THE POWER OF ONE IDEA

BURNET'S CLONAL SELECTION THEORY


The Walter and Eliza Hall Institute of Medical Research
Frank Macfarlane Burnet’s theory of clonal selection profoundly and forever changed the way that scientists all over the world understand the working of immunity. In doing so, he brought to Victoria and The Walter and Eliza Hall Institute of Medical Research an international focus on immunological research and application. Today, immunology remains one of Australia’s strongest sciences. One third of the nation’s immunologists work in Victoria and four Australians of the Year have been immunologists.

By comparison with today’s overwhelmingly collaborative nature of research and authorship, the circumstances of the creation of Burnet’s paper in 1957 appear quite amazing. While today we are accustomed to more than a dozen researchers acknowledged as contributors to a paper and papers likely to have been drafted many times over many months, by contrast Burnet’s paper was precisely that – Burnet’s alone; and he wrote the paper over the course of a weekend at home. Equally astonishing is the fact that such a revolutionary theory, which caused a seismic shift in thinking, was encapsulated in only a few pages of text.

Part of the measure of the greatness of Burnet’s achievement is that today’s immunologists tell us that Burnet’s theories so thoroughly infuse their thinking that it seems impossible to imagine that the world of immunology could ever have been any other way. This universal infusion of Burnet’s theories marks him as one of Australia’s greatest ever scientists.
Setting the Scene

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Three centuries before Burnet’s time, Isaac Newton had generously and accurately observed that he had been able to see further than others because he stood on the shoulders of giants. Likewise, Burnet drew upon the knowledge of great scientists who preceded him, yet the genius of Burnet was to take existing knowledge, interpret it from a radically new perspective, then add his own insights to create an entirely original pattern of understanding. Such profound reorientations in our perception of the world are exceedingly rare. And yet, such a thing did happen, at WEHI in Parkville in 1957.

Burnet created a new conception of how the immune system responds to infection and how a type of white blood cell – the lymphocyte – is selected to recognise specific antigens on micro-organisms that invade the body. His theory postulated that the immune system naturally produces millions of lymphocytes, each with different and specific antigen receptors. When a particular lymphocyte encounters its matching foreign antigen, those lymphocytes are stimulated to create many clones of themselves to fight the infection effectively. This theory was a revelation and stimulated an enormous number of scientific experiments around the world. Burnet’s protégé, Gustav Nossal, in collaboration with Joshua Lederberg, was able to publish the first of countless experiments that continue to confirm Burnet’s principles and illuminate the immense subtlety of our immune defences.
Burnet reportedly referred to himself as “the last of the great amateurs”, but the Burnet we more readily recognise was a colossus on the world scientific stage.

Because his achievements remain so central to contemporary immunology, it’s astonishing to recall that Burnet was born late in the reign of Queen Victoria and grew up in the optimistic Edwardian era that preceded the cataclysm of the First World War. Burnet was born in the town of Traralgon in regional Victoria in 1899. In his youngest years, while growing up in another Victorian country town, Terang, he displayed a keen interest in the natural world and most especially in beetles. The general direction of his life’s work in biology was thus foreshadowed.

