Peter C. Roberts

Challenged by Complexity: My Twentieth Century in Immunology

Peter C. Doherty

Department of Microbiology and Immunology, University of Melbourne, Victoria 3010, Australia; and Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105; email: peter.doherty@stjude.org

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Abstract

My research career has focused on complex experimental systems, principally virus-induced infectious processes. I have always run my own experimental program and never had a major mentor, although I have had many great colleagues. After graduating from the School of Veterinary Science at the University of Queensland, Australia, I worked for nine years on diseases of domestic animals. During that interval I completed a part-time PhD at the University of Edinburgh while employed as an experimental neuropathologist. Returning to the John Curtin School of Medical Research in Canberra, I focused on cell-mediated immunity, started to work seriously with mice, and thus became both an immunologist and a basic medical scientist. It was there in 1973 that Rolf Zinkernagel and I discovered MHC I–restricted $CD8^+$ T cell recognition, a finding that, together with the "single T cell receptor/altered self" hypothesis that we developed to explain our results, led to the 1996 Nobel Prize for Physiology or Medicine. Part of my focus since then has been to communicate the societal value and power of science to the broader community. As my scientific life is not yet over, I confine the present historical account to the twentieth century.

Vertebrates use two great complex systems (1) to respond to and deal specifically with challenges from the external environment: the central nervous system (CNS), with its associated sensory and effector organs, and the adaptive immune system (AIS). Although we share many functions of the AIS with other, higher vertebrates, our big cerebral cortex makes us unique in the biota.

Science is a specifically human activity: a function of mind and the conscious brain expressed in the spoken and the written word. The conceptual shorthand of any scientific discipline can be both clarifying and limiting. And, with apologies to Ludwig Wittgenstein, language conditions thought (2). Immune terminology is certainly a barrier when it comes to interacting with people outside our field, whether they are other scientists or health-conscious members of the lay public. We cannot avoid this problem completely, but we have to recognize that words we use routinely may have very different meanings for others. In addition, many in society are unwilling to grapple with novel insights that challenge accepted beliefs, and others seem to have little interest in evidence-based reality. Bringing science to the broader public thus offers its own complex challenges.

Immunologists and neuroscientists also use terms such as response, memory, challenge, and recall in superficially interchangeable ways, but the mechanisms are very different until, perhaps, we come down to the molecular machinery within individual cells. Consciousness is obviously the province of neuroscience, although the autonomic nervous system that controls gut motility, innervates the lymph nodes, and so forth functions, like immunity, at a subconscious level. Immunologists and medical professionals may become aware of the AIS at work when circulating cytokines make us feel drowsy during the course of an infection (3), or when we endure pain as a consequence of swelling that is due to distension of a lymph node or joint capsule. Without specific education, however, most humans would not relate such effects to immunity.

The capacity for diverse CNS responses depends on distinct recognition (eyes, nose, pain receptors) and effector organs (muscles, hands) that are anatomically remote from one another (1). The specific functions of the AIS, on the other hand, are mediated via the individual responder cells that act at short (T cells) or long (B cells) range via their membrane attached (TCR, BCR) or secreted immunoglobulin (Ig) receptors. As a generalization, the brain can be regarded as an anatomically stable central processing unit (CPU) that controls specific actions via hard-wired pathways, whereas the AIS has no controlling CPU and uses mobile response elements that are themselves the effectors of immunity. Of course, there are exceptions: T cells activate macrophages that can be armed by Ig, whereas both neurohormones and secreted cytokines operate at distal sites subsequent to dissemination via the blood. Perhaps the thymus could be thought of as some sort of CPU for the T cells, although its operation is remote in both space and time from the effector phase of immunity.

Much of the initial part of my research career interfaced the CNS and the AIS, although in the somewhat brutal context of virus-induced disease processes. I had a good grounding in morbid anatomy and worked on the pathology of disease processes in domestic animals. My PhD is in experimental neuropathology. These were the subjects of the scientific meeting that I attended over the first nine years of my research career. Anatomical context is clearly a major determinant of CNS function, with much of the analysis then and now only possible in vivo. This early involvement with the CNS and pathology influenced both my thinking about immunity and my experimental strategies, which have always been focused by the idea of in vivo veritas, the conviction that both macro- and microenvironments (4) within the host are major determinants of any immune phenotype. There are

many interactive variables, some of which are very difficult to access experimentally, and the complexity is enormous.

As I come to the final phase of my life as a research scientist, I also find myself speculating more about a different facet of the interaction between the CNS and the AIS: the limits of mind when it comes to understanding how immunity works. The AIS seems more chaotic than the CNS, perhaps because it is the latest evolving of all vertebrate systems and has, as a consequence, drawn greatly from pre-existing mechanisms and pathways. Are some of the processes we try to understand so complex, or so varied in possibility, that we will not develop useful generalizations from the reductionist approaches that have generally (though not always) served us well? To what extent does it help to augment experiments with mathematical modeling and speculative theoretical constructs? I also marvel at how wrong we (which includes me) have sometimes been, and how unthinkingly we have persisted with major misinterpretations.

The latter, of course, belongs to the province of history, and, although I will not still be around, it would be fascinating to read an independent, dispassionate, "warts and all" view of the achievements, failures, and practices of immunology through this past half century. It is probably too early to attempt such a synthesis, although it would be of great value if everyone who lived through this extraordinary time in our field wrote (or dictated) a direct, unembellished, honest account of what they experienced and how they worked, an account that could be accessed by future science historians. Maybe we need an immunology archive that could be sealed for, say, 50 years and then made available to serious scholars. We have lived through an era in scientific discovery that will not be repeated. It would be a great pity if the available personal accounts are restricted to the few people who are asked to write for this type of inevitably sanitized format.

