Chapter 6. Professor of Microbiology, John Curtin School of Medical Research, 1949 to 1967: Research

Research in Melbourne, February 1950 to November 1952

As mentioned in the previous chapter, The Australian National University had arranged with the Director of the Walter and Eliza Hall Institute, Sir Macfarlane Burnet, to provide me with two laboratories, on the same floor as his laboratory, for as long as it took to provide laboratories in Canberra. I worked in the room previously occupied by gifted research worker Dora Lush, who had died in 1943 from scrub typhus contracted during her work (Burnet, 1971).

Molecular biology was unknown in the early 1950s, and although I wanted to get back to virology, I thought that I had skimmed the cream from the study of ectromelia virus. Subsequently it was used by several groups in the John Curtin School as their model virus disease and they continue to use it in studies of molecular virology. At first, Burnet suggested that I might like to take over the field that he had been working on, the genetics of influenza virus. However, I did not want the work of my new department to be too closely associated with someone as distinguished as Burnet, so I did not take up his offer.

Studies on *Mycobacterium tuberculosis* and *Mycobacterium ulcerans*

Initially, I carried on working with *Mycobacterium tuberculosis*, the major work being a long review article on the vaccine strain, BCG (Fenner, 1951). With a research assistant, Ronald Leach, I also continued laboratory studies of tubercle bacilli and began serious studies of the 'Bairnsdale bacillus'. The first use of the name *Mycobacterium ulcerans* for this mycobacterium (since then the official name) appears as a footnote in my Inaugural Lecture, given in Canberra on 17 August ,1950, as a new professor in The Australian National University (Fenner, 1950). This organism is characterized by its low ceiling temperature, 34˚C (meaning that it will not grow, in culture or *in vivo*, at higher temperatures). It is now known to have a world wide distribution, and is particularly common in tropical Africa, where the disease is known as Buruli ulcer (Asiedu et al., 2000). It is a very interesting organism, not least because the severe skin ulceration is due to a soluble toxin, previously unknown among mycobacteria. Initially, with Leach, I showed that it was antigenically distinct from other mycobacteria. The feature which I investigated in detail, in parallel with my work on myxomatosis over the period 1952 to 1957, was the relation between its ceiling temperature and its pathogenicity (Fenner, 1956). This investigation

was made more interesting by comparison with another mycobacterium which was also temperature-sensitive and also produced skin lesions in humans, named *Mycobacterium balnei* by two Swedish workers (Linell and Nordén, 1954). I had a long correspondence with Åke Nordén, before and after I had visited him at the University of Lund in 1953. In mice, both bacteria produced severe skin lesions when inoculated in the manner used in studies on ectromelia, i.e., in the footpad. *M. balnei*, which grew rapidly in culture, produced progressive lesions within 4 days which became very severe within 9 days. On the other hand, *M. ulcerans,* which grew as slowly as tubercle bacilli in culture, did not produce progressive lesions until the fourth week, and they became severe by 7 weeks. However, because of their low ceiling temperature, neither organism produced visceral lesions after intranasal, intraperitoneal or intravenous inoculation, but after a moderate interval in the case of *M. balnei* and long interval in the case of *M. ulcerans*, ulcerating lesions developed on the hairless peripheral parts of the body and on the scrotum. The low ceiling temperature is clearly the reason that in experimental animals, as well as in humans, the lesions are restricted to the skin. *M. balnei* is a saprophyte which is associated with water, sometimes water in swimming pools. *M. ulcerans* also appears to be associated with swamps; cases seem to be more common after disturbances to the water environment. According to his paper (Shepard, 1960), one interesting result of our work was that it led him to successfully exploit footpad inoculation as a way of growing leprosy bacilli in mice. Ron Leach did not come up to Canberra, and I was solely responsible for the later work, described in the 1956 reference.