As Sir Gustav Nossal noted in a personal tribute in 1999, Burnet “saw himself essentially as a naturalist, and Charles Darwin was his greatest hero.” Nossal further observed of Burnet that “it is for the power of his insights unaided by elaborate equipment or extensive resources that we most honour him.” Herein lies a hint to the “great amateur” status that Burnet so happily conferred upon himself. Burnet had travelled extensively and was well aware of the relative material poverty of Australian science compared to the resources available to his counterparts in the United Kingdom and the United States. Even so, Nossal again recalls that Burnet was wedded to the primacy of the intellect above the need for sophisticated laboratory apparatus. And while no-one could be in any doubt of the deep earnestness of Burnet’s approach to his scientific work, Burnet himself could be whimsically moved to observe that “anyone who has made a significant discovery knows that experimental research is fun. In the future we will need to think more about the importance of play in the affluent society. Science to me is the finest sport in the world”. It was a “sport” that, as Frank Fenner noted, Burnet was determined to pursue in a world-class fashion in Australia, despite lucrative offers made to Burnet to move overseas.
And what wonderful achievements emerged from a scantily resourced institute at the far ends of the earth. In the 1940s, Burnet perfected a technique for growing sufficient quantities of influenza virus in embryonated hens’ eggs to produce vaccines. That technique remains in use today, which is a rare thing to be said of any research technique more than sixty years old. In 1957, Burnet famously abandoned the institute’s research mainstay, virology, and turned instead to immunology. It was an inspired decision. Before the year was over, Burnet had published the short paper on antibody production - or “clonal selection” - that rocketed his already considerable reputation into the scientific stratosphere. Burnet’s other monumental achievement pertained to the theory of immunological tolerance and the body’s (usual) capability to distinguish between self and non-self. Among other eventual practical applications, this was essential to the development of organ transplantation.

Burnet’s working and publishing life was not only extraordinarily rich, but almost six decades long. His first paper was published in 1924 and his last in 1983, just two years before his death in Melbourne. His twenty-one year tenure as WEHI Director from 1944 saw the institute rise from relative obscurity to global prominence. Quite properly, his dazzling achievements were recognised by the many supreme honours accorded to him, including a Royal Medal, Lasker Award, Order of Merit, Copley Medal, Knight of the British Empire, Knight of the Order of Australia, inaugural Australian of the Year and the Nobel Prize for Medicine. A “great amateur” indeed.

Medawar and Burnet share the Nobel Prize in Medicine in 1960
Speculating about what keeps us well and what makes us ill has been a human obsession for thousands of years. In Western culture some 2,500 years ago, many of the ancient Greeks ascribed human fate to the whim and caprice of often vengeful gods. If the gods decided that a person should be driven insane or endure horrendous suffering, there was no escape. A person’s fate was unavoidably sealed and any attempts to foil the gods’ desires only intensified the victim’s suffering.

Yet not all prominent Greek thinkers were so fatalistic. Thucydides recorded the brutalities of the war between Athens and Sparta in his History of the Peloponnesian War. Thucydides had a sceptical mind and scandalised society in classical antiquity by questioning the role of the gods in human and natural affairs. It was in his History that we find the first written reference to what we would recognise as immunity. Thucydides observed the impact of the plague in Athens in 430 BC. Visitation by the plague was by no means a rare event in Athens, and Thucydides noted that those people who had survived an earlier infection could comfort new plague victims without themselves contracting the disease a second time. Thucydides did not recognise it himself, but his objective empirical observation of disease and immunity, made without reference to supernatural agency, was the beginning of evidence-based immunology.

Nethertheless, for many centuries afterwards, gods in various guises continued to be ascribed powers over the life and death of humans. As Gloucester puts it in Shakespeare’s King Lear:

As flies to wanton boys are we to the gods;
They kill us for their sport.
would confer immunity from smallpox. Fortunately for the eight-year-old James Phipps, who was inoculated in both arms, Jenner was right. Phipps was subsequently exposed to smallpox but showed no ill effects. Immunity had thus been conferred. Thereafter and quite rapidly, inoculation (or variolation, as it was sometimes called) became accepted in Great Britain and the West, leading to a steep decline in widespread smallpox outbreaks.

While the stream connecting Thucydides to Jenner was two millennia in the making, the nineteenth and twentieth centuries witnessed a roaring torrent of immunological innovation.

Giants of immunology included Louis Pasteur, Emil von Behring, Karl Landsteiner, Paul Ehrlich, Linus Pauling, Niels Kaj Jerne and, of course, Macfarlane Burnet.

