australia', and he 'tried hard to develop a balanced approach to the part science, basic and applied,... should play in relation to medicine and other practical affairs of the community' (212). He was outstandingly successful in this role, and helped greatly in the establishment of the Science and Industry Forum. After he had retired from the Presidency the Council established the Burnet Lecture and Medal to mark his contributions during this period. This lecture is now the Academy's premier award in the biological sciences, being given alternately with the Matthew Flinders Lecture and Medal, which, since 1972, has become the Academy's highest award in the physical sciences.

The more important committees on which Burnet served are listed below:

1947–52 Defence Research and Development Policy Committee (Commonwealth of Australia)
1947–53 National Health and Medical Research Council—Medical Research Advisory Committee (Commonwealth of Australia)
1955–59 Radiation Advisory Committee (Commonwealth of Australia), Chairman
1962–69 Papua New Guinea Medical Research Advisory Committee (Territory of Papua and New Guinea), Chairman

1957–64 Nuffield Foundation, Australian Advisory Committee
1963–69 Queen Elizabeth II Fellowships Committee (Commonwealth of Australia), Chairman
1965–74 Britannica Australia Awards, General Council, Britannica Australia Awards Medical Committee, Chairman
1952–69 World Health Organization, Expert Advisory Panels on Virus Diseases and on Immunology
1953–57 International Association of Microbiological Societies, President
1959–63 World Health Organization Medical Research Advisory Committee
1977 International Congress of Immunology, President
1966–69 The Commonwealth Foundation, Chairman
1966–70 La Trobe University Council
1982–83 Australian Advisory Council of Elders, Patron

No attempt will be made to describe his contributions to all of these committees, but a few comments on some of them will give a flavour of Burnet's contributions to public policy. The Medical Research Advisory Committee of the National Health and Medical Research Council, which advised the Council on grants for medical research, was the major source of support of medical research in Australia, and thus of the work in the Institute. He also served on several technical committees of the Council, and contributed especially to the work of the Epidemiology Committee.

As a member of the Defence Research and Development Policy Committee, from 1948–52, and its Chemical and Biological Warfare subcommittees, Burnet became involved in investigation of the rumours circulated by the People's Republic of China about biological warfare in Korea, an activity that he felt disqualified him for a visit to China in 1964, something he always regretted.

Burnet was the first Chairman of the National Radiation Advisory Committee; he accepted the invitation because of his concern that the Australian population was being exposed to unnecessary medical, dental, industrial and commercial irradiation. He made this matter, and the dangers of cigarette smoking, the central topics of his Presidential address to the Australia and New Zealand Association for the Advancement of Science in 1957 (163). Problems with fallout from nuclear weapons testing arose after he had left the committee, but he entered, at a late stage, into the nuclear energy debate in Australia. At first, in a widely publicized lecture, he opposed the use of nuclear energy on the grounds of the risk it posed for further escalation of nuclear weapons (238). In a letter to the Melbourne newspaper *The Age* on 22 August 1977, he withdrew his objections to the mining of uranium in Australia on the grounds that he was convinced of the necessity of the use of nuclear energy to cover a world 'energy gap' before fusion or renewable energy sources would become available.

He enjoyed his role in medical affairs in Papua New Guinea. Although until 1956 he had never been there, he had a vicarious interest in the Territory because his only son, Ian, was a patrol officer there, and later became Secretary for Transport. In 1956–57 Dr Carleton Gajdusek was a guest worker at the Hall Institute, and while there this inveterate

traveller had visited New Guinea and became aware of the existence of the disease locally called kuru (Farquhar & Gajdusek 1981). (In 1976 Gajdusek was to receive a Nobel Prize for his work on kuru.) Burnet was asked for advice about research on kuru by the Director of Public Health of New Guinea, Dr J. T. (later Sir John) Gunther, and this request led to a series of regular visits to the Territory, from 1962 to 1969 as Chairman of its Medical Research Advisory Committee. Building on his own experience Burnet persuaded the Australian government, which then administered the Territory, to establish a medical research institute in New Guinea, but because of his appreciation of the vital importance of population growth for the future of this tropical country it was called, at his suggestion, the Papua New Guinea Institute of Human Biology. The Institute played a vital role in the combined Australia–United Kingdom contribution to the International Biological Programme (Human Adaptability), operated jointly by the Australian Academy of Science (during Burnet's Presidency) and the Royal Society. A visit to Madang by representatives of both bodies, including Sir Lindor Brown as Secretary, Biological Sciences, of the Royal Society, and Professor R. J. Walsh, Secretary, Biological Sciences, of the Australian Academy, coincided with Burnet's 70th Birthday and was marked by a notable open-air banquet at the Smugglers Inn, on the coral shores of Madang Harbour. Through his activities as Chairman of the Medical Research Advisory Committee and the Council of the Institute of Human Biology, Burnet played an important role in the development of medicine and science in Papua New Guinea. From 1967–72 he acted as medical editor of the *Encyclopaedia of Papua New Guinea*, and he retained a lifelong interest in kuru (200, 227).

In the wider international field two of his public activities stand out: those associated with the Commonwealth Foundation and the World Health Organization. He was the first chairman of the Commonwealth Foundation, which was set up in London in 1966 with the broad aim of 'increasing interchanges between Commonwealth organizations in professional fields throughout the Commonwealth'. The Foundation, now a well-established and active body, owes much to Burnet's leadership during its formative years. Burnet was for a long time a member of the World Health Organization Expert Advisory Panel on Virus Diseases, his major contributions being in the fields of poliomyelitis and influenza. Later he became a member of the first Medical Research Advisory Committee of the World Health Organization, a body that included the cream of the world's medical research leaders.

Burnet's writings and lectures probably played an even more important part than his service on committees in the formulation of public attitudes and policy on a variety of biological topics. He expressed his opinions fearlessly, even when he knew that they would be unpopular. His scientific stature assured an audience and his clarity of expression ensured that his

writings would be widely understood. He was particularly worried about possible developments in molecular biology (201, 226), sensing its fascination for scientists but feeling that it might be the biologist's equivalent of nuclear fission in its potential for danger. He was offended by the 'arrogance' of some molecular biologists, and saw little chance that their work would contribute much to the betterment of human health, although he did not dispute its scientific interest. He continued to sound warnings about molecular biological studies of the virulence of viruses (234, 237), but he could not resist the scientific attraction of the contributions that molecular biology was making to the understanding of the problem with which he had wrestled for most of his life, the diversity of antibodies, and to his ideas on intrinsic mutagenesis. At the time young molecular biologists were greatly concerned by Burnet's comments, because they believed that these would undercut their funding, but as time passed it was clear that Burnet could not stop the tide. As Burnet himself said, 'no-one has ever heeded the words of a Cassandra'.

As well as publications in scientific journals and books Burnet spoke freely with newspaper reporters. His pronouncements were often controversial, but were always made with sincerity and usually after considerable thought, not 'off the cuff'. His contributions to the media are covered in some detail in the first biography of Burnet, other than his autobiography (Sexton 1988).

Honours and awards

Burnet was by far the most highly decorated and honoured scientist to have worked in Australia; in this respect he and Florey stand out in a separate category from all other Australian-born scientists. Various categories of these honours and the years in which they were received are listed below.