BRISBANE, EDINBURGH, INFLAMMATION, AND NEUROPATHOLOGY

My first experiments at the Animal Research Institute in Brisbane were focused on monitoring the spread and pathogenesis of *Leptospira pomona* infection in cattle. Intrigued by the prominent inflammatory response in the kidney, I wondered, from comparing the kinetics of spirochaete control with serum and urine antibody levels, whether there might be local antibody production in that site. This stimulated my interest in pathogenesis, which returned to an undergraduate focus on viruses when I started reading papers by Cedric Mims (5) and met one of his former graduate students, John Roberts. After learning some basic virology techniques and working a little with chicken viruses, I applied for a PhD scholarship with Cedric at the Australian National University (ANU), but I was turned down and told to reapply later because he only took one student at a time. With the impatience of youth, I then tried for a position as an experimental pathologist at the Moredun Research Institute in Edinburgh that had been advertised in *Nature*. In those days, we boarded a slow ship and sailed for the Northern Hemisphere.

The job at the Moredun involved both experimental and diagnostic neuropathology, the latter for the Scottish Veterinary Investigation Service. My boss, Dick Barlow, taught me both neuropathology and how to write clear, concise scientific English. Dick was from Lancashire, but he had signed on to the belief of the Edinburgh Scots that the purest form of the language is spoken in their beautiful, gray city. Over the years, some scientific reviewers (particularly in the United States) have found my writing style to be too telegraphic, too committed to a Scots parsimony. But a major reason that English is the language of science is that in it complex ideas can be conveyed with precision. Lately, the occasional reviewer from the literary world has made me realize I need to be a bit more

expansive as I attempt to write about science for a general audience. The genres are different.

When I arrived in Scotland, my intention was to focus on the prion disease scrapie, which had been a major focus at the Moredun for more than 30 years. However, as I was also keen to complete a PhD thesis, I quickly realized that scrapie was not for me, or for anyone who, in those days before Stan Prusiner burst onto the scene, had limited time to spend on a project. Stan, of course, invented the word prion that has changed our thinking about the pathology that results from abnormal protein-protein interactions in the brain (6). Back in the late 1960s, the prevailing view was that scrapie is caused by some odd and elusive, slow virus (7).

Very respectable virologists broke their careers on the scrapie problem, whereas others in the field were, at the time, more than a little bit mad in some of the pronouncements they made. In Edinburgh, I had the privilege of sharing an office with Hugh Fraser who, working with the geneticist Allan Dickinson, was in the process of very long-term, rigorous experiments on genetic susceptibility to scrapie in mice that have stood the test of time and proved to be of real value in the later, prion era (8). This was the first time I perceived the power of mouse genetics that was to be so important in my subsequent career. Hugh, a Cambridge-trained neuropathologist, also taught me a great deal about the morphology of brain damage in the mouse, but I was happy to leave scrapie to him.

Working with louping ill virus, a tick-borne Flavivirus, I focused on the nature of the virus-induced damage and associated inflammatory processes in the CNS. The experiments that Hugh Reid and I did on louping ill encephalitis in sheep during the late 1960s generated good evidence for the extravasation of primed B cells, then long-term antibody production (9) by plasma cells in the brain (10). This study utilized the technologies of the time: electron microscopy, immunofluorescence to demonstrate both Ig-producing cells and the sites of virus protein production, and comparison of cerebrospinal fluid and serum antibody levels to the virus and to an irrelevant protein to infer that only the virus-specific Ig was being made locally in the CNS.

The immune response is, of course, a central part of the pathology/pathogenesis equation, but until then it had not been my major technical or conceptual interest. The local immunologists, Spedding Micklem and Angus Stuart, organized an immunology seminar and discussion program called the Metchnikoff Club. Attending one evening, I heard a talk by Mel Greaves that dealt particularly with T cell–mediated immunity. I realized that all my thinking was focused on antibody and that I knew absolutely nothing about T cells. These were, of course, very early days. Bede Morris, a colorful personality and talented surgeon who was a considerable authority on lymphocyte recirculation, was, with the subtlety that Australians are known for, widely quoted as saying that B and T are the first and last letters of a well-known end-product of the beef industry.

CANBERRA AND THE DISCOVERY OF MHC RESTRICTION

When I left Edinburgh in 1971 and joined the John Curtin School of Medical Research (JCSMR) at the ANU, I thought I was taking a short-term detour from my basic career path in veterinary research and experimental pathology so that I could learn more about viral pathogenesis and T cell–mediated immunity. The seminal papers of Cedric Mims and Bob Blanden on ectromelia (mouse pox) virus pathogenesis that described experiments done at the JCSMR before I arrived have long been classics in the field. I have discussed elsewhere (11) how those themes reflected an Australian scientific lineage that stretched back to the virologist, then immunologist F.M. (Mac) Burnet (12), who shared the 1960 Nobel Prize for

medicine with P.B. Medawar for the theory of immunological tolerance.

Cedric Mims left to take a job in London shortly after I arrived in Canberra, and I inherited a small laboratory and a technician, Gail Essery, from him. I focused on asking how T cells contribute to inflammatory processes in the brain, following the interest that I had developed in Edinburgh. My first studies used Semliki Forest virus–induced encephalitis (13), but I soon switched to lymphocytic choriomeningitis virus (LCMV). Because I had infected myself accidentally (needle stick) with louping ill virus during my time in Scotland (14), I was initially reluctant to work with LCMV, as it can be lethal in humans (15). However, it soon became apparent that the LCM immunopathology model is infinitely superior when it comes to studying virus-specific T cell responses. Here, I was following the insights and experiments of others, particularly John Hotchin in Albany, New York; Fritz Lehmann Grube in Hamburg; Mogens Volkert and Ole Marker in Copenhagen; Gerry Cole, Neal Nathanson, and Don Gilden at Hopkins; Mike Oldstone at the Scripps; and, of course, Cedric Mims. All science builds on the work of those who go before. The only one of those that I did not get to know over the ensuing years was John Hotchin, who was the first to develop the key insight that immune cells were causing the fatal neurological crisis characteristic of LCMV infection in previously unexposed adult mice (16).