Curiously enough, there was for Pasteur, too, a Greek connexion of sorts. A contemporary of Thucydides, the philosopher Democritus, believed that diseases were neither supernatural in origin nor attributable to foul-smelling “miasmas” hovering in the atmosphere. The latter belief was certainly still current in the 1840s and beyond, during Pasteur’s lifetime. Though he could offer no proof, Democritus had speculated that diseases were caused by infinitesimally small infectious agents, thus anticipating Pasteur’s then controversial but experimentally provable germ theory. With his cultivation of microbes, Pasteur debunked the decidedly unscientific but then conventional theory of “spontaneous generation” as a cause of disease. Part of Pasteur’s genius was to recognise that the principles of inoculation would apply not only to smallpox, but to a very wide range of diseases. Among other things, Pasteur went on to accurately characterise and develop vaccines for rabies and anthrax. Pasteur was also an advocate of hygienic practices, sparing countless patients the agonies of incidental infection.

As the scientific revolution continued apace, medical researchers built upon ever more complex and secure foundations of knowledge. Von Behring theorised and demonstrated that “active immunity” induced by personal encounters with infectious agents was due to the appearance of “antibodies” in the serum. He went further and established that antibodies raised in the serum of animals could be transferred to infected patients and protect them against disease. Von Behring thus proved the notion of “passive immunity”. He went on to develop a serum therapy against
two big killer diseases, diphtheria and tetanus.

Ehrlich, a colleague and rival of von Behring, made a series of important practical and theoretical advances in the young science of immunology at the beginning of the 20th century. He suggested that antibody specificity was the result of the complementarity of molecular shape and that antigen and antibody would fit together as a lock and key. This general insight into molecular shape recognition was revolutionary and broadly applicable. Ehrlich imagined that disease causing germs would present their own unique collection of shapes — allowing antibodies to be developed specific for the germ. Ehrlich also foresaw that drugs might be found that, by chance, had a shape that would inhibit the growth and activities of the germ and have no effect on the patient. He named such compounds ‘magic bullets’ and was able to find the first organic anti-syphilitic agent Salvarsan. This work anticipated the development of antibiotics.

As powerful as the insights into how immunity might be manipulated were, there remained the significant mystery of the mechanism by which antibody against any infectious agent was induced.

Ehrlich presented an early hypothesis. He suggested that the various molecules on the cell’s surface each played a role in cell vitality. By chance an infection would bind and choke off the normal function of one such molecule leading to overproduction and secretion of the self component as antibody. This is an example of a selection theory — where all the possible antibodies pre-exist and the foreign invader itself plays a role in selecting the appropriate response.

Ehrlich’s, and in fact any selection theory, was effectively killed off by experiments from immunochemist Landsteiner, which showed that antibodies could be made against chemical compounds that were unlikely to have existed on earth before. Thus, it seemed that the potential range of antibody shapes was infinite. Therefore, it seemed impossible that all antibody shapes could pre-exist in the body. As a consequence, thoughts turned exclusively to ‘instructional’ theories. Breinl and Haurowitz and later Pauling, described by Francis Crick as “the father of molecular medicine”, developed template theories for folding protein bonds around the antigen.

Instructional theories held sway for decades. Burnet would write: “At the time it was regarded as inconceivable that a mechanism could exist which would recognise in positive fashion all foreign material.” Nevertheless, he was aware of
deep problems with these theories, particularly their inability to distinguish self molecules from foreign.

The first shot against the domination of instructional theories was provided in 1955 by Niels Kaj Jerne, whom Burnet declared to be “the most intelligent immunologist alive.” Jerne presented a natural selection theory that predicted at least a million different specificities were pre-made and secreted into serum. The antigen, as in Ehrlich’s earlier selection theory, played a role in selecting the most complementary antibody. Jerne imagined a mechanism for replicating the successful antibody; however, his concepts for replicating protein were a weak link in an otherwise brilliant renaissance of these ideas.

Jerne’s resurrection of selection theories had a powerful impact on Talmage working in Chicago and Burnet in Melbourne. Both saw clearly the advantages of selection theories for solving the key problems and both puzzled as to a way to replicate the selected form of antibody. Importantly, both hit upon the idea that cells would be selected and expanded. Talmage was first to publish his ideas and wrote “only those cells are selected for multiplication whose synthesised product has affinity for the antigen injected.”