The History of Myxomatosis

Myxomatosis constituted the major part of my personal research between 1952 and 1967. To put it in perspective, I will begin with a very brief outline of its history, which is covered in detail in Fenner and Fantini (1999). Myxomatosis was first recognized as a virus disease when it killed European rabbits *(Oryctolagus cuniculus)* in Giuseppe Sanarelli's laboratory in Montevideo, Uruguay, in 1896. In 1911, workers in the Oswaldo Cruz Institute in Rio de Janeiro observed the disease in their laboratory rabbits and correctly classified the causative agent as a large virus. Henrique de Beaurepaire Aragão, working at the Oswaldo Cruz Institute, showed that it could be transmitted mechanically by insect bite. In 1942, he showed that the reservoir host in Brazil was the local wild rabbit, *Sylvilagus brasiliensis*, in which the virus produced a localized nodule in the skin (Figure 6.1B). Knowing that the European rabbit was a major pest animal in Australia, and impressed by the lethality of the disease in these rabbits (Figure 6.1A), in 1919 Aragão wrote to the Australian government suggesting that it should be used here for rabbit control, but the quarantine authorities would not permit its importation.

The idea was revived by Jean Macnamara, a Melbourne paediatrician who had worked with Macfarlane Burnet and thus had an interest in virus diseases. In 1934, she went on a world tour to investigate poliomyelitis, which was her main professional interest. In America, she visited the laboratory of Richard Shope, in the Princeton branch of the Rockefeller Institute. He was investigating a tumour in local cottontail rabbits *(Sylvilagus floridanus),* which he showed was caused by a poxvirus related to myxoma virus. He called it fibroma virus. At the time there was an epizootic of myxomatosis in domestic European rabbits *(O. cuniculus)* in California, which was later found to have a different reservoir host *(Sylvilagus bachmani)*. Shope found that fibroma virus would protect laboratory rabbits against myxomatosis. Learning of this fatal rabbit disease, Macnamara wrote to the Australian High Commissioner in London asking him to help her convince the Government to use the virus for rabbit control.

Francis Noble Ratcliffe

Born in Calcutta in 1904, Ratcliffe studied zoology at Oxford. In 1928, he came to the notice of the London representative of the Council for Scientific and Industrial Research (CSIR), and this led to his invitation to come to Australia as Sir David Rivett's 'biological scout', to study flying foxes and erosion in arid lands, as a result of which he produced a classic book, *Flying Fox and Drifting Sand*. He returned to Britain in 1932 as Lecturer in Zoology in Aberdeen, but was invited back to Australia as a scientific adviser to the CSIR Executive in 1935. In 1937, he was transferred to the Division of Economic Entomology to work on termites. In 1942, he joined the Australian Army and served with distinction as Assistant Director of Entomology. Since I was serving in New Guinea as a malariologist at that time, I saw quite a lot of him then. After demobilization he served briefly as assistant to the Chief of the Division of Entomology, but in 1948 he was appointed Officer-in-Charge of the newly created Wildlife Survey Section of CSIR. Initially he had to work on rabbit control, and after some disappointments succeeded in introducing myxomatosis. Study of this disease preoccupied the Section for several years, but later he was able to broaden studies of the biology of the rabbit and introduce biological studies of native animals as an important part of the work of the Section, which by then had been expanded to the Division of Wildlife and Ecology. He retired from CSIRO in 1969. He played a major role in setting up the Australian Conservation Foundation in 1964, and devoted a great deal of time to its expansion to become Australia's peak environmental non-government organization, until he had to retire for health reasons in 1970 (see Coman, 1998; Mackerras, 1971).

