Burnet of Australia

IAN J. WOOD
M.D.(Melb.), F.R.C.P.

Royal Melbourne Hospital, Melbourne, Australia

'Darwin is the greatest of all scientists, greater even than Newton or Einstein, and I am quite certain that my own thinking has been more deeply influenced by the evolutionary concepts of Darwin than by anything else' (Burnet, 1966).

'Life must have begun as some particular configuration of atoms, an inconceivably tiny knot of molecular structure, which by some freak of circumstance was able to build more of itself from the matter and energy freely available . . . Somehow a large molecule, or a random complex of molecules, came into being which was capable of doubling itself at the expense of the surrounding chaos. The key event needed to occur only once and from that moment Life was on its way' (Burnet, 1968).

'Life is everywhere—to be wondered at or understood, as it presents itself in culture tubes of the laboratories; as the living fascinating inhabitants of earth, air and sea, or in our own human form, behaviours and aspirations' (Burnet, 1966).

Thus spoke Frank Macfarlane Burnet.

And what of the achievements of James Cook of the *Endeavour* whose memory is celebrated by this Journal? Do they in any way simulate the achievements of Burnet?

An account of the clinical features of the dread affliction scurvy was made by Jacques de Vitry in 1244. It was not until 1796 that the British Admiralty ordered lemon juice to be added to the rations of sailors, and scurvy disappeared from the British Navy (Major, 1945).

In 1768 Captain James Cook sailed in the *Endeavour* from England to observe the Transit of Venus from the Island of Tahiti in the Pacific Ocean. The Royal Society had asked the Admiralty to invite Joseph Banks aged 25 to join the *Endeavour*, a wise move as he not only was versed in geographical and astronomical science, but had a deep love of botanical and natural science (Beaglehole, 1962).

After making a disappointing observation of the Transit of Venus, because of adverse weather conditions, Cook set out on a voyage of discovery. On 19 April 1770 he sighted the southern tip of Australia and proceeded north to land at a picturesque harbour.

Cook and Banks journeyed into the Australian bush and were delighted to see large gum trees,

kangaroos, flocks of parrots and many new species of plants. They called the harbour Botany Bay. During this historic voyage Cook, aided by Banks, paid particular attention to the diet and hygiene of his crew, maintaining a supply of vegetables and fruit. They thus remained healthy and free of the dreaded scurvy till the end of their voyage (Cameron, 1952).

On 10 July 1776 Captain James Cook was waiting in his ship *Resolution*, about to make his third voyage of discovery, when he received news of a great honour. He wrote to Banks, no longer a member of his crew: 'Sir John Pringle writes me that the Council of the Royal Society has decreed me the Prize Medal of the year. I am obliged to you and my other good friends for this unmerited honour' (Cameron, 1952).

Cook received the Copley Medal, the most treasured award of the Royal Society for his account of the prevention of scurvy during his first voyage to Botany Bay.

Some 183 years later Macfarlane Burnet was awarded the Copley Medal for his outstanding work on biological science in Australia. In his recent book *Changing Patterns. An Atypical Biography* Burnet wrote: 'The Copley Medal is traditionally the second-highest honour that the Royal Society can offer, the first being, of course, election as President . . . When I was awarded the Copley Medal for 1959 it gave me an overpowering sense of continuity of History that my name was now on the roll that included Benjamin Franklin and Captain James Cook' (Burnet, 1968). The signatures of James Cook and Macfarlane Burnet are shown in Fig. 1.

The turn of the wheel of Fate decreed that, just as 200 years ago James Cook and Joseph Banks wandered in the Australian bush at Botany Bay to discover new biological specimens which were to make them world famous, so 60 years ago Macfarlane Burnet began his climb to fame in the world of biological science by wandering in the Australian bush at his birthplace, Traralgon, a small country town some 500 miles from Botany Bay. In his wanderings Burnet studied the birds, butterflies, yabbies and whirling beetles—he wrote: 'Perhaps this sort of activity laid down the beginnings of my interest in

FIG. 1. 1776 and 1959. Signatures of Captain James Cook and Sir Macfarlane Burnet. In these years they received the Copley Medal, the most treasured award of the Royal Society. (By kind permission of the Royal Society and Sir Macfarlane Burnet.)

biology. I am by temperament an ecologist, a naturalist, a collector of beetles, a snapper up of unconsidered trifles' (Burnet, 1968).