Decorations

1951	Knight Bachelor
1953	Elizabeth II Coronation Medal
1958	Order of Merit
1961	Second Order of the Rising Sun (with Double Rays)
1969	Knight Commander of the Order of the British Empire
1977	Elizabeth II Jubilee Medal
1978	Knight of the Order of Australia

Membership of learned academies and professional bodies

1942	Fellow of the Royal Society
1944–65	Professor of Experimental Medicine, University of Melbourne
1948	Fellow of the Royal Australasian College of Physicians
1950	Honorary Member, New York Academy of Sciences
	Honorary Fellow, Royal Society of Medicine
	Honorary Member, American Public Health Association

1953 Fellow of the Royal College of Physicians (London)
Fellow of the Royal College of Physicians (Edinburgh)
1954 Foundation Fellow of the Australian Academy of Science; President, 1965–69
Foreign Associate, U.S. National Academy of Sciences
1956 Honorary Member, College of Pathologists of Australia
1957 President of Australian and New Zealand Association for the Advancement of Science
Foreign Member, Royal Swedish Academy of Science
1958 Foreign Member, American Academy of Arts and Sciences
1960 Honorary Member, Royal Society of New Zealand
Foreign Member, American Philosophical Society
1961 Honorary Member, American Association of Immunologists
Honorary Member, Association of American Physicians
1962 Fellow, International Society of Haematology
1963 Honorary Fellow, American College of Physicians
Fellow, Australian Postgraduate Federation of Medicine
1965 Professor Emeritus of the University of Melbourne
1966 Honorary Fellow, Royal Institute of Public Health & Hygiene
Honorary Member, American Society of Microbiology
1967 Honorary Fellow, College of Pathologists (London)
1968 Fellow of the Royal College of Surgeons (England)
1970 Honorary Fellow, Royal Society of Edinburgh
1971 President, Pacific Science Congress
Honorary Member, International Epidemiological Association
1974 Honorary Fellow, American Academy of Allergy
1977 Honorary Member, Asociacion Medica Argentina
1978 Foreign Correspondent Academia de Ciencias Medices Argentina
1981 Fellow, Queensland Institute of Medical Research

Honorary degrees

Doctor of Science: Cambridge (1946), Western Australia (1948), New Zealand (1957), London (1960), Harvard (1960), Sydney (1961), New South Wales (1967), Oxford (1968), Monash (1968), Newcastle (1974).
Doctor of Medicine: Hahnemann Medical College, Philadelphia (1958).
Doctor of Medical Science: Medical University of South Carolina (1984).
Doctor of Laws: Melbourne (1962).

Awards

1935 Stewart Prize, British Medical Association
1938 Walter Burfitt Prize, Royal Society of New South Wales
1939 Cilento Medal, Australian Institute of Anatomy
1947 Royal Medal, the Royal Society
1953 Lasker Award, American Public Health Association
Charles Mickle Fellowship, University of Toronto
1954 Von Behring Prize for 1952, University of Marburg
James Cook Medal, Royal Society of New South Wales
1958 Galen Medal, Worshipful Society of Apothecaries of London
1959 Copley Medal, the Royal Society
Matthew Flinders Medal, Australian Academy of Science
1960 Nobel Prize in Physiology or Medicine
1962 Mueller Medal, Australian and New Zealand Association for the Advancement of Science
New York University Medal
1963 James Spence Medal, British Paediatric Association
1967 Royal Institute of Public Health & Hygiene Medal
Silver Medal, l'Institut de Microbiologie et d'Hygiene de l'Université de Montreal
1971 First International Congress of Immunology Award
1973 Distinguished Service Award, International Association of Allergy

International lectureships

1944 Dunham Lectures, Harvard University
1950 Croonian Lecture, the Royal Society
Herter Lectures, Johns Hopkins University
Moynihan Lecture, Royal College of Surgeons of England
Wright Lecture, St Mary's Hospital, London
Holme Lecture, University College Hospital, London
1952 Woodward Lecture, Yale University
Dyer Award Lecture, U.S. National Institutes of Health
1954 Price Lecture, Royal College of Physicians (Edinburgh)
CIBA Foundation Lecture, London
Litchfield Lecture, Oxford University
1956 Wyckoff Lecture, New York University
1958 Abraham Flexner Lectures, Vanderbilt University
Cutter Lecture, Harvard University
1959 Croonian Lectures, Royal College of Physicians (London)
1960 Herzstein Medical Lectures, Stanford University
Schorstein Lecture, London Hospital
Nobel Lecture, Royal Swedish Academy of Science
1962 Jephcott Lecture, Royal Society of Medicine
Chouke Lecture, College of Physicians of Philadelphia
1963 Eli Lilly Lecture, American College of Physicians
Aschoff Lecture, Freiburg, Germany
1964 Sommer Memorial Lectures, Portland, Oregon
Marcy Lecture, University of Pittsburgh
1966 Harben Lectures, Royal Institute of Public Health and Hygiene
1967 Noranda Lecture, Expo' 67, Montreal
Cameron Lecture, College of Pathologists, London
1973 Sir Douglas Robb Lectures, University of Auckland
1975 MacArthur Postgraduate Lecture, University of Edinburgh
1978 Aharon Katchalsky-Katzir Memorial Lectures, Weizmann Institute of Science, Rehovot, Israel
1980 William S. Paley Lecture, New York Hospital–Cornell Medical Center, New York

Other marks of recognition

1963 CIBA Foundation Study Group: *The Immunologically Competent Cell*, in honour of Sir Macfarlane Burnet.
1965 CIBA Symposium: *The Thymus*, in honour of Sir Macfarlane Burnet, held in Melbourne.
Australian Journal of Experimental Biology and Medical Sciences, Frank Macfarlane Burnet Commemoration Issue, July.
1966 Nuffield–Burnet Laboratories, Walter and Eliza Hall Institute, named.
1969 Burnet Lecture, Australian Academy of Science, established.
Australasian Annals of Medicine, Burnet Symposium Issue, November.
1977 Sir Macfarlane Burnet Lecture, Australasian Society for Infectious Diseases, established.
1979 Walter and Eliza Hall Institute Annual Review 1978–79. *A tribute to Sir Macfarlane Burnet*.
1981 'Australian of the Year'.
1986 Macfarlane Burnet Centre for Medical Research, Fairfield Hospital, Melbourne, named.
Burnet Memorial Oration, Australian Society of Immunology, established.
Burnet Clinical Research Unit of the Walter and Eliza Hall Institute, named.

Sources of information

Burnet did not prepare biographical notes for either the Royal Society or the Australian Academy of Science, probably because of the large number of sources of information on his life and work that had been published during his lifetime. These include his autobiography, *Changing patterns* (1968), the annual reports of the Walter and Eliza Hall Institute of Medical Research during the period of his directorship, and the collected tributes prepared in honour of his 70th and 80th birthdays, published in *Australasian Annals of Medicine*, November 1969, and *The Walter and Eliza Hall Institute of Medical Research Annual Review 1978–79*, respectively.

Burnet's large collection of diaries, notebooks and personal correspondence is being sorted and listed by the Australian Science Archives Project before being deposited in the University of Melbourn Archives. It will form a rich primary source for the future biographers. The first biography of Sir Macfarlane Burnet, by Christopher Sexton, will be published in 1988.

Acknowledgements

Many colleagues of Sir Macfarlane Burnet have provided me with assistance in the preparation of this memoir. In particular, I am grateful to his children, Mrs Elizabeth Dexter and Mr Ian Burnet, for information on his personal life, and Mr Christopher Sexton for various personal details and information on his later publications. I am also indebted to various colleagues of Sir Macfarlane for their help, in particular Professor G. L. Ada, Mrs Joyce Fazekas de St Groth (*née* Stone), Dr Margaret Holmes, Mr A. Hughes, Emeritus Professor D. O. Lancaster, Professor J. Lederberg, For.Mem.R.S., Dr I. R. Mackay, Sir Peter Medawar, F.R.S., Professor D. Metcalf, F.R.S., Sir Gustav Nossal, F.R.S., Associate Professor Margaret Sabine (*née* Edney), Emeritus Professor E. Saint, Professor D. O. White, and the late Sir Ian Wood.

The photograph reproduced was taken by Walter Bird in about 1967.

Papers by Burnet referred to in the text*

(1) 1924 Preliminary note on a new method of serological investigation in cases of suspected typhoid fever. *Med. J. Aust.* **1**, 205–208.

(2) Observations on the agglutinins in typhoid fever. *Br. J. exp. Path.* **5**, 251–260.

(3) 1929 'Smooth–rough' variation in bacteria in its relation to bacteriophage. *J. Path. Bact.* **32**, 15–42.

(4) Further observations on the nature of bacterial resistance to bacteriophage. *J. Path. Bact.* **32**, 349–354.

* The complete bibliography appears on the accompanying microfiche no. 1.