And so to Burnet, whose revolutionary scientific achievements are the subject of our current conference. Burnet was motivated by Talmage’s paper to pen his famous distillation of the principles of “clonal selection theory” – reproduced here. The paper is still alive and fresh today and the clarity a joy to read. His key insight was that a mechanism for randomisation of the coding for the antibody within each lymphocyte makes it unique and provides enough diversity to create the millions of different specificities envisaged by Jerne. The rest of the theory follows easily: a period when clones reactive to self would be eliminated accounts for self tolerance. Later exposure to complementary molecular shapes would lead to proliferation of specific clones and the secretion of the receptor as a soluble antibody. Once the pathogen was eliminated the expanded clone would contribute to memory cells that would ensure immunity on reinfection. These principles are familiar to every modern immunologist. They were written clearly by Burnet in the short paper in The Australian Journal of Science for the first time.

The whole system of rational scientific enquiry and experimentation, founded on cycles of bold hypothesis and critical experiment, that enabled Burnet’s discoveries, is, in long historical terms, a relatively recent innovation, evolving from the European Enlightenment, which was itself partly based on the rediscovery of the glories of classical antiquity. For many centuries before the Enlightenment, what purported to be science was often disfigured by obscurantism. But if we go back far enough, we encounter certain Greek philosophers, whose determination to set evidence-based rationalism above all else provided us with a significant part of our priceless Hellenistic inheritance. Ultimately, it’s thanks to the exemplary approach of the Greek rational philosophers of antiquity that great innovations have been made possible in medical science. One suspects that even the capricious gods of ancient Greece might give pause to stand in awe of such human achievements.
A Modification of Jerne’s Theory of Antibody Production using the Concept of Clonal Selection

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There are three current theoretical interpretations of antibody production which, following Talmage (1957) may be referred to as the direct template theory in which the antigen serves as a template against which the specific pattern of the antibody is synthesized, the indirect template theory which postulates a secondary template incorporated into the genetic-synthetic processes of the antibody producing cells (Burnet 1956), and the natural selection theory in which the antigen acts essentially by selection for excess production, of natural antibody molecules of corresponding type (Jerne, 1955).

The two latter theories were devised primarily to account for two sets of phenomena for which the direct template theory seems quite irrelevant. The first is the absence of immunological response to ‘self’ constituents and the related phenomena of immunological tolerance; the second is the evidence that antibody production can continue in the absence of antigen. Some means for the recognition and differentiation of potentially antigenic components of the body from foreign organic material must be provided in any acceptable formulation. In Burnet and Fenner’s (1949) account a positive recognition of ‘self’ material was ascribed to

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the presence of ‘self-markers’ in all potentially antigenic macromolecules, and corresponding recognition units in the scavenger cells of the body. At the time it was regarded as inconceivable that a mechanism could exist which would recognise in positive fashion all foreign material and no attempt was made to devise one, despite the fact that we have always recognised the clumsy character of the self-marker self-recognition scheme.