I was well into a series of LCMV immunopathogenesis experiments (17) when Rolf Zinkernagel arrived to work with Bob Blanden on bacterial immunity. Owing to a crowding problem, he ended up in my laboratory. We started to talk and decided to work together to determine whether the inflammatory cells that I was recovering from LCMV-infected mouse brain contained cytotoxic T lymphocyte (CTL) effectors. Our first experiment showed that LCM meningeal exudate cells were extraordinarily potent killers in the ^{51}Cr release CTL assay (18) that had been popularized by Jean Charles Cerrotini and Teddy Brunner, leading figures in the Lausanne Institute where Rolf had worked previously (19). We soon found that these LCMV-specific CTL were also prominent in spleen. This gave us a readily manipulated in vitro assay system with an incredibly clean readout. In addition, I had developed a very sensitive and reproducible adoptive transfer approach that allowed me to look quantitatively at the capacity of LCMV-specific T cells to induce severe meningitis in LCMV-infected recipients (20). Good science is all about accurate measurement, and we had, for that time, fantastic systems for quantifying T cell activity in both cell culture and mouse model systems.

How this experimental dissection of LCMV-induced immunopathology led directly to the discovery of MHC class I–restricted CD8$^+$ T cell recognition has been told previously, and I will not repeat it in detail again here (21, 22). The fact that we were able to establish the basic rules for T cell targeting to MHC so quickly in 1973–1975 depended totally on the preceding efforts of the mouse geneticists who had spent years generating a diverse spectrum of inbred and recombinant mouse strains for analyzing first graft rejection, then the so-called immune response genes. This effort began with the intellectual insights of George Snell (23), and then continued with the work of his colleagues Don Bailey and Jack Stimpfling at the Jackson Laboratory in Bar Harbor. The scope of that analysis, and the resultant mouse genetic technology, was later broadened by many others, including Don Shreffler, Jan Klein, Chella David, Igor Egorov, Roger Melvold, and Hugh McDevitt. What Rolf and I did, quite by chance, was to marry viral immunity and transplantation genetics in an analysis that would not have been possible without these defined mouse strains. Those who argue that animal experiments are not central to progress in biomedical research are either deluded or deliberately duplicitous.

That position became even more untenable with the development of the genetically engineered knockout and knockin mice.

Our analysis in the early 1970s led very rapidly to the insight that the so-called transplantation system is, in fact, a self-surveillance system. In those early papers, we alienated the term "immunological surveillance" (24, 25) from Mac Burnet and Lewis Thomas, although they had used it principally in the context of limiting the emergence of cancer. If we had made our discovery before the transplantation era, we would all be talking about a self-surveillance complex rather than a major histocompatibility complex. A short article we wrote for the hypothesis section of *The Lancet* in 1975 got the $CD8^+$ T cell recognition story about right, although we did not, because of the technological limitations of that time, have any real molecular understanding of the underlying interactions (26).

The first two *Nature* papers and *The Lancet* article (24–26) are reprinted as appendices in the U.S. edition of *The Beginner's Guide To Winning The Nobel Prize* (27), my first attempt at a popular book that tries to bring the nature and workings of science to a general audience. Looking at the *Nature* letters again, I share a perception voiced by Roger Perlmutter while introducing me at a recent lecture: They are archaic! We no longer write like this. *Nature* would now require a much longer article that nails down the details and is supported by reams of supplementary data in some electronic database. At times, by diminishing the opportunity to speculate a little, we may, in fact, be losing the plot. We are better at seeing the details of the trees, but we sometimes lose sight of the fact that those trees are just one part of an extraordinary forest. That is one reason why we must think broadly about immunity as a complex, interactive system.

Although our 1973–1975 experiments provided both an explanation for graft rejection and the realization that killer T cells function primarily by cell-cell contact, immunology had to wait another 10 years for Alain Townsend to come along and tell us about cytoplasmic processing and peptide presentation by MHC class I glycoproteins (28). Investigators like Baruj Benacerraf, Emil Unanue, and Howard Gray had been working along these lines for years for the MHC class II glycoproteins, so why did the whole field (including them and us) miss the obvious parallel for the MHC class I system? Part of the confusion resulted from the debate concerning one or two receptors that Rolf and I initiated. That was resolved in favor of a single T cell receptor (TCR) by Mark Davis and Steve Hedrick (29), Tak Mak (30), Don Wiley, Pam Bjorkman, and Jack Strominger (31) at about the time that Alain published his findings. The other source of confusion arose from the fact that viruses encode proteins that can be detected on the surface of infected cells. The clear analogy with the MHC class II system was there all along, but most of us were on the wrong path intellectually.

That type of confusion happens over and over as we try to deal with complex systems that test the limits of our understanding. Immunology is particularly susceptible to being intellectually locked in to the canalization of thought by language as we seek to develop simplifying paradigms that explain the enormous complexity we are dealing with. Generalizations like suppressor T cell circuits, idiotypic networks, and central and peripheral memory direct our thought processes and experimental strategies. Such direction is not a bad thing, as long as we have both the integrity to look very hard at our data and the intellectual capacity to break out of the conceptual restraints when they become shackles rather than mechanisms for focusing useful research activities. Shakespeare's Hamlet says, "There is nothing either good or bad, but thinking makes it so." As immunologists, we can probe ideas by experiment and generate solid data that, if we are astute, should enable us to discriminate between good and bad ideas. Sometimes, however, the bad ideas in immunology hang around far too long.

INFLUENZA AND PHILADELPHIA

The research collaboration with Rolf Zinkernagel ended in 1975 when Frank Dixon invited him to join the Scripps Institute in La Jolla, California. Soon after, I was recruited by Cedric Mims's friend, Hilary Koprowski, as an associate professor at the Wistar Institute in Philadelphia. Rolf and I wrote a few review articles after that, but our formal collaboration lasted for only two and a half years.