(5) 1929 A method for the study of bacteriophage multiplication in broth. *Br. J. exp. Path.* **10**, 109–115.
(6) Bacteriophage in its clinical aspects. *Med. J. Aust.* **1**, 406–410.
(7) (With M. McKie) Observations on a permanently lysogenic strain of *B. enteritidis Gaertner*. *Aust. J. exp. Biol. med. Sci.* **6**, 277–284.
(8) (With J. Macnamara) The activity of stored antipoliomyelitic serum in experimental poliomyelitis. *Med. J. Aust.* **2**, 851–855.
(9) 1930 Bacteriophage activity and the antigenic structure of bacteria. *J. Path. Bact.* **33**, 647–664.
(10) A physical difference amongst bacteriophages. *Aust. J. exp. Biol. med. Sci.* **7**, 27–35.
(11) Bacteriophage and cognate phenomena. In *A system of bacteriology in relation to medicine*, vol. 7, pp. 463–509 (Medical Research Council, Great Britain). London: H.M.S.O.
(12) (With M. McKie & I. J. Wood) Investigations on bacillary dysentery in infants with special reference to bacteriophage phenomena. *Med. J. Aust.* **2**, 71–78.
(13) 1931 (With M. McKie & I. J. Wood) A study of bacteriophage in relation to infantile bacillary dysentery. *Med. J. Aust.* **2**, 714–716.
(14) (With J. Macnamara) Immunological differences between strains of poliomyelitic virus. *Br. J. exp. Path.* **12**, 57–61.
(15) 1933 The classification of dysentery-coli bacteriophages. II. The serological classification of coli-dysentery phages. *J. Path. Bact.* **36**, 307–318.
(16) A virus disease of the canary of the fowl-pox group. *J. Path. Bact.* **37**, 107–122.
(17) 1934 The propagation of the virus of infectious laryngo-tracheitis on the chorio-allantoic membrane of the developing egg. *Br. J. exp. Path.* **15**, 52–55.
(18) The phage-inactivating agent of bacterial extracts. *J. Path. Bact.* **38**, 285–299.
(19) The bacteriophages. *Biol. Rev.* **9**, 332–350.
(20) Psittacosis in Australian parrots. *Med. J. Aust.* **2**, 743–746.
(21) (With J. D. Ferry) The differentiation of the viruses of fowl plague and Newcastle disease: experiments using the technique of the chorio-allantoic membrane inoculation of the developing egg. *Br. J. exp. Path.* **15**, 56–64.
(22) (With I. A. Galloway) The propagation of the virus of vesicular stomatitis in the chorio-allantoic membrane of the developing hen's egg. *Br. J. exp. Path.* **15**, 105–113.
(23) (With G. A. C. Gough) The chemical nature of phage-inactivating agent in bacterial extracts. *J. Path. Bact.* **38**, 301–311.
(24) 1935 Enzootic psittacosis amongst wild Australian parrots. *J. Hyg., Camb.* **35**, 412–420.
(25) Propagation of the virus of epidemic influenza on the developing egg. *Med. J. Aust.* **2**, 687–689.
(26) (With D. Lush) The staphylococcal bacteriophages. *J. Path. Bact.* **40**, 455–469.
(27) (With P. M. Rountree) Psittacosis in the developing egg. *J. Path. Bact.* **40**, 471–481.
(28) 1936 Inapparent (subclinical) infection of the rat with louping-ill virus. *J. Path. Bact.* **42**, 213–225.
(29) Inapparent virus infections with special reference to Australian examples. *Br. med. J.* **1**, 99–103.
(30) Immunological studies with the virus of infectious laryngotracheitis of fowls using the developing egg technique. *J. exp. Med* **63**, 685–701.
(31) Influenza virus on the developing egg. 1. Changes associated with the development of an egg-passage strain of virus. *Br. J. exp. Path.* **17**, 282–293.
(32) Influenza on the developing egg. 2. Titration of egg-passage virus by the pock-counting method. *Aust. J. exp. Biol. med. Sci.* **14**, 241–246.
(33) Influenza on the developing egg. 3. The 'neutralization' of egg virus by immune sera. *Aust. J. exp. Biol. med. Sci.* **14**, 247–258.
(34) Observations of the effect of louping-ill virus on the developing egg. *Br. J. exp. Path.* **17**, 294–301.
(35) (With D. Lush) Induced lysogenicity and mutation of bacteriophage within lysogenic bacteria. *Aust. J. exp. Biol. med. Sci.* **14**, 27–38.
(36) (With D. Lush) The immunological relationship between Kikuth's canary virus and fowl-pox. *Br. J. exp. Path.* **17**, 302–307.
(37) (With D. Lush) Inapparent (subclinical) infection of the rat with the virus of infectious ectromelia of mice. *J. Path. Bact.* **42**, 469–476.
(38) (With D. Lush) The propagation of the virus of infectious ectromelia of mice in the developing egg. *J. Path. Bact.* **43**, 105–120.

(39) 1936 *The use of the developing egg in virus research*. Special Report No. 220. London: Medical Research Council.
(40) 1937 Influenza virus on the developing egg. IV. The pathogenicity and immunizing power of egg virus for ferrets and mice. *Br. J. exp. Path.* **18**, 37–43.
(41) Influenza virus on the developing egg. 5. Differentiation of two antigenic types of human influenza virus. *Aust. J. exp. Biol. med. Sci.* **15**, 369–374.
(42) (With M. Freeman) Experimental studies on the virus of 'Q' fever. *Med. J. Aust.* **2**, 299–305.
(43) (With E. V. Keogh & D. Lush) The immunological reactions of the filterable viruses. *Aust. J. exp. Biol. med. Sci.* **15**, 227–368.
(44) (With D. Lush) Influenza virus on the developing egg. 6. Complement fixation with egg membrane antigens. *Aust. J. exp. Biol. med. Sci.* **15**, 375–383.
(45) 1938 Tissue culture of the rickettsia of 'Q' fever. *Aust. J. exp. Biol. med. Sci.* **16**, 219–224.
(46) (With M. Freeman) The rickettsia of 'Q' fever: further experimental studies. *Med. J. Aust.* **1**, 296–298.
(47) (With D. Lush) Influenza virus on the developing egg. VII. The antibodies of experimental and human sera. *Br. J. exp. Path.* **19**, 17–29.
(48) (With D. Lush) Influenza virus on the developing egg. 8. A comparison of two antigenically dissimilar strains of human influenza virus after full adaptation to the egg membrane. *Aust. J. exp. Biol. med. Sci.* **16**, 261–274.
(49) 1939 A note on the occurrence of fatal psittacosis in parrots living in the wild state. *Med. J. Aust.* **1**, 545–546.
(50) Changes of twenty-five years in the outlook on infectious disease. *Med. J. Aust.* **2**, 23–28.
(51) (With M. Freeman) Note on a series of laboratory infections with the rickettsia of 'Q' fever. *Med. J. Aust.* **1**, 11–12.
(52) (With M. Freeman, E. H. Derrick & D. W. J. Smith) The search for immunological relationship between 'Q' fever and other rickettsioses. *Med. J. Aust.* **2**, 51–54.
(53) (With M. Freeman) A comparative study of rickettsial strains from an infection of ticks in Montana (United States of America) and from 'Q' fever. *Med. J. Aust.* **2**, 887–891.
(54) (With A. V. Jackson & E. G. Robertson) Poliomyelitis. 1. Intra-ocular inoculation as a standard method for the demonstration of neutralizing antibodies. *Aust. J. exp. Biol. med. Sci.* **17**, 253–260.
(55) (With A. V. Jackson & E. G. Robertson) Poliomyelitis. 3. The use of *Macacus cynomolgus* as an experimental animal. *Aust. J. exp. Biol. med. Sci.* **17**, 375–391.
(56) (With D. Lush & A. V. Jackson) The propagation of herpes B and pseudorabies viruses on the chorioallantois. *Aust. J. exp. Biol. med. Sci.* **17**, 35–40.
(57) (With D. Lush) The inactivation of herpes virus by immune sera: experiments using the chorio-allantoic membrane technique. *J. Path. Bact.* **48**, 275–286.
(58) (With S. W. Williams) Herpes simplex: a new point of view. *Med. J. Aust.* **1**, 637–642.
(59) 1940 The epidemiology of poliomyelitis, with special reference to the Victorian epidemic of 1937–38. *Med. J. Aust.* **1**, 325–326.
(60) Influenza virus infections of the chick embryo lung. *Br. J. exp. Path.* **21**, 147–153.
(61) Influenza virus infections of the chick embryo by the amniotic route. 1. General character of the infections. *Aust. J. exp. Biol. med. Sci.* **18**, 353–360.
(62) (With M. Foley) The results of intranasal inoculation of modified and unmodified influenza virus strains in human volunteers. *Med. J. Aust.* **2**, 655–659.
(63) (With A. V. Jackson) Poliomyelitis. 4. The spread of poliomyelitis virus in cynomolgus monkeys with particular reference to infection by the pharyngeal–intestinal route. *Aust. J. exp. Biol. med. Sci.* **18**, 361–366.
(64) *Biological aspects of infectious disease*. Cambridge: Cambridge University Press. (Later editions published under title *Natural history of infectious disease* (Italian edition: Einaudi, 1947).)
(65) 1941 Influenza virus infections of the chick embryo by the amniotic route. 2. Titrations and serum neutralization tests. *Aust. J. exp. Biol. med. Sci.* **19**, 39–44.
(66) A simple method for the propagation of influenza virus. *Aust. J. Sci.* **3**, 133.
(67) Growth of influenza virus in the allantoic cavity of the chick embryo. *Aust. J. exp. Biol. med. Sci.* **19**, 291–296.
(68) The biological approach to infectious disease. (Charles Mackay Lecture.) *Med. J. Aust.* **2**, 607–612.
(69) (With M. Foley) Two methods for the detection of influenza virus in human throat washings without the use of ferrets. *Med. J. Aust.* **1**, 68–72.