Burnet had a successful but uneventful progress through the University of Melbourne and the Melbourne Hospital. He was house doctor to Australia's most famous physician of the day, Richard Stawell.

Stawell, the son of William Stawell, Chief Justice of Victoria, was highly intelligent, eloquent and amusing. He devoted his life to teaching and made no significant contribution to medical knowledge. He was greatly admired and beloved by his students, and by Burnet. He provided a great stimulus for Burnet, and Burnet's admiration was enhanced by their contrasting personalities and approach to life—for Burnet was innately quiet and shy, escaping from the limelight to seek seclusion. But unlike Stawell, Burnet possessed a burning desire to probe the unknown, to fill the gaps in medical knowledge. Clinical bedside medicine, with its triumphs and failures, trials and tribulations, and petty frustrations, was not for Burnet. He chose to sit at the bench, to enter the world of medical biological science where he could tackle the problems of his day.

Burnet was indeed fortunate that Charles Kellaway, an Australian physiologist, trained by Henry Dale in London, was Director of the Walter and Eliza Hall Institute of Medical Research which was attached to the Melbourne Hospital. This Institute was founded in 1914 to investigate problems in clinical medicine. Like Stawell, Kellaway was an extrovert with high intelligence, but he was devoted to research and made no claim to be a competent physician. He was happiest in his laboratory where he studied the life cycle of the hydatid and the snake venoms of Australia. He also loved to wander in the Australian

bush—bird watching, fishing and, as part of his research, catching highly venomous snakes. Under the expert guidance of 'Pambo', his professional snake charmer, Kellaway learnt to catch a snake, handle it alive and plunge it into the snake bag, later to remove it and milk out the deadly venene. Eventually Kellaway was bitten by a tiger snake, a deadly poisonous variety. But fortunately 'anti-tiger venene' had just been discovered in Kellaway's laboratory—he was the first to be treated—he survived.

Kellaway was a most successful director of the Institute and selected Burnet for his team, to develop research in bacteriology. He selected three others who became famous and Fellows of the Royal Society: Hamilton Fairley, Gordon Cameron and Wilhelm Feldberg. In 1925 Kellaway wisely sent Burnet to London to work with C. J. Martin at the Lister Institute. He studied the bacteriophage and gained his Ph.D. (London).

Returning to Australia in 1927 Burnet was appointed Assistant Director of the Hall Institute under Kellaway. He soon became known to Australian scientists for his research on a staphylococcal toxin which had been liberated in a contaminated bottle of diphtheria toxin—anti-toxin. This resulted in a number of deaths in the North of Australia (Burnet & Kellaway, 1930). This study first stimulated Burnet's interest in the defence mechanisms of the body, both natural and acquired. His discerning mind led him to believe there were many fascinating problems to be solved in the field of immunity. He retained this memory: it slowly dominated his forward planning.

Burnet then resumed his studies of the bacteriophage, but a serious epidemic of poliomyelitis was occurring. Burnet and Macnamara transmitted the virus to monkeys and he was the first to show that there was more than one strain of poliomyelitis virus, an important step towards the ultimate production of the poliomyelitis vaccine by Enders, Salk and Sabin (Burnet & Macnamara, 1931).

In 1931 Henry Dale, Head of the National Institute of Medical Research, London, invited Burnet to work with him. This was a great success for Burnet. He developed Goodpasture's method of growing a virus on the membranes enveloping the developing chick embryo. In Dale's laboratories at that time much was happening for Burnet to observe—Elford and Barnard were measuring the size of virus particles with 'Elford' membranes, and were photographing them: Laidlaw, Andrewes and Wilson made their momentous discovery, the transmission of the influenza virus to ferrets (Burnet, 1968). It was a stimulating and fruitful experience for Burnet!

Burnet sailed for Australia in 1934 with many plans for his future researches. He joined Kellaway at the Hall Institute and began work on the influenza virus, studying an outbreak amongst the nursing staff of

the Melbourne Hospital. Using the egg membrane technique he was the first to adapt the influenza virus to the egg, identifying its presence after twenty passages (Burnet, 1935).