Founded by the Civil War Quartermaster General Isaac J. Wistar, the Wistar Institute of Anatomy and Biology that is located on the grounds of Benjamin Franklin's University of Pennsylvania (Penn) is the United States's first private biomedical research institute. It has strong links to Penn, which is the home of the country's oldest university medical school. Beginning in 1765, Penn was modeled on the Medical School at the University of Edinburgh. Many of the founding professors were Edinburgh MDs, and my PhD is from the University of Edinburgh Medical School.

At the Wistar, I started to work with my second major Swiss colleague, Walter Gerhard. Walter is from Zurich, and Rolf Zinkernagel is from Basle, and they could not be more different in personality or temperament. Both are MDs and had their early training from Jean Lindeman, the codiscoverer of type 1 interferon, who headed the immunology program at the University of Zurich. Walter was a PhD student with Lindeman, whereas Rolf was greatly influenced by a course for medical graduates given by Lindeman and his colleague, Hansrudi Ramseier (when I first met Rolf, he kept rattling on about Ramseier's obsession with idiotypes, but, thankfully, we managed to deflect him from this).

Walter Gerhard first came to Norman Klinman's laboratory at Penn, then moved across the street to the Wistar. As I arrived, Tom Braciale, who became a long-term friend in the world of influenza immunity, had just completed his MD/PhD training with Norm. He and Vivienne Lam Braciale were on the point of leaving for the JCSMR to learn about virus-specific T cell–mediated immunity. What Walter brought to the table in Norm Klinman's laboratory, then at the Wistar, was an expertise with the influenza A viruses.

Walter learned about influenza viruses from Stephen Fazekas de St. Groth at the Basle Institute for Immunology. Stephen, a refugee Hungarian count, was a scientific product of the Australian influenza virus research community. He worked with Mac Burnet at the Walter and Eliza Hall Institute in Melbourne, then moved to the JCSMR in Canberra, then to joint appointments with the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Sydney and the Basle Institute in Switzerland. Stephen had the reputation of being a very rigorous and sometimes difficult individual. He certainly transmitted that respect for scientific integrity to Walter, who is an absolutely impeccable research investigator. The same is true for Rob Webster, my current and long-time influenza virologist colleague at St. Jude Children's Research Hospital (SJCRH). Rob was Stephen Fazekas's PhD student when he was in Canberra. Many immunologists will know Stephen's daughter, Barbara Fazekas, who is also a very tough-minded, critical scientist.

As a consequence of being at the Wistar, I also became an adjunct professor at Penn and had access to first-class trainees through the Penn Immunology graduate group. My first two PhD students were Rita Effros and Jack Bennink, both of whom completed what is normally a five-year program in three years. The Penn system of horizontally organized graduate groups that work across the traditional university department structure is an extraordinarily successful model for research training. The glue that held it together at that time was NIH training and program grants headed by Norman Klinman and Darcy Wilson, both in the Department of Pathology. Norm was introduced to the antibody world by the eminent immunochemist, Fred Karush, at Penn. His program during the

years we both worked in Philadelphia was exploiting an experimentally powerful spleen focus assay to look at B cell clonality and antibody specificity. Norm's research passion then was summarized by the phrase "the exquisite specificity of the repertoire," which was the first time I had heard the term repertoire applied to something other than a musician. I was impressed. Judy Owen, who worked with Norm, later came to my laboratory and was an excellent colleague. She was the first of my younger associates to become a department head, at Haverford College.

Darcy Wilson learned T cell/transplantation immunology from Rupert (Bill) Billingham. Bill trained with Peter Medawar and was first author on the 1953 Billingham, Brent, and Medawar *Nature* paper that is reference number one in Medawar's Nobel Prize lecture. Initially recruited to the Wistar Institute, Bill later moved to Penn and had departed for the University of Texas, Southwestern (where I met him), before I arrived in Philadelphia.

Darcy, who was then working with T cells in a rat transplantation model, loves arguments and ideas and, with the NIH funding levels at that time, had enough money available to invite active young scientists to Penn to "play in my sandbox." Among the players who turned up for a month or two were Darcy's long-time friend Jonathon Howard, Kirsten Fischer-Lindahl, and Polly Matzinger. Darcy also recruited Jonathon Sprent as a faculty member. I first met Jon when he arrived in Philadelphia, but his father, the parasitologist John Sprent, taught me when I was a very young veterinary student at the University of Queensland. Sprent the elder's short course on parasitism was clearly influenced by both his own research and by the extensive writings of Mac Burnet. I was intrigued and read Burnet's very influential books on virology and immunology while I was still an undergraduate.

What Rolf and I had discovered in Canberra was that LCMV-specific $CD8^+$ T cells are targeted to particular MHC class I glycoproteins with a precision that can, for example, discriminate a single point mutation in the transplantation molecule in question. As far as viral specificity was concerned, we found that there was no cross-reactivity for T cells primed to LCMV, ectromelia virus, or Sendai virus, but that was the limit of our understanding. The influenza A viruses offered us the possibility of looking at a much more closely related and defined panel of pathogens. From both the serology and the epidemiology of influenza infection, we knew that the hemagglutinin (H) and, to a lesser extent, the neuraminidase (N) were evolving constantly (32) under antibody-mediated selection pressure (antigenic drift). Furthermore, Burnet had discovered while working with Margarete Edney (later Sabine) in 1951 that influenza A viruses recombine when two viruses are used to infect the same cells simultaneously. That is, put in H3N2 and H1N1 viruses, and H3N1 and H1N2 viruses may potentially be recovered from the mix. We now understand that this is a simple reassortment process: Each influenza A virus is composed of eight different segments that can simply repackage to produce new virus by the mechanism known as antigenic shift.

Working with Rita Effros and Jack Bennink, Walter and I set out to find whether we could map viral specificity using different, recombinant influenza A viruses. Several other groups had the same idea, but, together with Hans Zweerink, John Skehel, and Ita Askonas at the National Institute for Medical Research, Mill Hill, London, we got the right answer. Influenza virus–specific $CD8^+$ T cells are highly cross-reactive (33–35) and do not show any of the fine specificity that would be expected from the analysis of antibody responses directed at the H and N glycoproteins. In short, it seemed both from the MHC restriction findings and the influenza results that the then-elusive TCR was seeing something very different from the antigen recognized by the Ig-binding site. As a consequence, I found the whole situation very confusing when claims that the TCR was an Ig

heavy chain started to emerge. Of course, this was soon consigned to the substantial trash heap of immunological history.