(70) 1941 (With M. Foley) Influenza virus infections of the chick embryo by the amniotic route. 3. Changes in the activity of influenza virus on continued amniotic passage. *Aust. J. exp. Biol. med. Sci.* **19**, 101–105.
(71) (With M. Freeman) Studies of the X strain (Dyer) of *Rickettsia burneti*. I. Chorioallantoic membrane infections. *J. Immun.* **40**, 405–419.
(72) (With M. Freeman) Studies of the X strain (Dyer) of *Rickettsia burneti*. II. Guinea pig infections, with special reference to immunological phenomena. *J. Immun.* **40**, 421–436.
(73) (With G. V. Rudd) Intranasal infection of mice with the virus of psittacosis. *Aust. J. exp. Biol. med. Sci.* **19**, 33–38.
(74) (With M. Freeman, A. V. Jackson & D. Lush) *The production of antibodies : a review and theoretical discussion.* (Monograph from The Walter and Eliza Hall Institute of Research in Pathology and Medicine, no. 1.) Melbourne: Macmillan.
(75) 1942 The affinity of Newcastle disease virus to the influenza virus group. *Aust. J. exp. Biol. med. Sci.* **20**, 81–88.
(76) Influenza virus B. I. Observations on growth in chick embryos and on the occurrence of antibodies in Australian serum. *Med. J. Aust.* **1**, 671–673.
(77) Influenza virus B. II. Immunization of human volunteers with living attenuated virus. *Med. J. Aust.* **1**, 673–674.
(78) The rickettsial diseases in Australia. (Bancroft Memorial Lecture.) *Med. J. Aust.* **2**, 129–134.
(79) Red cell agglutination by viruses: the Hirst phenomenon. *Aust. J. Sci.* **5**, 5–7.
(80) Discontinuous variation in influenza virus. *Aust. J. Sci.* **5**, 81–83.
(81) (With W. I. B. Beveridge, D. R. Bull & E. Clark) Investigations of an influenza epidemic in military camps in Victoria, May 1942. *Med. J. Aust.* **2**, 371–376.
(82) (With D. D. Faris) The technique of quantitative chorioallantoic virus titration. *J. Bact.* **44**, 241–248.
(83) (With E. Clark) *Influenza : a survey of the last 50 years in the light of modern work on the virus of epidemic influenza.* (Monographs from The Walter and Eliza Hall Institute of Research in Pathology and Medicine, no. 4.) Melbourne: Macmillan.
(84) 1943 Human infection with the virus of Newcastle disease of fowls. *Med. J. Aust.* **2**, 313–314.
(85) Characteristics of the influenza virus–antibody reaction as tested by the method of allantoic inoculation. *Aust. J. exp. Biol. med. Sci.* **21**, 231–238.
(86) (With W. I. B. Beveridge) Titration of antibody against influenza viruses by allantoic inoculation of the developing chick embryo. *Aust. J. exp. Biol. med. Sci.* **21**, 71–78.
(87) (With D. R. Bull) Experimental immunization of volunteers against influenza virus B. *Med. J. Aust.* **1**, 389–394.
(88) (With D. R. Bull) Changes in influenza virus associated with adaptation to passage in chick embryos. *Aust. J. exp. Biol. med. Sci.* **21**, 55–69.
(89) 1944 Medical education and research: impressions of an American visit. *Med. J. Aust.* **1**, 557–562.
(90) Influenza and other respiratory infections. *Med. J. Aust.* **2**, 1–6.
(91) 1945 Poliomyelitis in the light of recent experimental work. *Hlth Bull., Melb.* **81**, 2173–2177.
(92) An unsuspected relationship between the viruses of vaccinia and infectious ectromelia of mice. *Nature, Lond.* **155**, 543.
(93) Haemagglutination by mumps virus: relationship to Newcastle disease and influenza viruses. *Aust. J. Sci.* **8**, 81–83.
(94) (With W. I. B. Beveridge, J. McEwin & W. C. Boake) Studies on the Hirst haemagglutination reaction with influenza and Newcastle disease viruses. *Aust. J. exp. Biol. med. Sci.* **23**, 177–192.
(95) (With J. D. Stone) The significance of primary isolation of influenza virus by inoculation of mice or of the allantoic cavity of chick embryos. *Aust. J. exp. Biol. med. Sci.* **23**, 147–150.
(96) (With J. D. Stone) Further studies on the O–D change in influenza virus A. *Aust. J. exp. Biol. med. Sci.* **23**, 151–160.
(97) *Virus as organism : evolutionary and ecological aspects of some human virus diseases.* Cambridge, Mass.: Harvard University Press. (Russian edition: Moscow, 1947; Japanese edition: Tokyo: Ishiyaku, 1956.)
(98) 1946 Epidemiology today. *Med. J. Aust.* **2**, 825–830.
(99) Vaccinia haemagglutinin. *Nature, Lond.* **159**, 119–120.

(100) 1946 (With W. C. Boake) The relationship between the virus of infectious ectromelia of mice and vaccinia virus. *J. Immun.* **53**, 1–13.
(101) (With J. F. McCrea & J. D. Stone) Modification of human red cells by virus action. I. The receptor gradient for virus action in human red cells. *Br. J. exp. Path.* **27**, 228–236.
(102) (With J. D. Stone) The haemagglutinins of vaccinia and ectromelia viruses. *Aust. J. exp. Biol. med. Sci.* **24**, 1–8.
(103) (With J. D. Stone) The production of vaccinia haemagglutinin in rabbit skin. *Aust. J. exp. Biol. med. Sci.* **24**, 9–13.
(104) *The background of infectious diseases in man.* Melbourne: The Melbourne Permanent Postgraduate Committee.
(105) (With W. I. B. Beveridge) *The cultivation of viruses and rickettsiae in the chick embryo.* (Special Report No. 256.) London: Medical Research Council. (French edition: 1950.)
(106) 1947 (With S. G. Anderson) Sporadic and minor epidemic incidence of influenza A in Victoria, 1945–46. 1. Phase behaviour of influenza A strains in relation to epidemic characteristics. *Aust. J. exp. Biol. med. Sci.* **25**, 235–242.
(107) (With J. F. McCrea & S. G. Anderson) Mucin as substrate of enzyme action by viruses of the mumps–influenza group. *Nature, Lond.* **160**, 404–405.
(108) (With J. D. Stone) Desquamation of intestinal epithelium *in vitro* by *V. cholerae* filtrates: characterization of mucinase and tissue disintegrating enzymes. *Aust. J. exp. Biol. med. Sci.* **25**, 219–225.
(109) (With J. D. Stone) The receptor-destroying enzyme of *V. cholerae*. *Aust. J. exp. Biol. med. Sci.* **25**, 227–233.
(110) 1948 The mucinase of *V. cholerae*. *Aust. J. exp. Biol. med. Sci.* **26**, 71–80.
(111) The Edward Stirling Lectures. I. The basis of allergic disease. *Med. J. Aust.* **1**, 29–35.
(112) The Edward Stirling Lectures. II. The natural history of tuberculosis. *Med. J. Aust.* **1**, 57–63.
(113) The continuing conquest of disease. *Med. J. Aust.* **2**, 281–286.
(114) Mucins and mucoids in relation to influenza virus action. IV. Inhibition by purified mucoid of infection and haemagglutination with the virus strain WSE. *Aust. J. exp. Biol. med. Sci.* **26**, 381–387.
(115) Mucins and mucoids in relation to influenza virus action. V. The destruction of 'Francis inhibitor' activity in a purified mucoid by virus action. *Aust. J. exp. Biol. med. Sci.* **26**, 389–402.
(116) (With S. G. Anderson, S. Fazekas de St Groth, J. F. McCrea & J. D. Stone) Mucins and mucoids in relation to influenza virus action. VI. General discussion. *Aust. J. exp. Biol. med. Sci.* **26**, 403–411.
(117) (With F. Fenner) Genetics and immunology. *Heredity, Lond.* **2**, 289–324.
(118) 1949 Haemolysis by Newcastle disease virus. *Nature, Lond.* **164**, 1008.
(119) Some aspects of the epidemiology of poliomyelitis. *Proc. R. Australas. Coll. Physns* **4**, 95–100.
(120) (With J. D. Stone, A. Isaacs & M. Edney) The genetic character of O–D change in influenza A. *Br. J. exp. Path.* **30**, 419–425.
(121) (With F. Fenner) *The production of antibodies*, 2nd edn. (Monograph of The Walter and Eliza Hall Institute, Melbourne.) Melbourne: Macmillan.
(122) 1950 The natural history of surgical infection. *Ann. R. Coll. Surg.* **7**, 191–203.
(123) The haemolytic action of Newcastle disease virus. I. The two types of interaction between virus and red cell. *Aust. J. exp. Biol. med. Sci.* **28**, 299–309.
(124) (With P. E. Lind) Haemolysis by Newcastle disease virus. II. General character of haemolytic action. *Aust. J. exp. Biol. med. Sci.* **28**, 129–150.
(125) (With J. D. Stone & M. Edney) The failure of antibody production in the chick embryo. *Aust. J. exp. Biol. med. Sci.* **28**, 291–297.
(126) 1951 A genetic approach to variation in influenza viruses. 1. The characters of three substrains of influenza virus A (WS). *J. gen. Microbiol.* **5**, 46–53.
(127) A genetic approach to variation in influenza viruses. 2. Variation in the strain NWS on allantoic passage. *J. gen. Microbiol.* **5**, 54–58.
(128) The interaction of virus and cell surface. (Croonian Lecture.) *Proc. R. Soc. Lond.* B **138**, 47–64.
(129) Mucoproteins in relation to virus action. *Physiol. Rev.* **31**, 131–150.