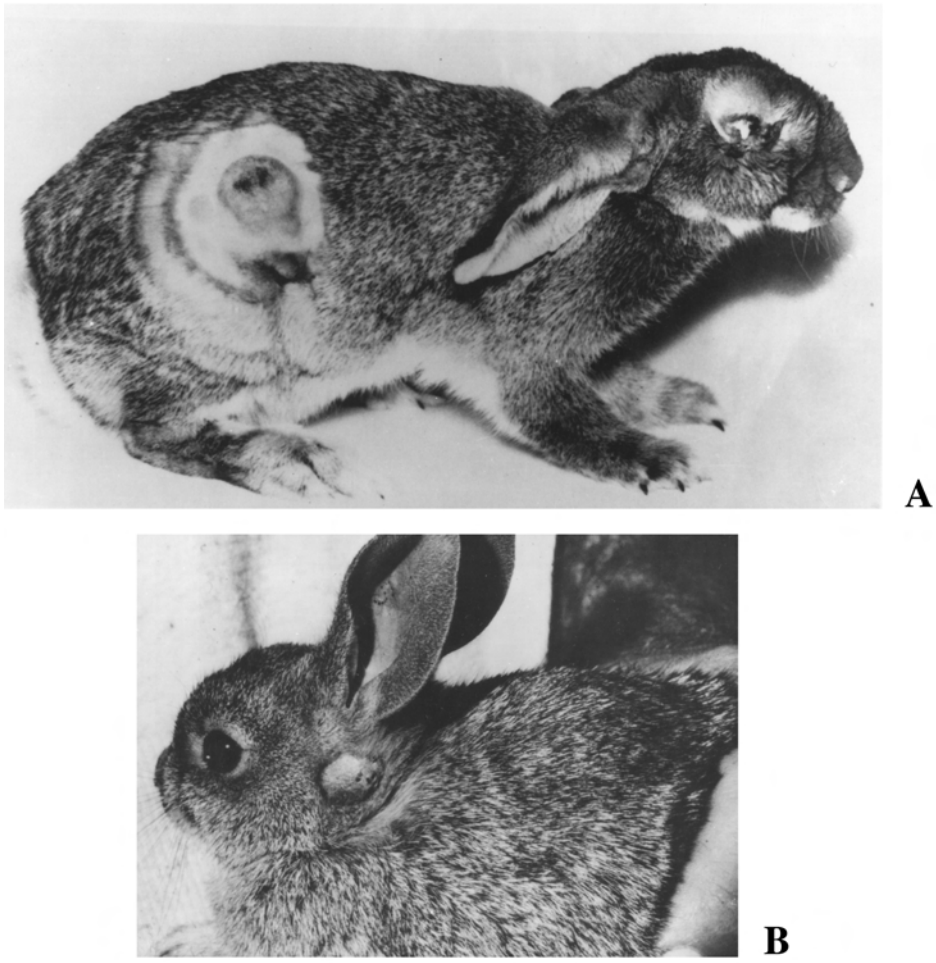

Figure 6.1. European and Brazilian Rabbit

Figure 6.1a. European rabbit *(Oryctolagus cuniculus)* 10 days after infection with the Standard Laboratory Strain of myxoma virus.
Figure 6.1b. Brazilian rabbit *(Sylvilagus brasiliensis)* three weeks after infection with the Standard Laboratory Strain of myxoma virus.

The Chief Quarantine Officer was again very reluctant to allow its importation, but allowed scientists in CSIR (which was transformed into the Commonwealth Scientific and Industrial Research Organization, CSIRO, in 1949), to test its species sensitivity against a wide range of domestic and native animals; they found that it infected only European rabbits. Several field trials were carried out, in dry inland areas, but the virus died out. Then came World War II, and in 1943 all investigations were stopped.

With so many country boys in the army, rabbit control, such as it was, had been neglected throughout the period 1939 to 1945, and by 1946 rabbits had increased

to unprecedented numbers. Jean Macnamara (now Dame Jean) wrote articles in the rural press highly critical of CSIR/CSIRO for not proceeding immediately to try myxomatosis for biological control of the pest. In 1948, a CSIR/CSIRO scientist, Francis Ratcliffe, was appointed Officer-in-Charge of the newly-established Wildlife Survey Section, but instead of studying the native fauna, Ian Clunies Ross, Chairman of the newly-formed CSIRO, insisted that he should first try out myxomatosis. Several field trials failed, but in the Christmas–New Year period of 1950–51 the disease escaped from one of the four trial sites in the Murray valley and spread all over the Murray-Darling basin, killing millions of rabbits.