The question of $CD8^+$ T cell specificity was pursued further for the influenza A viruses by Jack Bennink, in the close collaboration that he developed with Walter's former student, Jon Yewdell. They moved together to the NIH, Bethesda, after I left Philadelphia, and would soon have reached the right answer using the vaccinia recombinants (36) made by their collaborators Bernie Moss and Geoff Smith. Jack and Jon were, however, beaten to the post by Ita Askonas's former student, Alain Townsend (28). Alain showed us that much of the cross-reactive response that we had been analyzing for the influenza A viruses was directed at peptides derived from the relatively conserved, internal nucleoprotein. The viral immunologists thus changed the whole field of T cell–mediated immunity, first with the discovery of MHC restriction, then with the illumination of the cytoplasmic processing pathway.

Experiments done at the Wistar with both influenza viruses and vaccinia virus also established the existence of MHC-related immunodominance hierarchies in virus-specific $CD8^+$ T cell responses (37). Particularly intriguing was the observation that the presence of the $H2^k$ haplotype, or the $H2K^k$ allele, greatly diminished the magnitude of virus-specific CTL responses that map to $H2D^b$. When we went back to those experiments some 20 years later with the more sensitive peptide/interferon-γ, intracellular cytokine stimulation (ICS) assay, we replicated these early CTL results but found that the effects on virus-specific $CD8^+$ T cell numbers were much less absolute than we inferred from the bulk ^{51}Cr release assay (38). Current experiments are looking at this K^k/D^b interaction yet again, this time from the aspect of TCR repertoire usage (39). The ICS study suggested that there may be holes in the repertoire as a consequence of the need to maintain self-tolerance. Now that we have defined the profiles of TCR usage for several of the main D^b epitopes, the question whether negative selection is determining the level of responsiveness should be much more approachable.

The desire to quantitate virus-specific CTL numbers also led us to an involvement with limiting dilution analysis (LDA), an approach that was pursued at that time by Judy Owen and Michelle Allouche (40) and continued through later iterations in Canberra and Memphis (41), until it was superseded by tetramer staining and the ICS assay (42). The use of LDA allowed us to look more closely at immunodominance hierarchies in those prepeptide days, and, in the longer term, LDA experiments left us in no doubt that virus-specific $CD8^+$ T cells persist indefinitely after the resolution of acute infectious processes (43, 44). I was thus more than a little surprised when others claimed that $CD8^+$ T cell memory does not exist. That conclusion was, of course, quite wrong. However, as we all now realize from experiments using ICS and tetramers, the LDA approach gave us numbers that were far too low, which led to some later misinterpretation on my part that I have discussed elsewhere (45).

Other Philadelphia experiments with Bob Kornglold, Julia Hurwitz, Dave Schwartz, and Neil Greenspan made extensive use of monoclonal antibodies, bone marrow radiation chimeras, and thoracic duct filtration approaches (46), with the consistent focus on virus-specific $CD8^+$ T cell responsiveness and self-tolerance. Jack Bennink, Bob Korngold, and I learned thoracic duct cannulation from Jon Sprent; I have never been quite sure whether we should actually thank Jon for that. Bill Biddison showed that the H2L locus was associated with MHC I–restricted, virus-specific $CD8^+$ T cell recognition, and Ann Marshak demonstrated MHC restriction in a rat model. We took a further look at virus-induced inflammatory processes in the CNS and interacted with the rabies program headed by Tad Wiktor and Hilary Koprowski (47). Of other Wistar collaborations, Barbara Knowles (48, 49) and Peter Wettstein (50) helped us a lot on the immunogenetics front.

The laboratory was also funded by both the NIH and by the U.S. Multiple Sclerosis (MS) Society to work on experimental allergic encephalomyelitis (EAE). Some of our EAE radiation chimera experiments were interesting from the perspective of the genetics of susceptibility, but we otherwise made little impact on the field. I served on the NIH Experimental Virology study section when Garret Kiefer was executive secretary and was reclaimed by Gary when I returned to the United States some five years after I left Philadelphia. We were also funded for EAE work during my second spell in Canberra, again without making any major impact, and I was a member of review panels for both the Australian and the U.S. MS societies. With regret, I had to give up the latter after the 1996 Swedish intervention. Along with other autoimmune diseases, MS remains a major target for immunology research that has proven to be surprisingly unyielding.

LCM AGAIN IN CANBERRA

During 1982, I returned to the ANU to head the department of experimental pathology at the JCSMR. As Gordon Ada was working on the influenza virus–specific $CD8^+$ T cell response and I did not want to be in direct competition with him, I turned my interests back to the LCMV immunopathology model. Together with Jane Allan, Zsuzsanna Tabi, Narelle Bowern, Mike Uren, and Jane Dixson, we did a series of experiments that looked closely at the LCM inflammatory process, and we started studies of T cell specificity to flaviviruses that were funded by the Rockefeller Foundation. An extensive interaction with Felicity Lynch and Rhodri Ceredig led flow cytometry to become a major part of the laboratory's technical repertoire. An important discovery from that era was that both acutely activated and memory virus–specific $CD8^+$ T cells are $CD44^{high}$ (51,52). Barry Rouse came out from Tennessee as a sabbatical visitor, and we collaborated with Ian Clarke, Ian Ramshaw, and Dave Willenborg on EAE experiments.