(130) 1951 Some biological implications of studies on influenza viruses. (Herter Lectures, 1950.) I. The process of infection by the virus. *Bull. Johns Hopkins Hosp.* **88**, 119–137.
(131) Some biological implications of studies on influenza viruses. (Herter Lectures, 1950.) III. The ecological approach to the common virus diseases of today. *Bull. Johns Hopkins Hosp.* **88**, 157–180.
(132) Oecological approach to infectious disease. In *Modern practice in infectious fevers* (ed. H. S. Banks), pp. 1–15. London: Butterworth.
(133) (With P. E. Lind) A genetic approach to variation in influenza viruses. 3. Recombination of characters in influenza virus strains used in mixed infections. *J. gen. Microbiol.* **5**, 59–66.
(134) (With P. E. Lind) A genetic approach to variation in influenza viruses. 4. Recombination of characters between the influenza virus A strain NWS and strains of different serological subtypes. *J. gen. Microbiol.* **5**, 67–82.
(135) 1952 Haemagglutination in relation to host-cell–virus interaction. *A. Rev. Microbiol.* **6**, 229–246.
(136) The seeds of time: the impact of microbiology on human affairs since Lister's day. (Listerian Oration.) *Med. J. Aust.* **1**, 801–807.
(137) Poliomyelitis and Murray Valley encephalitis: a comparison of two neurotropic virus diseases. *Med. J. Aust.* **1**, 169–175.
(138) Murray Valley encephalitis. *Am. J. publ. Hlth* **42**, 1519–1521.
(139) Myxomatosis as a method of biological control against the Australian rabbit. *Am. J. publ. Hlth* **42**, 1522–1526.
(140) The pattern of disease in childhood. (Charles Clubbe Memorial Oration.) *Australas. Ann. Med.* **1**, 93–108.
(141) (With K. B. Fraser) Studies on recombination with influenza viruses in the chick embryo. I. Invasion of the chick embryo by influenza viruses. *Aust. J. exp. Biol. med. Sci.* **30**, 447–458.
(142) (With K. B. Fraser) Studies on recombination with influenza viruses in the chick embryo. II. Genetic interaction between influenza virus strains in the chick embryo. *Aust. J. exp. Biol. med. Sci.* **30**, 459–468.
(143) (With P. E. Lind) Studies on recombination with influenza viruses in the chick embryo. III. Reciprocal genetic interaction between two influenza virus strains. *Aust. J. exp. Biol. med. Sci.* **30**, 469–477.
(144) 1953 The influenza virus. *Scient. Am.* **188** (4), 27–31.
(145) Virus classification and nomenclature. *Ann. N. Y. Acad. Sci.* **56**, 383–390.
(146) Virology as an independent science. (Mathison Memorial Lectures.) II. The substance of virology. *Med. J. Aust.* **2**, 841–845.
(147) (With P. E. Lind) Influenza virus recombination: experiments using the de-embryonated egg technique. *Cold Spring Harb. Symp. quant. Biol.* **18**, 21–24.
(148) (With P. E. Lind) Back-recombination of influenza A strains obtained in recombination experiments. *Aust. J. exp. Biol. med. Sci.* **31**, 361–372.
(149) (With B. T. Perry) Recombination studies with two influenza virus B strains. *Aust. J. exp. Biol. med. Sci.* **31**, 519–528.
(150) *Viruses and man.* Melbourne: Penguin Books. (2nd edn (revised), 1955; Italian edition: Milan: Bompiani, 1960.)
(151) 1954 Current thought on the prophylaxis of poliomyelitis. *Med. J. Aust.* **2**, 192–194.
(152) (With P. E. Lind) Recombination of influenza viruses in the de-embryonated egg. 1. The use of periodate-treated sera for *in vitro* characterization of influenza virus strains. *Aust. J. exp. Biol. med. Sci.* **32**, 145–152.
(153) (With P. E. Lind) Recombination of influenza viruses in the de-embryonated egg. 2. The conditions for recombination and the evidence for the possible existence of diploid influenza virus. *Aust. J. exp. Biol. med. Sci.* **32**, 153–164.
(154) (With P. E. Lind) Reactivation of heat inactivated influenza virus by recombination. *Aust. J. exp. Biol. med. Sci.* **32**, 133–144.
(155) (With P. E. Lind & K. M. Stevens) A new technical approach to the interpretation of 'incompleteness' in influenza virus. *Aust. J. Sci.* **16**, 145–147.
(156) 1955 The Salk poliomyelitis vaccine. *Med. J. Aust.* **1**, 660.
(157) (With P. E. Lind) Recombination between the influenza virus strains WSE and CAM. *Aust. J. exp. Biol. med. Sci.* **33**, 281–296.
(158) (With P. E. Lind & K. M. Stevens) Production of incomplete influenza virus in the de-embryonated egg. *Aust. J. exp. Biol. med. Sci.* **33**, 127–142.

(159) 1955 (With C. H. Andrewes & F. B. Bang) A short description of the *Myxovirus* group (influenza and related viruses). *Virology* **1**, 176–184.

(160) *Principles of animal virology*. New York: Academic Press. (Polish edition: Warsaw: Panstwowy Zaklad Wydawnictw Lekarskich, 1958; Japanese edition: Tokyo: Kyoritsu Shuppan, 1959.)

(161) 1956 *Enzyme, antigen and virus: a study of macromolecular pattern in action*. Cambridge: Cambridge University Press.

(162) 1957 Cancer—a biological approach. *Br. med. J.* **1**, 779–786, 841–847.

(163) Biology and medicine. (Presidential address, Australian & New Zealand Association for the Advancement of Science.) *Med. J. Aust.* **1**, 405–410.

(164) A modification of Jerne's theory of antibody production using the concept of clonal selection. *Aust. J. Sci.* **20**, 67–69.

(165) (With P. E. Lind) Reversion of virulence in an influenza virus mutant. *Aust. J. exp. Biol. med. Sci.* **35**, 225–240.

(166) (With F. Fenner) A short description of the poxvirus group. (Vaccinia and related viruses.) *Virology* **4**, 305–314.

(167) (With P. E. Lind) Recombination between virulent and non-virulent strains of influenza virus. 1. The significance of heterozygosis. *Aust. J. exp. Biol. med. Sci.* **35**, 57–66.

(168) (With P. E. Lind) Recombination between virulent and non-virulent strains of influenza virus. 2. The behaviour of virulence markers on recombination. *Aust. J. exp. Biol. med. Sci.* **35**, 67–78.