Research on Myxomatosis, February 1951 to November 1952

Stimulated by a remark by my friend Professor Hugh Ward, I decided to make myxomatosis the main topic of my research. From Burnet's diaries, I later found that the day I made this decision was 1 February, 1951. I promptly made contact with Ian Clunies Ross, who was delighted to have a virologist working on this topic, for at the time there were no virologists in CSIRO. I also met with Francis Ratcliffe, who was in charge of the new Wildlife Survey Section of CSIRO, and recruited Gwen Woodroofe, MSc, from the Department of Microbiology of the University of Adelaide and Ian Marshall, a new BAgSc graduate of the University of Melbourne, initially as research assistants. Gwen and Ian worked with me on myxomatosis until about 1960. Gwen finished up as a Fellow and Ian as a Senior Fellow, both working on arboviruses.

Gwendolyn Marion Woodroofe

Born in 1918, Gwen graduated BSc at the University of Adelaide in 1940 and gained an MSc degree in bacteriology for work on salmonellosis. In 1951, she joined my department as a research assistant, to work on myxomatosis. She later became a Research Fellow, graduated PhD and was promoted a Fellow until she retired in 1978. She and Ian Marshall were my collaborators in laboratory studies of myxomatosis between 1951 and 1966. She then went to work with Ian on arboviruses. On her retirement, she became very active in work for UNICEF, for which she was awarded a Medal in the Order of Australia in 1997. After my wife Bobbie died in 1995 and I moved into the extension to our house, Gwen became one of several friends who now come around for a drink and a chat on weekend afternoons.

Ian David Marshall

Born in 1922, Ian Marshall served in the Royal Australian Navy in the World War II. After discharge, he graduated BAgSc in the University of Melbourne in 1951 and immediately joined my department to work on myxomatosis. He participated in fieldwork carried out by our CSIRO colleagues and also in laboratory studies. He graduated PhD in 1956, later becoming a Research Fellow, Fellow and Senior Fellow, before formal retirement in 1987. He played a major role in virological investigations of myxomatosis between 1951 and 1959, when he went to work with arboviruses with Bill Reeves at the University of California at Berkeley for two years. While in California he also collaborated with David Regnery of Stanford University in classical studies of the epidemiology of myxomatosis in California, where the host is a different species of *Sylvilagus (S. bachmani* rather than *S. brasiliensis)* and the virus also differs significantly from that found in South America.

When he returned to the John Curtin School, he established an arbovirus laboratory, which became one of the major Australian centres of arbovirus research, on which he continued to work full-time long after his retirement.

The climatic conditions at the time of the outbreak of myxomatosis in the Murray-Darling Basin had been such that there was also an outbreak of encephalitis in that region, similar to X-disease, described by Cleland et al., (1918). As soon as this outbreak was reported, Burnet instructed two of his staff to investigate it, one (Gray Anderson) looking at the epidemiology and the other (Eric French) attempting to isolate the causative virus from the brains of fatal cases. French (1952) was successful in isolating the virus and showed that it was very similar to the one that caused Japanese encephalitis. Burnet made this information widely available to the Government and the press, but the claim that the encephalitis was due to myxoma virus was widely voiced and the Chairman of the Mildura Hospital Board challenged Burnet and R. G. Casey (Minister in charge of CSIRO) to test the harmlessness of myxoma virus on themselves. Burnet consulted me and we decided that it was absolutely safe. I prepared a suspension and injected Burnet subcutaneously with one, 10 and 100 rabbit-infectious doses; Burnet inoculated me. As soon as he heard of this, Clunies Ross said that, as Chairman of CSIRO, he was responsible for the use of the virus, and therefore he should be included in the tests, so I injected him. None of us showed lesions or an antibody response, Casey announced the results of the tests in Parliament and the public was reassured (Burnet, 1968).