Apart from some good scientific interactions, the experience of going back to Canberra was not a happy one. I had accepted the position because I thought that the JCSMR director, the neuroscientist Bob Porter, wanted to initiate a process of real reform in what was rapidly becoming a failing institution. The JCSMR was seriously underresourced and in considerable difficulty because it retained an antique, hard-money structure that had the director doling out the available resources. This worked fine for the first 20 years or so after the founding of the ANU in the early 1950s, but, with the development of strong research foci in other Australian universities, the national political priorities were such that the size of the direct grant supporting the JCSMR gradually eroded in real dollar terms. This "death by a thousand cuts," together with an uncomprehending university administration and a top-heavy structure dominated by tenured faculty who were at the end of their careers, made it impossible for the institution to react flexibly to the new challenges posed by the molecular era.

Some of us in the senior science leadership group got together to try to change that equation, suggesting that the ANU should give up a proportion of its direct grant from the Australian Federal Government so that the active scientists in the institution could compete for National Health and Medical Research Council (NHMRC, equivalent to the NIH extramural program) peer-reviewed grants. In addition, we made the obvious point that it was unwise to tenure young people until age 65 and then never review them again. These heretical ideas were, in fact, implemented to the considerable benefit of the university some 10 years after I left. At that time, however, the linked proposals of performance review and competitive funding were greeted with rage and contempt. As I discuss (27) in *The Beginner's Guide To Winning the Nobel Prize*, hard-money funded institutes like the

old JCSMR can prosper if they have outstanding, critical leadership and no absolute tenure. Otherwise, they are generally a disaster, especially when resources are in short supply.

Three of us were members of a formally constituted committee that made these recommendations and were, as a consequence, vilified throughout the university. We were accused of academic Thatcherism and heaven knows what other profound evils. It became very unpleasant. That is the first and last time that I have ever become involved in university or institutional politics. All of us left the ANU, two for the United States. Rob Webster heard that I was not happy, and, after looking at some other terrific possibilities, I was recruited to head the immunology department at SJCRH by the then-director, Joe Simone. My absolute criterion at that stage was that I would only consider private, free-standing research institutes that were not in any sense controlled by a university administration. My perceptions have mellowed over the years, and I now spend some of my life trying to defend universities against the more regressive elements in society that want to stifle debate and open inquiry. At the moment, those forces are unusually strong, both in Australia and in the United States.

IMMUNOLOGY IN MEMPHIS

The escape from Canberra in 1988 was aided and abetted by the fact that Jane and Bill Alan, together with two first-rate young technicians, Dianne Hartley and Andrew Cleary, came with me to set up the new laboratory. This time I was admitted to the United States as an eminent alien, a category that is also used for rock stars and sports identities. St. Jude provided a very generous setting-up grant that allowed us to establish a first-class cell sorting and phenotyping facility. One simply cannot do rigorous, in vivo cellular immunology experiments without ready access to a sophisticated flow cytometry resource. The other piece of equipment that was used very heavily until 1997 was a 10-channel, Cobra γ counter for LDA experiments. After the tetramers came on the scene, the Cobra became a monument to the past, and we had to expand further the FACS facility. The work that we did during the 1990s is summarized in a number of accessible reviews written about that period (44, 53–59). I will not repeat it here as, again, some of the studies are ongoing and not yet history.

Given the presence of Rob Webster and Yoshi Kawaoka in the then-prominent virology department at SJCRH, my research focus switched back again to the influenza A viruses. We also started to collaborate with Alan Portner and Jackie Katz on experiments with the murine parainfluenza type 1 virus, Sendai virus (43). Again, this was in some sense a reprise to an earlier time as, during my initial stay in Canberra, I had published the first analysis of the Sendai virus–specific CTL response. We later wrote a program project grant on this work.

Although I was a department head, St. Jude has no teaching mission other than hands-on clinical specialist and postdoctoral training, and the departments are small. After I had been there about a year we moved into new space, 10 laboratories, each of about 650 square feet, with separate offices for the principal investigators. I inherited few faculty from the former department and, as even senior people at St. Jude are employed on renewal five-year contracts, there were none of the long-term, lack-of-productivity problems that sometimes occur in university departments. The absence of bitter, angry, failed academics was both a relief and a good reason for choosing St. Jude after my previous time in Canberra. Of those who were there when I arrived, Bill Walker remained and, after I was made much too busy as a consequence of the Swedish decision, took on the role of vice chair and effectively ran the department.

I have never been interested in administration and have thus tended to do the minimum on the theory that "if you keep a low profile, they'll leave you alone to do something interesting." I have, though, been enormously

appreciative of talented, perceptive people who have given themselves over to running large operations. Joe Simone, the St. Jude director who recruited me, was a case in point. A fine pediatric oncologist, he delegated effectively, consulted before making clear decisions, and generally ran the linked clinical/research St. Jude operation by the strategy of "management by walking about." Any medical academic who has not read "Simone's maxims"(60) should take the trouble to dig them out. He was, along with Hilary Koprowski, who was simply entertaining to be around for all sorts of reasons, my best experience as an institute director. From what I have seen over the years, the worst thing that can happen to any research operation is to be taken over by a humorless, insecure, self-serving micromanager who cannot delegate. Maybe you also know one or two of those.

Joe Simone and Hank Herrod, the amiable clinical immunologist who was to go on to be dean of the University of Tennessee Medical School, were instrumental in recruiting Mary-Ellen Conley. Mary-Ellen, a leading figure in the area of pediatric immunodeficiency disease, educated me on the clinical and emotional realities of dealing with very sick children. Dario Vignali joined us from Jack Strominger's laboratory to provide an expanded molecular immunology component. Julia Hurwitz and Chris Coleclough returned from Basle. Chris focused much of his effort on analyzing aspects of the B cell response to viruses, whereas Julia continued her work on thymic differentiation and tolerance, then decided to take a much more practical line and has, with Karen Slobod, been developing a multi-component HIV/AIDS vaccine that is currently in Phase 1 trial. Deming Sun and Chris collaborated on studies of EAE, whereas Bill Walker continued his life-long work with macrophages.