(169) (With P. E. Lind) Further studies of recombination between heat-inactivated virus and active virus. *Aust. J. exp. Biol. med. Sci.* **35**, 531–540.

(170) 1958 Leukemia as a problem in preventive medicine. (Cutter Lecture, Harvard University.) *New Engl. J. Med.* **259**, 423–431.

(171) (With P. E. Lind) Genetic suppression of virulence in the influenza virus strain WS−. *Aust. J. exp. Biol. med. Sci.* **36**, 159–172.

(172) 1959 Population dynamics of body cells. In *Ciba Foundation 10th anniversary symposium on significant trends in medical research* (ed. G. E. W. Wolstenholme, C. M. O'Connor & M. O'Connor), pp. 60–70. London: Churchill.

(173) The biology of cancer. *Proc. 3rd Canadian Cancer Conference, Honey Harbour, Ontario, 1958* (ed. R. W. Begg), pp. 433–443. New York: Academic Press.

(174) (Editor, with W. M. Stanley) *The viruses, biochemical, biological and biophysical properties*, vols 1–3. New York: Academic Press.

(175) *The clonal selection theory of acquired immunity*. Cambridge: Cambridge University Press; Nashville: Vanderbilt University Press. (Japanese edition: Tokyo: Iwanami-shoten, 1963.)

(176) 1960 (With D. Burnet) Graft versus host reactions on the chorioallantoic membrane of the chick embryo. *Nature, Lond.* **188**, 376–379.

(177) *Principles of animal virology*, 2nd edn. New York: Academic Press.

(178) 1961 (With D. Burnet) Analysis of major histocompatibility factors in a stock of closely inbred white leghorn fowls using a graft-*versus*-host reaction on the chorioallantoic membrane. *Aust. J. exp. Biol. med. Sci.* **39**, 101–110.

(179) (With M. Holmes & J. Gorrie) Transmission by splenic cells of an auto-immune disease occurring spontaneously in mice. *Lancet* ii, 638–639.

(180) (With N. L. Warner) The influence of testosterone treatment on the development of the bursa of Fabricius in the chick embryo. *Aust. J. biol. Sci.* **14**, 580–587.

(181) (With N. L. Warner) The influence of anti-inflammatory corticosteroids on the growth of the chick embryo and the manifestations of the Simonsen phenomenon. *Aust. J. exp. Biol. med. Sci.* **39**, 235–248.

(182) 1962 Auto-immune disease. (Keith Inglis Memorial Lecture.) *Med. J. Aust.* **1**, 1–6.

(183) The immunological significance of the thymus: an extension of the clonal selection theory of immunity. *Australas. Ann. Med.* **11**, 79–91.

(184) Auto-immune disease: experimental and clinical. (Jephcott Lecture.) *Proc. R. Soc. Med.* **55**, 619–626.

(185) (With M. C. Holmes) Immunological function of thymus and bursa of Fabricius. Thymus lesions in an auto-immune disease of mice. *Nature, Lond.* **194**, 146–147.

(186) (With H. Hilgard & D. Burnet) Tolerance as shown by the Simonsen reaction on the chorioallantoic membrane. *Aust. J. exp. Biol. med. Sci.* **40**, 233–240.

(187) 1962 (With A. Szenberg, N. L. Warner & P. E. Lind) Quantitive aspects of the Simonsen phenomenon. II. Circumstances influencing the focal counts obtained on the chorioallantoic membrane. *Br. J. exp. Path.* **43**, 129–136.

(188) (With N. L. Warner & A. Szenberg) The immunological role of different lymphoid organs in the chicken. I. Dissociation of immunological responsiveness. *Aust. J. exp. Biol. med. Sci.* **40**, 373–388.

(189) 1963 An experimental model of autoimmune haemolytic anaemia. *Australas. Ann. Med.* **12**, 3–5.

(190) Immunologically competent cells in the fowl. In *Ciba Foundation study group no.* 16. *The immunologically competent cell : its nature and origin* (ed. G. E. W. Wolstenholme & J. Knight), pp. 77–82. London: Churchill.

(191) (With M. C. Holmes) The influence of splenectomy in NZB mice. *Aust. J. exp. Biol. med. Sci.* **41**, 449–456.

(192) *The integrity of the body : a discussion of modern immunological ideas.* Cambridge, Mass.: Harvard University Press. (New York: Athenaeum, 1966; Russian edition: Moscow: Mir, 1964; Polish edition: Warsaw: Panstwowe Wydawnictwo Naukowe, 1965; Japanese edition: Tokyo: Kinokuniya, 1966; Italian edition: Turin: Borinchieri, 1966.)

(193) (With I. R. Mackay) *Auto-immune diseases : pathogenesis, chemistry and therapy.* Springfield: Charles C. Thomas. (Spanish edition: 1965; Japanese edition: 1967.)

(194) 1964 Immunological factors in the process of carcinogenesis. *Br. med. Bull.* **20**, 154–158.

(195) (With M. C. Holmes) Thymic changes in the mouse strain NZB in relation to the auto-immune state. *J. Path. Bact.* **88**, 229–241.

(196) (With M. C. Holmes) The inheritance of autoimmune disease in mice: a study of hybrids of the strain NZB and C3H. *Heredity, Lond.* **14**, 419–434.

(197) (With M. C. Holmes) Experimental studies of thymic function in NZB mice and the F_1 hybrids with C_3H. *Aust. J. exp. Biol. med. Sci.* **42**, 589–600.

(198) 1965 Somatic mutation and chronic disease. *Br. med. J.* **1**, 338–342.

(199) (With M. C. Holmes) Genetic investigations of autoimmune disease in mice. *Nature, Lond.* **207**, 368–371.

(200) (With J. D. Mathews) The changing face of kuru. *Lancet* i, 1138–1142.

(201) 1966 Men or molecules? A tilt at molecular biology. *Lancet* i, 37–39.

(202) Implications for autoimmune disease in man of studies on NZB mice and their hybrids. (The Harben Lectures.) *Jl R. Inst. publ. Hlth Hyg.* **29**, 87–112.

(203) (With J. D. Hicks) Renal lesions in the 'auto-immune' mouse strains NZB and F_1 NZB × NZW. *J. Path. Bact.* **91**, 467–477.

(204) (With M. C. Holmes) The characteristics of F_1 and backcross hybrids between 'high leukaemia' (AKR) and 'auto-immune' (NZB) mouse strains. *Aust. J. exp. Biol. med. Sci.* **44**, 235–250.

(205) (With P. J. Russell & J. D. Hicks) Cyclophosphamide treatment of kidney disease in (NZB × NZW) F_1 mice. *Lancet* i, 1279–1284.

(206) 1967 Autoimmune disease. In *Pathologic physiology : mechanisms of disease* (ed. W. A. Soderman & W. A. Soderman Jr), 4th edn, pp. 15–33. Philadelphia: Saunders.

(207) Immunological aspects of malignant disease. (Roy Cameron Memorial Lecture of the College of Pathologists.) *Lancet* i, 1171–1174.

(208) Concepts of autoimmune disease and their implications for therapy. *Perspect. Biol. Med.* **10**, 141–151.

(209) The impact of ideas on immunology. *Cold Spring Harb. Symp. quant. Biol.* **32**, 1–8.

(210) 1968 The concept of autoimmunity. *Biblphia. haematol.* **29** (2), 423–435.

(211) *Biology and the appreciation of life.* Melbourne: Sun Books. (Based on the Boyer Lectures of the Australian Broadcasting Commission for 1966.) (Spanish edition: Mexico City: Siglo XXI, 1970.)

(212) *Changing patterns ; an atypical autobiography.* Melbourne: Heinemann. (New York: Elsevier, 1969; Melbourne: Sun Books, 1970; Japanese edition: Tokyo, 1978.)

(213) 1969 The evolution of adaptive immunity in vertebrates. *Acta path. microbiol. scand.* **76**, 1–11.

(214) *Cellular immunology.* (Books 1 and 2 combined.) Melbourne: Melbourne University Press; Cambridge: Cambridge University Press. (Russian edition: Mir, 1973.)

(215) 1969 *Self and not-self*. (Book 1 of *Cellular immunology*.) Melbourne: Melbourne University Press; Cambridge: Cambridge University Press. (Japanese edition: Tokyo: University of Tokyo Press, 1972; German edition: Stuttgart: Thieme, 1973; Italian edition: Bologna: Zanichelli, 1974.)