Clunies Ross financed the building of a new animal house at the Hall Institute for holding the large numbers of rabbits that I expected to use. When I went to

Canberra, the animal house was initially made available to Geoff Douglas, who was in charge of the myxoma virus inoculation campaigns in Victoria. Later, when Douglas had established the Keith Turnbull Research Institute in Frankston, where continuing research on changes in virus virulence and genetic resistance of rabbits was carried out, the Hall Institute animal house building was converted into laboratories. I also immediately made contact with Ratcliffe's team: Ken Myers, Bernard (Bunny) Fennessy, Alan Dyce, Roman Mykytowycz, Bill Poole and later Bill Sobey, with whom I continued to collaborate over the next 15 years. On one of my frequent trips to Canberra for meetings with the ANU administration, I made contact with Max Day, of the CSIRO Division of Entomology, who was working on insect transmission of plant viruses, and some of my first work, started in 1951, was to collaborate with him on insect transmission of myxomatosis. Other work carried out while I was still in Melbourne involved collaboration with a CSIRO electron microscopist on a comparison of the morphology of myxoma and vaccinia viruses and comparison of the pathogenesis of myxomatosis with that of mousepox.

Research on Myxomatosis, 1953 to 1967

Gwen Woodroofe came up to Canberra a few weeks before I did, and Ian Marshall a little later, and they had the laboratory equipment organized within the new temporary laboratories, in which I had arranged to have a large animal house for infected rabbits. I resumed work on myxomatosis as soon as Bobbie and I had settled into the house that I had rented from the ANU. Our studies had two components: Gwen and I worked on various aspects of the disease that could be studied in the laboratory; and Ian worked in the field with the CSIRO scientists and in the lab with me, our basic interest being the evolution of virulence of the virus and the genetic resistance of the rabbit. Each of them also did some independent work related to their PhD requirements.

In the laboratory, we studied the active immunity conferred by previous infection (in the rare rabbit that recovered) and following vaccination with fibroma virus, and passive immunity in kittens borne by immune does. Gwen collaborated in the later work done with Max Day on insect transmission and Ian and I wrote two long papers on the topics of major importance in considering the evolution of virus and host (Fenner and Marshall, 1957; Marshall and Fenner, 1960). There were also some important papers that involved close collaboration with us in the laboratory and the CSIRO scientists in the field (Myers et al., 1954, Fenner et al., 1957).

Another aspect of the work on myxomatosis followed my first study leave in 1953, when I met Harry Thompson and learnt more about myxomatosis in England. The virus that spread through Europe (the Lausanne strain) was more virulent than the one used in Australia, and in 1957 it was introduced in Australia. In 1961–62, during study leave as an Overseas Fellow of Churchill

College, Cambridge, I spent most of my time investigating myxomatosis in Europe.

Harry V. Thompson

Born in 1918, Harry Thompson graduated in zoology at the University of London in 1940 and then worked at the Bureau of Animal Population at the University of Oxford, where he came under the influence of the famous British ecologist, C. S. Elton, with whom Francis Ratcliffe also worked when on leave in England in 1948. In 1946, Thompson joined the Ministry of Agriculture, Fisheries and Food, where he became head of the department dealing with wild animals and birds affecting agriculture. Inevitably he became interested in rabbits, and he was at the forefront of work on myxomatosis in Britain. In 1959, he set up the Ministry's Worplesdon Laboratory at Guildford, Surrey, and remained its Director until retiring in 1982 to become a private consultant. Besides serving on most committees dealing with rabbits and myxomatosis and numerous national and international bodies concerned with wildlife and conservation, Thompson published numerous scientific papers and two important books on the European rabbit, in 1956 and 1994. Over the period 1952–65, I always tried to see him when I went to England, and after he retired I maintained a steady correspondence with him.

Deliberate spread of myxomatosis was made illegal in Britain in 1954. Nevertheless, the disease spread all over the country. A meeting with Paul Chapple, an English virologist who was working on myxomatosis, led to a study of the evolutionary changes in the Lausanne strain of the virus between 1954 and 1962 (Fenner and Chapple, 1965). I also visited scientists involved with myxomatosis in France, where the Lausanne strain was initially introduced by Dr P. F. Armand Delille, by inoculating two wild rabbits on his estate at Maillebois on 14 June 1952, whence it spread all over Europe.