It is the great virtue of Jerne’s hypothesis that it provides an approach to this alternative method of recognising self from not self. There is no doubt about the presence in all mammalian or avian sera of a wide range of reactive globulins which can legitimately be called ‘natural antibodies’. Jerne assumed that amongst these globulin molecules were all the possible patterns needed for specific immunological type reaction with any antigen, except for those patterns corresponding to body antigens which would be eliminated by in vivo absorption. When a foreign antigen enters the blood it unites, according to Jerne’s scheme, with one of the corresponding natural antibody molecules. The complex is taken up by a phagocytic cell in which the antigen plays no further part, but the antibody globulin provokes the production by the cell of a fresh crop of similar molecules which are liberated as antibody. If this basis is accepted, most immunological phenomena can be well described in terms of the theory. Its major objection is the absence of any precedent for, and the intrinsic unlikelihood of the suggestion, that a molecule of partially denatured antibody could stimulate a cell, into which it had been taken, to produce a series of replicas of the molecule.
Talmage (1957) has suggested that Jerne’s view is basically an extension of Ehrlich’s side-chain theory of antitoxin production and that it would be more satisfactory if the replicating elements essential to any such theory were cellular in character *ab initio* rather than extracellular protein which can replicate only when taken into an appropriate cell. Talmage does not elaborate this point of view but clearly accepts it as the best basis for the future development of antibody theory. He stresses the multiplicity of the globulin types that can be present in the blood and is profoundly sceptical of any approach which attempts too ‘unitarian’ an interpretation of antibody. In his view properdin has as much right to be called an antibody as any other globulin.

Before receiving Talmage’s review we had adopted virtually the same approach but had developed it from what might be called a ‘clonal’ point of view. This is simply a recognition that the expendable cells of the body can be regarded as belonging to clones which have arisen as a result of somatic mutation or conceivably other inheritable changes. Each such clone will have some individual characteristic and in a special sense will be subject to an evolutionary process of selective survival within the internal environment of the body.

It is believed that the advantages of Jerne’s theory can be retained and its difficulties overcome if the recognition of foreign pattern is ascribed to clones of lymphocytic cells and not to circulating natural antibody. The resulting formulation may be stated as follows:

The plasma $\gamma$-globulins comprise a wide variety of individually patterned molecules and probably several types of physically distinct structure. Amongst them are molecules with reactive sites which can correspond probably with varying degrees of precision to all, or virtually all, the antigenic determinants that occur in biological material other than that characteristic of the body itself. Each type of pattern is a specific product of a clone of mesenchymal cells and it is the essence of the hypothesis that each cell automatically has available on its surface representative reactive sites equivalent to those of the globulin they produce. For the sake of ease of exposition these cells will be referred to as lymphocytes, it being understood that other mesenchymal types may also be involved. Under appropriate conditions, cells of most clones can either liberate soluble antibody or give rise to descendant cells which can.

It is assumed that when an antigen enters the blood or tissue fluids it will attach to the surface of any lymphocyte carrying reactive sites which correspond to one of its antigenic determinants. The capacity of a circulating lymphocyte to pass to tissue sites and there to initiate proliferation is now relatively well established (cf. Gowans, 1957; Simonsen, 1957). It is postulated that when antigen-natural antibody contact takes place on the surface of a lymphocyte the cell is activated to settle in an appropriate tissue, spleen, lymphnode or local inflammatory accumulation, and there undergo proliferation to produce a variety of descendants. In this way preferential proliferation will be initiated of all those clones whose reactive sites correspond to the antigenic determinants on the antigen used. The descendants will include plasmacytoid forms capable of active liberation of soluble antibody and lymphocytes which can fulfil the same functions as the parental forms. The nett result will be a change in the composition of the globulin molecule population to give an excess of molecules capable of reacting with the antigen, in other words the serum will now take on the qualities of specific antibody. The increase in the number of circulating lymphocytes of the clones concerned will also ensure that the response to a subsequent entry of the same antigen will be extensive and rapid, i.e. a secondary type immunological response will occur.

Such a point of view is basically an attempt to apply the concept of population genetics to the clones of
mesenchymal cells within the body. It is clear that the internal environment involved is an exceedingly complex one and in all probability many factors will impinge on clones of antibody-producing cells from that environment. It is equally certain that inheritable changes (at the clonal level) will occur as a result of somatic mutation or of the still obscure processes responsible for differentiation during development or regeneration and repair.

It would be inappropriate to elaborate this view much further in a preliminary communication, but it should be immediately evident that it has highly relevant implications for the general function of the lymphocyte, for the fact that sensitization and homograft immunity reactions seem to be mediated by lymphocytes or other mesenchymal cells without liberation of classical antibody, and for recent findings of extremely rapid liberation of antibody from normal cells. A preliminary survey of a variety of pathological conditions involving anomalous immune reactions also suggests that this cellular approach has greater relevance to the problems than any of the other hypotheses. These aspects will be elaborated in a more extensive contribution now in preparation.