This provided Burnet with an excellent model for research, especially when Hirst of New York described the clumping of chicken red cells by the influenza virus. Now the influenza virus could be grown in the egg and its presence revealed by the Hirst test. Burnet was delighted to discover two strains of influenza virus in an outbreak at a school (Burnet, 1937). Later it was shown by other workers that there were many and changing strains of the influenza virus—this posed a problem in the production of an effective vaccine. Burnet made a killed vaccine and used it to immunize troops in the Second World War, but it was not successful. He then made an attenuated live virus vaccine, considering this might prove more satisfactory—it was only moderately successful (Burnet, 1943).

Before Burnet switched his interests from virology to immunology in 1957, the study of the influenza virus was the sheet anchor of his biological studies and the chick embryo his culture medium. Two of his major achievements were first the discovery of 'virus recombination', the recombination of two strains of virus to create a new strain; secondly the discovery of the receptor destroying enzyme, later shown by Gottschalk in the Institute to be neuraminidase (Burnet & Lind, 1949; Gottschalk, 1958).

In 1942 General Douglas McArthur of the American Army journeyed through the streets of Melbourne and observed an impressive new hospital (Fig. 5). It was to be the new Melbourne Hospital including the new Walter and Eliza Hall Institute—but completion and occupation had been postponed till the end of the War. McArthur struck a bargain with the Australians—America would pay for the immediate completion of the hospital and would occupy it for the duration of the war. This was done, but the new Institute was taken over by Kellaway and Burnet. This brought Burnet into close and happy contact with the Americans.

In 1943 Burnet journeyed to America to deliver the Durham Lectures at Harvard University. Later he was offered a full Chair at Harvard with research facilities—but his loyalties remained in Australia, particularly as Kellaway was departing for London to become Scientific Director of the Wellcome Foundation, and Burnet had been offered the post of Director of the Hall Institute and Professor of Experimental Medicine in the University of Melbourne. He accepted the Australian appointment (Burnet, 1968).

In 1935 Burnet made a study of psittacosis, a rickettsial infection of birds and humans. Several human cases were diagnosed and Burnet found a reservoir of infection in the wild parrots of the

Australian bush (Burnet, 1934). Indeed psittacosis may have been endemic in the birds shot by the crew of the *Endeavour*. 'The trees over our heads', wrote Joseph Banks in 1770, 'abounded very much with loryquets and cockatoos of which we shot several; both these sorts flew in flocks of several scores together' (Beaglehole, 1962).

In 1934 Derrick of Brisbane investigated abattoir workers with fever and bronchopneumonia. He transmitted an infective agent from their blood to guinea-pigs. The illness was called 'abattoir fever' and later 'Q fever', the 'Q' being for 'query' as the cause of the illness was unknown (Derrick, 1953). Derrick suspected a tick-borne virus infection and in 1936 sent the spleen of an infected guinea-pig to Burnet at the Hall Institute. However, Burnet and Mavis Freeman discovered a Rickettsial organism, which was called '*Rickettsia burneti*' and later '*Coxiella burneti*' to acknowledge Harold Cox's finding of a similar organism in the American Rocky Mountains (Burnet & Freeman, 1937; Burnet, 1968). Subsequently Q fever was found to be widely distributed in Europe. In 1947 Haubner and Luoto showed that the air of the abattoirs became polluted by infected droplets and dust to cause infection of the workers by inhalation, rather than by the bite of infected ticks (Derrick, 1964).

In 1950 an outbreak of encephalitis occurred in the region of the Murray River which separates Victoria from New South Wales (Fig. 2). The brain from a fatal case was taken to Burnet at the Hall Institute and there French grew a virus on egg membrane. This virus proved to be a new strain, resembling in some respects the virus of Japanese B encephalitis and St Louis encephalitis. Anderson and his colleagues at the Institute identified the virus as being mosquito-borne, antibodies being found in the blood of the local inhabitants and in their horses and domestic fowls (Anderson, 1952; French, 1952).