It is impossible to cover the work on myxomatosis in this autobiography. As well as two substantial books, Fenner and Ratcliffe (1965) and Fenner and Fantini (1999), I wrote several review articles and book chapters on it and I used it as the topic for a Harvey Lecture in New York in 1957 and the Florey Lecture to The Royal Society in 1983.

The production of my second book, *Myxomatosis*

In 1949, at Burnet's request, I had been a co-author of the second edition of his book, *The Production of Antibodies,* but my contribution to this was minor, mainly looking up references on transplantation immunology. In 1957, I thought that the time was ripe to begin a book on myxomatosis. Since most of my papers

on the subject had been published in one of the Cambridge University Press (CUP) journals, the *Journal of Hygiene*, I wrote to CUP in July 1957 to suggest that they might publish such a book and followed this up when I was in Cambridge in September 1957. The response of the Syndics was positive, but for various reasons I did not start it until 1960, when I knew that I would be going to Churchill College, in Cambridge, for a year in 1961–62. In a letter dated 23 June, 1960, I set out a rough outline of the book and told them that Francis Ratcliffe had agreed to be a co-author and that this would ensure that there would be adequate coverage of the ecological aspects. We signed a Memorandum of Agreement on 22 September, 1961; my first guess was that it would be about 100 pages long and that it would be finished in March 1963.

However, I had not allowed for the large amount of additional material I was able to get about myxomatosis in Europe during my year at Churchill College through travel in the United Kingdom and the Continent, as well as the extensive correspondence initiated with scientists there who had information on the disease. It was a pleasure to work with Francis on this book. He lived in Mugga Way, just up the street from my home in Monaro Crescent, and we met at his place after work to plan it and discuss its progress. The manuscript and figures were sent to CUP early in 1964 and it was finally published in October 1965. CUP provided us with copies of the reviews. There were four in Australian journals, one in an Austrian journal, four in French journals, seven in German journals, two in Italian journals, two in Romanian journals, two in South African journals, and eight in journals in the United States. There were also three in Australian newspapers and 16 in newspapers in the United Kingdom. I would like to quote from two of journal reviews. *The Lancet* said:

> It is a splendid book. Not a word and not a picture are wasted, and it is a pleasure to read. The authors have drawn on every available source of information, as much by personal contact as from the printed word. The result is a complete story which ranges from the introduction of wild rabbits into Australia (domestic strains failed to take root) to the changes in virulence of the virus and susceptibility of the host which are still taking place.

Science said:

> Without doubt man's own evolution has been greatly affected by racial experience with plagues of various types, ranging from malaria, typhus and smallpox to tuberculosis and other similar diseases; great die-offs in population create conditions favorable for evolutionary change. Nearly all virulent diseases, newly introduced, have become attenuated with time by mutual adaptations of host and parasites. The Australian investigators are to be congratulated on providing such a lucid and well-documented account of how such modifications actually take place.

Genetic Studies of Poxviruses

By 1957, it was clear that genetic changes in the virulence of myxoma virus were the major factor in the changing epidemiology of the disease and made possible changes in the genetic resistance of rabbits. However, it was also clear to me that although myxomatosis was a superb 'natural experiment' in evolution, myxoma virus was not a good virus with which to study viral genetics. I therefore initiated work on this with a survey of various marker properties of several orthopoxviruses, mostly different strains of vaccinia and cowpox viruses, which were ideal agents for laboratory investigations (Fenner, 1958). Following selection of two with contrasting characters, I demonstrated, for the first time, intramolecular genetic recombination between animal viruses (Fenner, 1959). Travelling across USA on study leave in 1957 and discussing this work, as mentioned earlier, I was quickly convinced by Salvador Luria, then at Urbana, Illinois, that it would be impossible to delve deeply into mechanisms of recombination if I used two different wild type viruses. As with bacterial viruses, which he had studied, it was essential to use a suite of viruses derived from a single parent. Fortunately, I had such material on hand, the white pock mutants of rabbitpox virus (Gemmell and Fenner, 1960), and initiated work on these which later extended to the use of host-cell dependent and temperature-sensitive conditional lethal mutants (reviews, Fenner and Sambrook, 1964; Fenner, 1970).