(216) 1970 The biology of ageing. (Sydney Rubbo Memorial Lecture.) *Ann. gen. Prac.* **15**, 205–208.

(217) The newer immunology: an evolutionary approach. In *Infectious agents and host reactions* (ed. S. Mudd), pp. 1–21. Philadelphia: Saunders.

(218) Impressions and comments. In *Immune surveillance* (ed. R. T. Smith & M. Landy), pp. 512–518. New York: Academic Press.

(219) Immunological surveillance: an evolutionary approach. In *Immunity and tolerance in immunogenesis. (Proc. IV Perugia Quadrennial Int. Conf. on Cancer, Perugia, 1969* (ed. L. Severi), vol. 1, pp. 45–61. Perugia: Division of Cancer Research.

(220) An immunological approach to ageing. *Lancet* ii, 358–360.

(221) *Immunological surveillance*. Oxford: Pergamon Press; Sydney: Pergamon (Australia).

(222) *Dominant mammal : the biology of human destiny*. Melbourne: Heinemann. (New York: St Martin's Press, 1971; Penguin Books, 1971; Spanish edition: Madrid: Alianza, 1973; Danish edition: Copenhagen: Gyldendal, 1973; Japanese edition: Tokyo, 1973.)

(223) 1971 Immunological surveillance in neoplasia. *Transplantn Rev.* **7**, 3–25.

(224) Reflections on kuru. *Hum. Biol. Oceania* **1**, 3–9.

(225) *Walter and Eliza Hall Institute 1915–1965*. Melbourne: Melbourne University Press.

(226) *Genes, dreams and realities*. Aylesbury: Medical and Technical Publications. (Harmondsworth: Penguin Books, 1973; Italian edition: Milan: Edizioni Scientifiche e Techniche Mondadori, 1974; French edition: Paris: Flammarion, 1975.)

(227) 1972 Kuru. In *Encyclopaedia of Papua and New Guinea* (ed. P. Ryan), pp. 586–588. Melbourne: Melbourne University Press.

(228) The implications of global homeostasis. *Impact Sci. Soc.* **22**, 305–314.

(229) Speed of change: the quandary of a human biologist. *Proc. 5th. Aust. comp. Conf.*, pp. 1–5.

(230) (With D. O. White) *Natural history of infectious disease*, 4th edn. Cambridge: Cambridge University Press.

(231) *Auto-immunity and auto-immune disease : a survey for physician or biologist*. Lancaster: Medical and Technical Publishers.

(232) 1973 A genetic interpretation of ageing. *Lancet* ii, 480–483.

(233) The influence of a great pathologist: a tribute to Ernest Goodpasture. *Perspect. Biol. Med.* **16**, 333–347.

(234) 1974 Hazards of virus research. *Doc. Geigy* (*Hazards of Modern Medicine issue*), pp. 3–4.

(235) *Intrinsic mutagenesis : a genetic approach to ageing*. Lancaster: Medical and Technical Publishers.

(236) *The biology of ageing*. Auckland: Auckland University Press; Oxford: Oxford University Press. (Japanese edition: Tokyo: Kinokuniya, 1976.)

(237) 1976 Experiments with viruses. *Trends biochem. Sci.* **1**(10), N228.

(238) *Uranium : for good or evil?* Melbourne: The Alfred Deakin Lecture Trust.

(239) *Immunology : readings from Scientific American with introductions and additional material by F. M. Burnet*. San Francisco: Freeman.

(240) *Immunity, ageing and cancer : medical aspects of mutation and selection*. San Francisco: Freeman.

(241) 1977 Morphogenesis and cancer. (Brailsford Robertson Memorial Lecture.) *Med. J. Aust.* **1**, 5–9.

(242) 1978 Cancer: somatic–genetic considerations. *Adv. Cancer Res.* **28**, 1–29.

(243) *Endurance of life, the implications of genetics for human life*. Melbourne: Melbourne University Press.

(244) 1979 *Credo and comment : a scientist reflects*. Melbourne: Melbourne University Press.

(245) 1982 Immunology, ageing and cancer. *Recent Adv. geriat. Med.* **2**, 5–18.

(246) 1984 To understand and to be good. In *Biological foundations and human nature* (ed. M. Balaban), pp. 139–158. New York: Academic Press.

References to other authors

Ada, G. L. & Byrt, P. 1969 Specific inactivation of antigen-reactive cells with ^{125}I-labelled antigen. *Nature, Lond.* **222**, 1291.

Ada, G. L. & Nossal, G. J. V. 1987 How cells make antibody: the clonal selection theory of immunity. *Scient. Am.*

Ada, G. L. & Perry, B. T. 1954 The nucleic acid content of influenza virus. *Aust. J. exp. Biol. med. Sci.* **32**, 453.

Ada, G. L. & Perry, B. T. 1956 Infuenza virus nucleic acid: relationship between biological characteristics of the virus particle and properties of the nucleic acid. *J. gen. Microbiol.* **4**, 623.

Andrewes, C. H. & Elford, W. J. 1933 Observations on anti-phage sera. I. The percentage law. *Br. J. exp. Path.* **14**, 367.

Baca, O. G. & Paretsky, D. 1983 Q fever and *Coxiella burnetii*: a model for host–parasite interactions. *Microbiol. Rev.* **47**, 127.

Bail, O. 1923 Versuche über die Vielheit von Bakteriophage. *Z. ImmunForsch. exp. Ther.* **38**, 57.

Bedson, H. S. & Dumbell, K. R. 1961 The effect of temperature on the growth of poxviruses in the chick embryo. *J. Hyg., Camb.* **59**, 457.

Bielschowsky, M., Helyer, B. J. & Howie, J. B. 1959 Spontaneous haemolytic anaemia in mice of the NZB/B1 strain. *Proc. Univ. Otago med. Sch.* **37**, 9.

Bishop, J. M. 1984 Exploring carcinogenesis with retroviruses. *Symp. Soc. gen. Microbiol.* **36**, 121.

Breinl, F. & Haurowitz, F. 1930 Chemische Untersuchung des Prazipitates aus Hamoglobin und Anti-Hamaglobin-Serum und Bemerkungen über die Natur der Antikorper. *Hoppe-Seyler's Z. physiol. Chem.* **192**, 45.

Cohn, M. 1979 Burnet, lysogeny and creativity. *The Walter and Eliza Hall Institute Annual Review 1978–79*, pp. 9–13. Melbourne.

Cox, H. R. 1938 A filter-passing infectious agent isolated from ticks. III. Description of organism and cultivation experiments. *Publ. Hlth Rep., Wash.* **53**, 2270.

Dale, H. H. 1953 Charles Halliley Kellaway. *Obit. Not. Fell. R. Soc. Lond.* **81**, 503.

Derrick, E. H. 1937 Q fever, a new fever entity: clinical features, diagnosis and laboratory investigations. *Med. J. Aust.* **2**, 281.

Derrick, E. H. 1944 The epidemiology of Q fever. *J. Hyg., Camb.* **43**, 357.

Doherty, P. C., Knowles, B. B. & Wettstein, P. J. 1984 Immunological surveillance of tumors in the context of major histocompatibility restriction of T cell function. *Adv. Cancer Res.* **42**, 1.

Elford, W. J. & Andrewes, C. H. 1932 The sizes of different bacteriophages. *Br. J. exp. Path.* **13**, 446.

Ellis, E. L. & Delbrück, M. 1939 The growth of bacteriophage. *J. gen. Physiol.* **22**, 365.

Enders, J. F., Weller, T. H. & Robbins, F. C. 1949 Cultivation of Lansing strain of poliomyelitis virus in cultures of various human embryo tissues. *Science, Wash.* **109**, 85.

Fenner, F. 1968 *The biology of animal viruses*. New York: Academic Press.

Fenner, F. 1979 Burnet and infectious diseases. *The Walter and Eliza Hall Institute of Medical Research Annual Review 1978–79*, pp. 25–30. Melbourne.

Farquhar, J. & Gajdusek, D. C. (ed.) 1981 *Kuru. Early letters and field-notes from the collection of D. Carleton Gajdusek*. New York: Raven Press.

Flexner, S. 1936 Respiratory versus gastro-intestinal infection in poliomyelitis. *J. exp. Med.* **63**, 209.

Francis, T. 1947 Dissociation of hemagglutinating and antibody-measuring capacities of influenza virus. *J. exp. Med.* **81**, 1.