So Burnet's studies in his laboratory were extended from time to time to clinical problems in the field, including staphylococcal infections, poliomyelitis, psittacosis, Q fever and Murray Valley encephalitis. But his basic studies on the influenza virus dominated his field of interest. Lunch time at his Institute was a time of great debate for Burnet and his colleagues, gathered around the round table. Over a somewhat unappetizing sandwich and tea Burnet would lead the arguments concerning the current problem, stimulating the thoughts and opinions of his many young colleagues from Australia, England, Europe, America and Asia. They were often joined by senior scientists from overseas. During these discussions Burnet often referred to a potentially fertile field of research—immunology. He considered immunology in its broadest sense had not been studied in depth. There was a call for a study of Man's natural and

FIG. 2. Members of the Walter and Eliza Hall Institute are collecting water birds and mosquitoes, infected with Murray Valley encephalitis virus, from a billabong in the Australian bush adjoining the Murray River.

acquired antibody systems, the impact of his experience with infecting organisms, the part played by his genetic makeup, his experience *in utero*, and after birth.

Over the years before 1957 Burnet recorded his thoughts on immunity, his major work being his collaboration in 1949 with Frank Fenner, then a member of the Institute. They traced the development of natural and acquired immunity in Man, stressing the great importance of Man's experience. Man learnt to tolerate his own tissue, and to recognize and destroy foreign tissues—the conception of 'self' and 'not self' came into being. In their monograph *Production of Antibodies* Burnet and Fenner wrote: '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' (Burnet & Fenner, 1949). Indeed Burnet attempted to produce immunological tolerance to bacteria by injecting a bacterial vaccine into the chick embryo—but this failed. Later Medawar working with mice produced immunological tolerance to skin grafts by injecting at birth skin from a genetically

different strain of mice. The secret of Medawar's success was that skin survived and so acted as a continuing antigenic stimulus, so promoting continuing tolerance—whereas Burnet's experiment failed as the injected dead bacterial vaccine did not persist (Burnet, 1968). It is, therefore, history that the judges in their wisdom decreed that Burnet and Medawar should share the Nobel Prize for the concept of 'Immunological Tolerance' (Fig. 3).

It is also history that the work of Burnet and Medawar sparked off a conflagration of intense enthusiasm for the study of immunity and this revealed the true nature of the autoimmune diseases. Later work revealed the nature of the host-*versus*-graft reaction, and led to the gradual development of methods aimed at suppressing the homograft rejection reaction which followed kidney, heart and liver transplantation—these methods included tissue typing, the immunosuppressive drugs and anti-lymphocyte sera—so far only partial success has been achieved.

The year 1957 saw a master stroke by Burnet—he abandoned virus research to transfer all his energies, and those of his Institute, to the study of immunity. Now, 13 years later, even though he has left the

FIG. 3. 1956. A gift from Major H. W. Hall (right) to Sir Macfarlane Burnet (left). Major Hall's uncle, Mr Walter Hall, the original benefactor of the Walter and Eliza Hall Institute, is shown in the portrait (rear). Mr Geoffrey Grimwade (centre) was President of the Institute.

Institute, Burnet derives great pleasure in the recollection of those fruitful days which followed 1957—the 'big switch' had paid a remarkably rich dividend.

The Nobel Prize was awarded to Burnet and Medawar for the concept of immunological tolerance, that Man had learnt to tolerate his own tissues, to tolerate 'self'—and was intolerant to foreign tissue, to 'not self'. However, it was for his 'clonal selection theory' that Burnet achieved his greatest fame. Based on Neil Jerne's work in 1955 on a natural selection theory of antibody production, Burnet postulated that antibodies are produced by lymphoid cells, each cell having a genetic pattern capable of stimulation by a specific antibody (Burnet, 1957). There is a wide, but not infinite, range of lymphoid cells so there will be at least some to react to form antibody to any form of foreign material which may enter the body. Thus the antigen selects a clone of lymphoid cells which will react against itself—it promotes self-destruction—such is the 'Clonal Selection Theory' of Burnet. He also postulated that there is a mechanism in the body which destroys any collection of lymphoid cells which would react damagingly against the body's

own tissues, it destroys these 'forbidden clones'. Thus under normal conditions the body maintains 'immunological tolerance'—the body tolerates its own tissues. Any failure of immunological tolerance implies that there is a build-up of forbidden clones and the body attacks itself, causing an autoimmune disease such as Hashimoto's thyroiditis, acquired haemolytic anaemia and systemic lupus erythematosus. Treatment is aimed at suppressing or destroying these forbidden clones (Burnet, 1969).