One aspect, however, should be mentioned. The theory requires at some stage in early embryonic development a genetic process for which there is no available precedent. In some way we have to picture a ‘randomization’ of the coding responsible for part of the specification of gamma globulin molecules, so that after several cell generations in early mesenchymal cells there are specifications in the genomes for virtually every variant that can exist as a gamma globulin molecule. This must then be followed by a phase in which the randomly developed specification is stabilized and transferred as such to descendant cells. At this stage, again following Jerne, any clones of cells which carry reactive sites corresponding to body determinants will be eliminated. The necrotic effect of tuberculin on sensitized fibroblasts might be taken as a crude analogue of the process by which clones with unwanted reactivity can be eliminated in the late embryonic period with the concomitant development of immune tolerance.

The hypothesis has many of the same implications as the Burnet-Fenner and the Jerne theories. Its chief advantage over the former is its relevance to the nature of normal antibodies including the red cell isoagglutinins and the simpler interpretation of tolerance to potential antigens experienced in embryonic life. Its advantages over Jerne’s theory are its capacity to cover homograft and related types of immunity as well as the production of classical antibody, and to eliminate the very unlikely assumption that entry of a globulin molecule into a cell will stimulate the cell to produce exact replicas of that globulin.

Despite the speculative character of much of the detail of this modification of Jerne’s theory – which might be called the ‘clonal selection hypothesis’ – it has so many implications calling for experimental enquiry that it has been thought justifiable to submit this preliminary account for publication.

References
1957 was a momentous year. Burnet’s audacious decision, as Director of WEHI, to completely reorient the research focus of the Institute from virology to immunology was accompanied by the creation of his paper on clonal selection. While the research reorientation of WEHI is said to have taken place metaphorically “overnight”, Burnet’s writing of the paper took place quite literally over a weekend. Burnet shut the door of his office on the Friday evening, wrote his paper over the weekend at his home in Kew, and presented the finished product for opinion to a bemused Gus Nossal on the Monday. The short paper was soon after published in the somewhat obscure *Australian Journal of Science*. Such were the astonishingly simple yet somehow archetypal Australian circumstances that attended the publication of a paper that utterly transformed immunology.

In 1958 he gave a series of lectures on his theory at Vanderbilt University in the United States. These lectures were expanded and published as a book, *The Clonal Selection Theory of Acquired Immunity*. In his history of WEHI, Burnet recalled “as might be expected, [the theory] encountered opposition and lack of comprehension, rather than acceptance, for several years. Everyone recognised, however, that it was a good theory in the sense that it could be proved wrong – if it was wrong. More important, with every advance in the understanding of how proteins were synthesized in the cell and of the structure of antibodies, it became more and more obvious that the general concept of the 1957 paper must be right... At the meeting on Antibodies, at Cold Spring Harbor in 1967, where I gave the opening address and Niels Jerne summed up the whole discussion, clonal selection was accepted as the standard theoretical approach to a subject which had grown enormously in the decade since I first outlined the theory.”

In his own words in his WEHI history, Burnet explained his theory thus: “The essence of clonal selection theory is that antibody pattern is produced by genetic processes in the cells as they develop during embryonic life, a process rather analogous to the way sets of random numbers can be produced by a computer. Each relevant cell...carries only one of these thousands of random patterns. When the foreign antigen enters the body, one can picture millions of antigen molecules in regions where there are millions of these randomly patterned cells. Sooner or later an antigen molecule will find the right sort of cell with which it can make firm contact. Simplifying things a little, we can say that such contact selects that cell for multiplication and eventual antibody production. Multiplication of a single cell gives rise to 2, 4, 8 etc. descendants, all producing the same antibody. Such a family of cells is called a clone, a word derived from the Greek for a branching twig – hence the term ‘clonal selection’ by which the theory is known.”
In 1958, Gustav Nossal and Joshua Lederberg, working at WEHI, showed that one B cell always produces only one antibody. This was the first experimental evidence for Burnet’s clonal selection theory.