From my point of view, the most important faculty recruitments were David Woodland and Marcia Blackman from the National Jewish Hospital at Denver. Pippa Marrack recommended that we consider Marcie and Woody, and that proved to be very good advice. Given the opportunities at St. Jude, they switched their efforts to viral immunity, and we collaborated extensively over the years. Now at the Trudeau Institute, they are senior members of the viral immunology community who, for example, take a prominent role in organizing Keystone symposia in this area of research.

Of those who worked in my laboratory through the 1980s and 1990s, Jane Allan, Sam Hou, Ralph Tripp, Dave Topham, Maryna Eichelberger, Sally Sarawar, Rhonda Cardin, Janice Riberdy, Jan Christensen, Mark Sangster, Gabrielle Belz, and Philip Stevenson all went on to faculty-level appointments in substantial research institutes or universities. Most of the focus was on the acute and memory $CD8^+$ T cell response to the influenza A viruses and Sendai virus, although we also worked on aspects of $\gamma\delta$ T cell, $CD4^+$ T cell, and B cell immunity. The less said about the $\gamma\delta$ T cells the better, as we got nowhere useful with this problem. With help from John Sixbey at SJCRH and Tony Nash and Stacey Efstathiou in Cambridge, UK, we initiated a program with the murine γ herpesvirus 68 (MHV68). My interest in MHV68 was to find a model of persistent infection other than LCMV, which dominates experimentally in this regard, to learn whether it is possible prevent superinfection by priming only the T cell compartment (61, 62). The answer was no. I therefore dropped MHV68 and focused exclusively on influenza. Marcy Blackman, Gabrielle Belz, and Philip Stevenson have continued at one level or another with MHV68.

Other collaborations include those with Kim Bottomly and Simon Carding at Yale; Martin Zijilstra and Rudolph Jaenisch, Peter Mombaerts, and Luc Van Kaer and Susuma Tonegawa (all then at MIT); Susan Watson and Linda Bradley at University of California, San Diego; and Bob Coffman at DNAX. With these colleagues, we looked at aspects of the influenza-specific cytokine response and the characteristics of immunity and protection

in the newly available knockout mice. Hiroshi Kiyono from the University of Alabama, Birmingham, taught us how to do ELISPOT assays. We also worked with Jim Ihle, Bill Thierfelder, Jan van Deursen, Ted Strom, Art Nienhuis, Michale Brown, Malcolm Brenner, Brian Sorentino, and Sandra d'Azzo on the immunological analysis of various knockout mice produced in Gerard Grosveld's operation at St. Jude. Our whole effort on $CD8^+$ T cells was transformed in 1997 when we started the interaction with Rafi Ahmed and John Altman at Emory that resulted in our having early access to the tetramer technology. I was incredibly busy on the public science stage through that year and am enormously grateful to Rafi for the help and advice he gave us then. With John's advice, we quickly established our own tetramer facility. I summarized this transition in an article I wrote for the 2000 edition of the *Annual Review of Immunology* (59).

The move to St. Jude in the late 1980s saved my scientific life. Although Memphis may seem an unlikely place to locate a major research operation, the local people are enormously supportive, and the institute was, especially in the early days, very warm, open, and friendly, while at the same time being a high-quality research environment. Over the years, it grew from about 800 people to more than 3500, so some of that early intimacy was lost. Still, I notice that the fellows, in particular, have a great time here.

A great tragedy in the laboratory was the sudden, unexplained death from exudative diathesis of a young Korean postdoctoral fellow, Sangjun Chun, who had just joined us from Barry Rouse's program in Knoxville. Although major efforts were made, no evidence was found that linked his death to any known pathogen, including the influenza, MHV68, or vaccinia viruses that were currently being used in our research effort. The department also lost Richard Carson from Dario Vignali's laboratory in a kayak accident. Richard was an expert canoeist, but fast-flowing streams are dangerous, and the fates do not always favor the brave.

SCIENCE COMMUNICATION

Although I had been in Memphis for eight years, I was still an Australian citizen when the Nobel Prize announcement was made in October 1996, and I was thus hosted by the Australian Ambassador, Judith Peade, during the time in Stockholm. I was the first Australian to be recognized in this way since 1975, but it was a big surprise when I received a call on Christmas Eve telling me that I had been named Australian of the Year. This meant that I had to be in Melbourne on Australia Day (January 26), the anniversary of Captain Arthur Philip's 1788 arrival at Sydney Cove with 11 ships and 1350 exhausted human beings, most of whom were either convicts or the soldiers who guarded them (after losing the American colonies in the War of Independence, the British had to find somewhere to send their human debris).

The reason that I mention the Australian of the Year event is that this began my additional career as a science communicator. The AOY organizers do their best to boost media exposure, as the intent of the award is to promote social awareness and a sense of national pride. I was required to do a speaking tour of all the Australian state capitals. The consequence is that I was featured in many media contexts, ranging from public lectures in city halls to an appearance on a national comedy program with the elegant name of Club Buggery: very Australian! This was, of course, quite a change for a laboratory scientist who had only previously been on the academic immunology circuit.

I quickly realized that there is a very important, and largely unfulfilled, role for professional scientists who are willing to devote at least part of their time to this type of activity. Although there are outstanding science communicators, such as Bill Nye the Science Guy in the United States and Robin Williams in Australia, active investigators like Susan Greenfield and Robert Winston in the UK and Michio Kaku in the United States also contribute greatly to raising public awareness

on science issues. In our field, Tony Fauci is, by virtue of his position as the director of NIAID and his clear and authoritative style, enormously effective in this regard.

Our profession has, however, a long way to go in communicating the nature of immunity to the general public. There is not, as far as I am aware, a single good, simple book on immunity written for a lay audience. One reason is that our subject is so complex that writing such a book would be a very difficult task. Even in "catastrophe books" on global infectious disease, any immunology component is minimal. In addition, the public has to some extent been turning its back on science. The warm fuzziness of manipulated fantasy is, in our advertising- and Hollywood-dominated world, much more appealing than evidence. Just look at contemporary national politics.