The years which followed 1957, the 'big switch', were full of discovery and excitement for Burnet. The world was his forum. He worked at high pressure with his colleagues in the laboratories of the Institute and joined forces with Ian Mackay to study the autoimmune diseases in the Clinical Research Unit, run conjointly by the Institute and the Royal Melbourne Hospital. He attended clinical conferences in the adjoining Clinical Research Ward, attended by many distinguished visitors from overseas, to debate the impact of autoimmune disease on Man. He proclaimed the mounting knowledge of the autoimmune diseases to be the most important advance in modern clinical medicine. In 1963 he collaborated with Mackay to write *Autoimmune Diseases*, a classic of the time (Mackay & Burnet, 1963).

FIG. 4. 1960. Sir Macfarlane Burnet returning to Australia from Stockholm with the Nobel Prize which he shared with Sir Peter Medawar of London.

FIG. 5. The Royal Melbourne Hospital buildings with the adjoining Walter and Eliza Hall Institute of Medical Research in the right foreground with the flag flying.

Burnet's pattern of life changed. With the upsurge of interest in the autoimmune diseases throughout the world he travelled widely, to debate the significance of his latest experiments and the validity of his theories. He gathered many friends working in his field, those who supported and those who vigorously opposed his theories. He had many fruitful discussions with Medawar, Dacie, Gowans, Miller, Roitt, Todd and Doll in England; with Jerne, Waldenstrom and Konrad Lorenz in Europe; with Lederberg, Pauling and Dameshek in America. When in England he was delighted by a visit to James Spence in his Childrens' Hospital to hear of his family studies and to visit some of Northumberland's stately homes and castles: Burnet was awarded the James Spence Medal in 1963. Another enjoyable visit was to W. N. Pickles at Wensleydale to observe his splendid field researches, particularly on the epidemiology of infectious hepatitis. Burnet would return home to Australia from these journeys refreshed, a healthy mixture of elation and bewilderment, immediately to indulge in a spate of laboratory research (Fig. 4).

For Burnet many exciting events took place over these years. Some came from his own laboratories. Thus, Nossal, stimulated by Lederberg, a Nobel Prize winner from America, demonstrated for the first time the *in vitro* production of a specific single antibody by a single lymphoid cell (Nossal & Leder-

berg, 1958). Metcalf had made successful studies of the thymus gland and Burnet described its important role in the development and maintenance of natural and acquired immunity (Burnet, 1962).

From overseas came much exciting news: the effect of thymectomy on the graft-rejection reaction, the monoclonal production of myeloma protein by plasmacytes, the significance of immunoglobulin estimations, and the discovery of the structure of the antibody molecule as two light chains and two heavy chains united by a small number of disulphide bonds. Finally there was the acceptance of acquired haemolytic anaemia as being the undisputed model of autoimmune haemolytic anaemia, for the haemolysis was caused by autoantibodies of monoclonal origin becoming attached to the surface of the red cells.

Burnet took great interest in systemic lupus erythematosus in humans and made extensive studies with Margaret Holmes on the animal counterpart, the New Zealand Black mice from Dunedin, which developed Coombs-positive haemolytic anaemia and kidney disease (Holmes & Burnet, 1963). He contrasted systemic lupus erythematosus where there are several different types of antibody with acquired haemolytic anaemia where there is a single antibody (Burnet, 1969). As the years passed more and more diseases of hitherto unknown aetiology appeared to be passing into the autoimmune group—pernicious

anaemia, primary Addison's disease of the suprarenal gland, myasthenia gravis and rheumatoid arthritis. What an exciting time it was for Burnet and his team at the Institute, and for their colleagues overseas (Fig. 5).

Burnet wrote extensively on biology and immunity. Between 1957 and 1969 he published 160 scientific papers and wrote nine books.

What impact on Burnet's personality was made by his marriage to the vivacious Linda Druce, his work at the Institute, his journeys overseas and his successes? He underwent a major mutation, he reacted vigorously to each new experience. He changed from the shy schoolboy grubbing in the Australian bush, to the silent virus worker, to the happy family man with children and grandchildren, finally to become almost an extrovert when he was an immunologist of world renown, the recipient of the Order of Merit and the Nobel Prize.

In his last phase he made pronouncements on the genesis, development and achievements of Man. He made predictions on the world to come, speculations steeped in cold logic, but often provocative. His predictions sometimes angered his fellow men, but Burnet was resolute and unperturbed.

Thus we leave Burnet, a fine scientist who achieved greatness through his high intellect, constructive thinking, endless hours of fruitful research at the bench, and his leadership of men.