At the time Burnet wrote his clonal selection paper in 1957, he was being visited for three months by Josh Lederberg, a brilliant molecular geneticist and virologist. Lederberg, who would win a Nobel Prize in the following year, was disappointed to find that Burnet was no longer working on influenza genetics. However, Lederberg soon became intrigued with Burnet’s concept of clonal selection. Like Burnet, he particularly liked the theory’s Darwinian flavour and its parallels with concepts of viral mutation and selection.

Lederberg was also familiar with single cell cultures and discussed experiments with a young researcher, Gus Nossal. They began to test Burnet’s theory with single cells cultured in drops to immobilise target bacteria. Although Lederberg departed in October 1958, Nossal continued with the experiments and eventually published a paper in *Nature* with Lederberg. This was an important step in consolidating the theory internationally.

Lederberg continued to champion the theory, penning his own version in 1959 that included a significant alternative suggestion on cell development. Lederberg’s familiarity with the genesis of the theory, and his own worldwide eminence in genetics, further consolidated Burnet’s theory.

Nossal went on to succeed Burnet as Director of WEHI in 1965, reinforcing further the institute’s prominence as a world centre of immunological thought and experimentation.
Jerne, who had reoriented the attention of Talmage and Burnet toward selection theories, played a further key role by developing a method for visualising antibody secreting cells using a “plaque assay.” Twelve years later, Kohler and Milstein used the same method to report their success at immortalising antibody secreting cells by fusing them to a tumour cell. To date, thousands of monoclonal antibody have been made as reagents and tools for scientists and clinicians. More recently, monoclonal antibody therapy has developed into a 14 billion dollar per year drug industry – realising the grand visions of von Behring and Ehrlich for stockpiling “magic bullets” to seek out unwanted elements in our bodies. For their contributions to medicine, Jerne, Milstein and Kohler shared the 1984 Nobel Prize.
The mechanism of antibody gene randomisation, boldly predicted by Burnet in 1957, was brilliantly elucidated by Susumu Tonegawa in 1976. He showed the somatic rearrangement of genes coding for antibody and their stabilisation in mature lymphocytes, a key attribute of the clonal selection theory (figure reproduced from paper). For this work, he received the Nobel Prize for medicine in 1987.

In the 1980s, three-dimensional molecular structures of antibody in complex with antigen were produced. The results stunningly confirmed the close complementarity in shape between the surfaces – envisaged by the pioneers of immunity but never before seen. (In the figure the complementary surfaces of antibody and a protein from influenza virus are shown. The structure was solved by Peter Colman, shown talking with Sir Macfarlane Burnet.)

The story of immunity has been an eventful journey from ancient Greece to the present day. The journey is likely to continue as long as humanity exists. While that long journey rolls on, tremendous medical consequences will continue to flow from advances in understanding immune regulation and function. The closer we look, the more complex and intriguing the immune system appears. In the years since the emergence of Burnet’s clonal selection theory, our appreciation of the subtleties of immunity has intensified enormously, spawning new theories that have stimulated experiment and illuminated the way forward. Burnet was unique and inimitable, but those of us who follow in his footsteps can at least hope to emulate, in our own ways, his superb interpretative and creative impulses.
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Sir Macfarlane Burnet\(^1\) must have been pleased not only to witness at this symposium the vindication of his Clonal Selection Theory of Acquired Immunity, but also to see how his stimulating ideas have led to a great proliferation of immunologists, and to know that the fate of immunology is deposited in so many capable hands.
As this younger generation of professionals is pressing rapidly toward the definitive solution of the antibody problem, we older amateurs had perhaps better sit back, waiting for the End.

REFERENCES


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