Friedenreich, V. 1928 Recherches sur le phénomène de l'hemoagglutination de Thomsen. Nature de la substance transformante. *C.r. Séanc. Soc. Biol.* **98**, 1267.

Froggatt, W. W. 1907 *Australian insects*. Sydney: William Brooks.

Gajdusek, D. C. & Mackay, I. R. 1958 An 'autoimmune' reaction against human tissue antigens in certain acute and chronic diseases. II. Clinical correlations. *Arch. Int. Med.* **101**, 30.

Gottschalk, A. 1957*a* Neuraminidase: the specific enzyme of influenza virus and *Vibrio cholerae*. *Biochim. biophys. Acta* **23**, 645.

Gottschalk, A. 1957*b* *The chemistry and biology of sialic acids and related substances*. Cambridge: Cambridge University Press.

Gottschalk, A. (ed.) 1966 *Glycoproteins: their composition, structure and function*. Amsterdam: Elsevier.

Greenwood, M., Hill, A. B., Topley, W. N. C. & Wilson, J. 1936 *Experimental epidemiology*. Medical Research Council Special Report Series, no. 209.

Hérelle, F. d' 1922 *The bacteriophage : its role in immunity*. Baltimore: Williams & Wilkins.
Hérelle, F. d' 1926 *Le bacteriophage et son comportement*. Paris: Masson.
Hirst, G. K. 1941 The agglutination of red cells by the allantoic fluid of chick embryos infected with influenza virus. *Science, Wash.* **94**, 22.
Huebner, R. J. & Todaro, G. J. 1969 Oncogenes of RNA tumor viruses as determinants of cancer. *Proc. natn. Acad. Sci. U.S.A.* **64**, 1087.
Isaacs, A. & Lindenmann, J. 1957 Virus interference. I. The interferon. *Proc. R. Soc. Lond.*, B **147**, 258.
Jerne, N. K. 1955 The natural selection theory of antibody formation. *Proc. natn. Acad. Sci. U.S.A.* **41**, 849.
Joske, R. A. & King, W. E. 1955 The 'L.E.-cell' phenomenon in active chronic viral hepatitis. *Lancet* ii, 477.
Kellaway, C. H., MacCallum, P. & Tebbutt, A. H. 1928 *Report of the Royal Commission into the fatalities at Bundaberg*. Canberra: Government Printer.
Kilbourne, E. D. 1969 Future influenza vaccines and the use of genetic recombinants. *Bull. Wld Hlth Org.* **41**, 643.
Lafferty, K. J. & Jones, M. A. S. 1969 Reactions of the graft versus host (GVH) type. *Aust. J. exp. Biol. med. Sci.* **47**, 17.
Lafferty, K. J., Prowse, S. J., Simeonovic, C. J. & Warren, H. S. 1983 Immunobiology of tissue transplantation: a return to the passenger leukocyte concept. *A. Rev. Immun.* **1**, 143.
Levens, J. H. & Enders, J. F. 1945 Hemoagglutinative properties of amniotic fluid from embryonated eggs infected with mumps virus. *Science, Wash.* **102**, 117.
Luria, S. E. & Delbrück, M. 1943 Mutations of bacteria from virus sensitivity to virus resistance. *Genetics, Princeton* **28**, 491.
Lwoff, A. & Gutmann, A. 1950 Recherches sur un *Bacillus megatherium* lysogene. *Annls Inst. Pasteur, Paris* **78**, 711.
Lwoff, A., Dulbecco, R., Vogt, M. & Lwoff, M. 1955 Kinetics of the release of poliomyelitis virus from single cells. *Virology* **1**, 128.
Mackay, I. R. 1979 Burnet and autoimmunity. *The Walter and Eliza Hall Institute of Medical Research Annual Review 1978–79*, pp. 39–45. Melbourne.
Marchal, J. 1930 Infectious ectromelia. A hitherto undescribed virus disease of mice. *J. Path. Bact.* **33**, 713.
McClelland, L. & Hare, R. 1941 Adsorption of influenza virus by red cells and a new *in vitro* method of measuring antibodies for influenza virus. *Can. J. publ. Hlth* **32**, 530.
Medawar, P. B. 1961 Immunological tolerance. *Science, Wash.* **133**, 303.
Mudd, S. 1932 A hypothetical mechanism of antibody formation. *J. Immun.* **23**, 423.
Murphy, B. R. & Webster, R. G. 1985 Influenza viruses. In *Virology* (ed. B. N. Fields *et al.*), p. 1179. New York: Raven Press.
Nagler, F. P. O. 1942 Application of Hirst's phenomenon to the titration of vaccina virus and vaccinia immune serum. *Med. J. Aust.* **1**, 281.
Nigg, C., Crowley, J. H. & Wilson, D. E. 1940 On use of chick embryo cultures of influenza virus in complement fixation tests. *Science, Wash.* **91**, 603.
Nossal, G. J. V. 1969 Burnet and science. *Australas. Ann. Med.* **4**, 311.
Nossal, G. J. V. & Lederberg, J. 1958 Antibody production by single cells. *Nature, Lond.* **181**, 1419.
Nossal, G. J. V. & Pike, B. I. 1976 Single cell studies on the antibody-forming potential of fractionated, hapten-specific B lymphocytes. *Immunology* **30**, 189.
Pauling, L. 1940 A theory of the structure and process of formation of antibodies. *J. Am. chem. Soc.* **62**, 2643.
Pons, M. W. & Hirst, G. K. 1968 Polyacrylamide gel electrophoresis of influenza virus RNA. *Virology* **34**, 386.
Robertson, J. S., Naeve, C. W., Webster, R. G., Bootman, J. S., Newman, R. & Schild, G. C. 1985 Alterations in the hemagglutinin associated with adaptation of influenza B virus to growth in eggs. *Virology* **143**, 166.
Roe, A. 1965 Changes in scientific activities with age. *Science, Wash.* **150**, 313.
Sabin, A. B. 1934 Studies on the B virus. I. The immunological identity of a virus isolated from a human case of ascending myelitis associated with visceral necrosis. *Br. J. exp. Path.* **15**, 248.
Sexton, C. 1988 *Sir Macfarlane Burnet : a biography*. Melbourne: Macmillan. (In the press.)
Simonsen, M. 1957 The impact on the developing embryo and newborn animal of adult homologous cells. *Acta path. microbiol. scand.* **40**, 480.

Simonsen, M. 1985 Graft-versus-host reactions: the history that never was, and the way things happened to happen. *Immun. Rev.* **88**, 5.
Smith, T. 1934 *Parasitism and disease*. Princeton: Princeton University Press.
Szenberg, A. & Warner, N. L. 1962 Dissociation of immunological responsiveness in fowls with a hormonally arrested development of lymphoid tissues. *Nature, Lond.* **194**, 146.
Talmage, D. W. 1957 Allergy and immunology. *A. Rev. Med.* **8**, 239.
Theofilopoulos, A. N. & Dixon, F. J. 1985 Murine models of systemic lupus erythematosis. *Adv. Immunol.* **37**, 269.
Thomas, L. 1959 In *Cellular and humoral aspects of the hypersensitive state* (ed. H. S. Lawrence), p. 529. New York: Hoeber-Harper.
Thomsen, O. 1926 Ein vermehrungsfahiges Agens als Veranderer des isoagglutinatorischen Verhaltens der roten Blutkorperchen, eine bisher unbekannte Quelle der Fehlbestimmung. *Z. ImmunForsch. exp. Ther.* **52**, 85.
Trikojus, V. M. 1975 Alfred Gottschalk. *Rec. Aust. Acad. Sci.* **3** (1), 53.
Varghase, J. N., Laver, W. G. & Colman, P. M. 1983 Structure of the influenza virus glycoprotein antigen neuraminidase at 2.9 Å resolution. *Nature, Lond.* **303**, 35.
Walter and Eliza Hall Institute of Medical Research Annual Review 1978–79, pp. 74–80. Melbourne.
Waterson, A. P. 1962 Two kinds of myxovirus. *Nature, Lond.* **193**, 1163.
Wolstenholme, G. E. W. & Porter, R. 1966 *Ciba Foundation Symposium : The thymus : experimental and clinical studies*. Churchill: London.
Woodruff, A. M. & Goodpasture, E. W. 1931 The susceptibility of the chorioallantoic membrane of chick embryos to infection with the fowlpox virus. *Am. J. Path.* **7**, 209.