This perceived disconnect between science and the lay public is one of the main reasons I wrote *The Beginner's Guide To Winning The Nobel Prize* (27), which, despite the somewhat discomfiting (particularly to me) title, is a book about the nature, history, and practice of science written for an intelligent, lay audience. As it turns out, many of the people who seem to enjoy reading it are scientists, especially young scientists or those who are thinking of going to graduate school. At the publisher's insistence (they thought up the title) there is a chapter on immunity that goes into both the history of the Nobel Immunology prizes and what Rolf Zinkernagel and I did some 30+ years ago.

What words can explain T cell recognition to nonscientists? I tried an analogy in which the $CD8^+$ killers were sea mines targeted to blow up enemy (virus-infected) ships. Some find this illuminating, others just confusing. What worked infinitely better was when I appeared on an Australian national television program hosted by Andrew Denton that attracts up to one million viewers, a big audience in a country of 20 million. The producers handed me a bowl of fruit, some nuts, and toothpicks prior to the show and told me to illustrate MHC restriction with these props. The target cell was a banana, the viruses were smoked almonds, MHC glycoproteins were toothpicks, and the killer T cells were grapes. The pMHC-1 "altered self" complex was one of those cocktail toothpicks with a little umbrella. Those who watched this fiasco, including some of my medical colleagues, said it was the first time they had ever understood T cell recognition. Looking at it later, it worked infinitely better than the verbal ships and sea mines in my book.

The point is that we need to do a much better job of establishing immunology awareness in the broader community. Throughout the Western world there is a substantial and dangerous antivaccination lobby. One can confront the immunity/diet racket in any drug store. On a talk radio program, a woman once told me that she did not need to immunize her child because she was taking a course and knew what foods would give her child a strong immune system. I asked her, "How do you ensure that this strong immunity does not lead to the later development of lupus or multiple sclerosis?" Evidently, she found my question offensive. How do we deal with this mixture of superstition, fantasy, and ignorance?

An initiative that the immunology community might embrace is the development of very good video presentations that address key aspects of basic immunology, vaccine protection, allergy, autoimmunity, and so forth. These could be available directly via the Internet for downloading by both individuals and the media who want to illustrate a particular point in a news report or in a more in-depth program. In addition, we might think of producing an immunology health handbook that combines a traditional, written volume with a digital video disc, such as what one might encounter in a foreign language program.

I started this personal, historical review writing about biological complexity, but this issue of science communication and the promotion of an evidence-based view in the public arena is an enormously complex and challenging social problem. Nothing could be more important for immunology and, in fact,

for the future of all basic biomedical research. The current rise in antiscience is inimical for human well-being, and we must do everything possible to promote the alternative view that science and active, unrestricted inquiry protects us and our world.

CONCLUSIONS

As I am firmly of the view that putting events in perspective takes time, I have chosen to confine most of this personal historical account to the twentieth century. My research career is not quite over, and the laboratory has, with the beginnings of the genomics era, taken some substantially new intellectual and technical directions since the beginning of the new millennium. The story of what we have been doing since 2000 belongs in the primary literature and in contemporary reviews. It is all too recent to include anything beyond a brief outline in this historical record.

Reflecting the possibilities offered by immediate electronic communication in this new, globalized world, the influenza immunity program that I currently share with Steve Turner is split between SJCRH and the University of Melbourne, where different aspects of the research effort are funded by the NIH and the NHMRC, respectively. The longer-term players in the Memphis and Melbourne sandboxes are Nicole La Gruta, Katherine Kedzierska, John Stambas, Paul Thomas, and Rachael Keating. Many of the more molecular immunology aspects are being pursued in Melbourne, whereas the reverse genetics engineering of viruses and in vivo experiments with the very dangerous H5N1 bird flu viruses are part of a St. Jude collaboration with Richard Webby and Rob Webster. At the time of writing, I have been associated with St. Jude for 18 years and the University of Melbourne for 7 years.

Looking back to the beginning, anything useful that I have done in science has focused on experimental models of infectious disease, with much of the initial emphasis on pathogenesis and pathology. I have run my own research programs since I was 22 years old and basically trained myself on the job. That is a high-risk strategy that I would not suggest for any young scientist, but, in the end analysis, I would have to say it worked for me. Sometimes, though, I stuck with unproductive lines of effort for too long, missed opportunities, and missed the true meaning of data on a couple of occasions. Any honest person who has worked for more than 30 years in cellular immunology would have to come to somewhat similar conclusions.

It is hard for young people to imagine an era when the TCR was enigmatic and when there were no monoclonal antibodies, no sequence information for low-abundance proteins, no PCR machines, no FACS analyzers, and no transgenic or knockout mice. The only cytokine that had been identified when I started in immunology was John David's macrophage inhibitory factor. In one sense, not knowing about the plethora of cytokines and chemokines allowed some of us to think more clearly, although it was, of course, a disaster for those biochemists who were trying to characterize the culture soups containing the various helper and suppressor factors.

Working with viruses and spanning, at least to some extent, the virology, pathology, and immunology cultures have had several great advantages. The first is that being exposed to different ways of looking at problems can trigger intellectual processes and technical approaches that are outside the box. The second is that, because the immune system is so complex, backtracking on the pathways and mechanisms that are used to control invading organisms allows us to be instructed by the experiments of nature. Those immunologists who have insisted on the primacy of some beautiful theoretical construct over data have, in my experience, inevitably failed to achieve their potential and have, at times, badly misled the more gullible and confused among us.

It would be intellectually pleasing if most advances in immunology resulted from profound conceptual insights. However, although thinking clearly and concisely is, of

course, enormously important, the real breakthroughs and discoveries are more often a consequence of a technological innovation that allows us to see more clearly. In some cases, seeing is simply a matter of being able to make better measurements. Although counting is not everything, we have, in the past at least, sometimes minimized the importance of numbers when it comes to understanding immunity. Among the major opportunities open to us may be the capacity to exploit new approaches that allow access to the enormous complexity of immunity in a more comprehensive and quantitative, yet visual way. We also need to communicate better with the general public on the societal value of what we do.

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