Today, during his lifetime, one cannot assess the degree of his greatness; this will fall to the lot of future generations. Will he then be placed amongst the great? Placed amongst the immortals such as Harvey, Pasteur and Darwin?

It may well be that a place will be gained by Banting and Best for their insulin, and by Fleming and Florey for their penicillin. Will a place be gained by Burnet and Medawar for their autoimmune diseases?

Acknowledgments

I wish to thank my colleagues for providing data for this paper and Mrs Alan Lawry for her generous help with its preparation.

References

- ANDERSON, S.G. (1952) Murray Valley encephalitis: epidemiological aspects. *Medical Journal of Australia*, **1**, 97.
- BEAGLEHOLE, J.C. (1962) *The Endeavour Journal of Joseph Banks*, Vol. 1. Angus & Robertson, Sydney.
- BURNET, F. M. (1934) Psittacosis in Australian parrots. *Medical Journal of Australia*, **2**, 743.
- BURNET, F. M. (1935) Influenza virus isolated from an Australian epidemic. *Medical Journal of Australia*, **2**, 651.
- BURNET, F. M. (1937) Influenza virus on the developing egg. V. Differentiation of two antigenic types of influenza virus. *Australian Journal of Experimental Biologic and Medical Science*, **15**, 369.
- BURNET, F.M. (1943) Experimental immunization of volunteers against influenza B virus. *Medical Journal of Australia*, **1**, 389.
- BURNET, F.M. (1957) A modification of Jerne's theory of antibody production using the concept of clonal selection. *Australian Journal of Science*, **20**, 67.
- BURNET, F.M. (1962) The immunological significance of the thymus: an extension of the clonal selection theory of immunity. *Australian Annals of Medicine*, **11**, 79.
- BURNET, F.M. (1966) *Boyer Lectures—1966*. Australian Broadcasting Commission Publication, Melbourne.
- BURNET, F.M. (1968) *Changing Patterns: An Atypical Biography*. William Heinemann, Melbourne.
- BURNET, F.M. (1969) *Cellular Immunity*. Melbourne University Press, Melbourne, and Cambridge University Press, London.
- BURNET, F.M. & FENNER, F. (1949) *The Production of Antibodies*, 2nd edn. Walter and Eliza Hall Institute for Research in Pathology and Medicine, Monograph No. 1. Macmillan, Melbourne.
- BURNET, F.M. & FREEMAN, M. (1937) Experimental studies of the virus of Q fever. *Medical Journal of Australia*, **2**, 299.
- BURNET, F.M. & KELLAWAY, C.H. (1930) Recent work on staphylococcal toxins with special reference to the Bundaberg fatalities. *Medical Journal of Australia*, **2**, 295.
- BURNET, F.M. & LIND, P.E. (1949) Recombination of characters between two influenza virus strains. *Australian Journal of Science*, **12**, 109.
- BURNET, F.M. & MACNAMARA, J. (1931) Immunological differences between strains of poliomyelitis virus. *British Journal of Experimental Pathology*, **12**, 57.
- CAMERON, H.C. (1952) *Sir Joseph Banks*, 1st edn. Angus & Robertson, Sydney.
- DERRICK, E.H. (1953) The epidemiology of Q fever: a review. *Medical Journal of Australia*, **1**, 245.
- DERRICK, E.H. (1964) The query fever. *Queensland Health*, **1**, 1.
- FRENCH, E.L. (1952) Murray Valley encephalitis: isolation and characterisation of the aetiological agent. *Medical Journal of Australia*, **1**, 100.
- GOTTSCALK, A. (1958) The influenza virus neuraminidase. *Nature*, **181**, 377.
- HOLMES, M. & BURNET, F.M. (1963) The natural history of autoimmune disease in NZB mice: comparison with the pattern of human autoimmune manifestations. *Annals of Internal Medicine*, **59**, 265.
- MACKAY, I.R. & BURNET, F.M. (1963) *Autoimmune Diseases*. Thomas, Springfield, Illinois.
- MAJOR, R.H. (1945) *Classical Descriptions of Disease*, 3rd edn. Thomas, Springfield, Illinois.
- NOSSAL, G.J.V. & LEDERBERG, J. (1958) Antibody production by a single cell. *Nature*, **181**, 1419.