The Reactivation of Animal Viruses

What Burnet (1960) described as 'the first example of what may be called genetic interaction between animal viruses' was the reactivation of heat-inactivated myxoma virus by infection of the same cells with live rabbit fibroma virus (Berry and Dedrick, 1936). This was later found by Hanafusa et al., (1959) and workers in our laboratory (Fenner et al., 1959) to be a non-genetic reactivation and was a general phenomenon among the poxviruses. It is now thought to be due to the fact that promoter sequences of an early gene are conserved among poxviruses; they are destroyed by heat inactivation, but may be supplied by another poxvirus infecting the same cell (review: Fenner, 1962).

My Work Pattern at the Bench

From childhood, I have been an early riser, going to bed about 10 pm and getting up when I woke at about 5 am. During most of the time covered in this chapter, I would come in to work shortly after a breakfast of fruit and cereal. Since the distance between my home and the John Curtin School building was only 6 kilometres and there was very little traffic at that time of the day, I usually arrived at the School between 6 and 7 am.

Figure 6.2. Frank Fenner at the bench, inoculating chick-developing embryos with a virus suspension

Throughout the period that I did bench-work (1946–67) biological experimentation was much simpler than it became after the expansion of molecular virology in the 1960s. Most of my papers had only one or two authors, there were no such things as animal ethics committees and most of my research involving experimental animals were carried out with the outbred Walter and Eliza Hall strain of mice and with captured wild rabbits or domestic rabbits bred in the ANU Animal Breeding facilities under the supervision, in Canberra, of a veterinarian, Wes Whitten. In those days we all wore laboratory gowns, but did not use gloves, so I would put on my gown and then look at the experimental animals and do autopsies when they were needed and take down eggs that had been inoculated on the chorioallantoic membrane and count the pocks, or else look at the tissue culture plates that had been inoculated a couple of days earlier. All results were entered in exercise books, in which the relevant experiments had been recorded. I would then consult Ian Marshall and Gwen Woodroofe and hear what they had to say, and also my PhD students. I rarely had more than two students at any one time and after a few months in my lab to learn the basic techniques and

decide on the topic on which they would work they would proceed on their own, but consult me whenever they wanted advice. At about 10.30 am we usually had morning coffee, on the lawn just outside our seminar room, and talk with my colleagues. I would then usually go up to the Library to look over all new periodicals dealing with viruses or infectious diseases.

I would often write drafts of papers as soon as I had an idea of what I wished to report, since this would give me a good idea of what additional experiments were needed. I read over all draft PhD theses and papers coming from members of the Department, usually in the evenings, and discussed them with the authors a few days later. I followed Burnet's practice of never putting my name on a paper unless I had carried out some of the bench work. Even from my earliest days in the laboratory, I produced review papers whenever I thought it appropriate, usually as sole author; on ectromelia in 1949, BCG in 1951, myxomatosis in 1954, 1959 and 1964 and the genetics of animal viruses in 1964 and 1970.

Of course, as head of a Department, on some days I would have to spend a good deal of time at meetings of the School Committee or the Board of the Institute of Advanced Studies, but I always had a few hours early in the morning to keep up with the lab work.

Book: *The Biology of Animal Viruses*

In December 1963, I received a letter from Kurt Jacoby, the Vice-President of Academic Press, telling me that Burnet had suggested to him that I should revise the second edition of his book, *Principles of Animal Virology*, which had been published in 1960. After discussions with Burnet, who said that he had switched to immunology and did not want to be involved, and considerable thought, I told Jacoby that I would not undertake a revision of Burnet's book, but would write a new book with much the same coverage, with the title, *The Biology of Animal Viruses*. After correspondence with many overseas virologists, it took me about two years to write, but eventually it was published in 1968 as a two volume book of 845 pages (excluding the subject and name indexes). It received excellent reviews and sold well enough for Academic Press to ask me to prepare a second edition. During the two years that I was writing this book, I did much less bench work than usual, and this influenced my decision to apply for the position of Director of the JCSMR when Hugh Ennor resigned in February 1967.

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