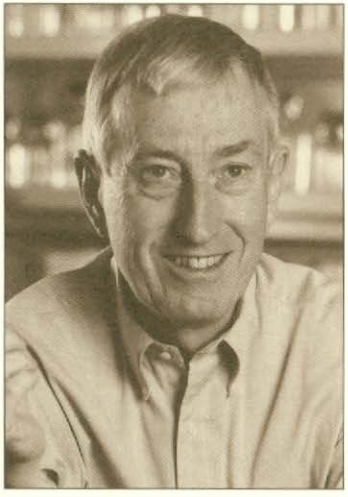
Doctor Honoris Causa

PETER CHARLES DOHERTY



Universitat Autònoma de Barcelona

Doctor Honoris Causa

PETER CHARLES DOHERTY

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PRESENTACIÓ
DE
PETER CHARLES DOHERTY
PER
LLUÍS FERRER

Peter C. Doherty: l'aventura de la investigació

Quina és la química de la reacció que transforma un inspector veterinari en un premi Nobel de Medicina i Fisiologia? Quines són les condicions, quin és el camí que s'ha de seguir?

Una lectura assossegada del *curriculum vitae* de Peter Doherty[1] revela les principals claus de la transformació d'un oficial veterinari a Brisbane, Austràlia, l'any 1967, en el professor guardonat amb el Premi Nobel de l'any 1996. I jo voldria destacar-ne dues, d'aquestes claus: d'una banda, una actitud valenta en acceptar el repte de la investigació i, de l'altra, una inquietud i una capacitat intel·lectuals fora del comú.

La investigació científica com a aventura

Una de les coses que més m'ha sobtat de l'extraordinari *curriculum vitae* de Peter Doherty ha estat, sense cap mena de dubte, la seva actitud al llarg de tota la seva carrera. L'absència absoluta de conformisme, de por davant dels canvis i de mandra. De mandra intel·lectual (de canviar de línia de recerca, d'hipòtesi, de model de treball), però també de mandra davant les incomoditats mundanes: canvi de país, de ciutat, de lloc de treball, renúncia a salaris llaminers... Alguns moments són força il·lustratius d'aquesta actitud. Després de treballar uns anys com a viròleg veterinari a Brisbane, amb una plaça en propietat i resultats professionals i científics que per a molts eren envejables, va decidir que volia aprofundir els mecanismes de les malalties víriques i, després de diferents intents, va acceptar una plaça per fer un doctorat al Moredun Research Institute a Edimburg —a l'altre cap de món—, on va treballar en la patogènia de malalties com la tremolor ovina (*scrapie*) i l'encefalomielitis ovina. Tot i que el nivell de les seves recerques augmentava notablement, el Dr. Doherty va considerar que calia estudiar molt més a fons els mecanismes immunològics de les infeccions víriques, en bona part estimulat per les recerques i els conceptes del reconegut professor Cedric Mims. I, sense, deixar-se dur per inèrcies i mandres, va tornar a la seva Austràlia per treballar a la John Curtin School of Medical Research. Allà va iniciar les seves investigacions immunològiques, que va continuar al Wistar Institute de Filadèlfia i, més tard, al St. Jude Children's Research Hospital, a Memphis, Tennessee. Tres continents, sis ciutats i canvis constants de residència i de condicions de treball.

De la mateixa manera, va canviar de línies de recerca i de models experimentals. Així, després de treballar, com hem dit abans, en l'encefalomielitis ovina i la tremolor ovina, va estudiar la patogènia de la infecció amb el *Semliki Forest virus* en el ratolí i, poc després, va canviar a la infecció murina amb el virus de la coriomeningitis limfocítica, un model experimental que

considera molt més potent. I més tard, va estudiar la resposta immunitària davant les infeccions víriques respiratòries.

I és que, no ens enganyem, la recerca d'alt nivell —el que els americans anomenen *blue sky research*— no és compatible ni amb el continuisme còmode, ni amb el funcionariat entès com a privilegi, ni amb l'endogàmia i el provincianisme.

La inquietud intel·lectual

La segona clau, segons la meva opinió, consisteix en la inquietud per trobar els mecanismes íntims que expliquen els fenòmens biològics. El rebuig a les explicacions superficials i simples i la cerca constant d'explicacions més complexes, però de major poder explicatiu; aquesta inquietud és la que fa que deixi el diagnòstic per l'experimentació. I això que el diagnòstic és un exercici intel·lectual força satisfactori, que comprèn fases d'anàlisi i de síntesi. No obstant això, és cert que el diagnòstic es queda en un exercici inductiu probabilístic simple[2]. I el mateix Doherty assenyala en el seu currículum que ell se sent seguidor de les teories deductivistes de Karl Popper, que sostenen que les hipòtesis només poden contrastar-se empíricament (contrastació deductiva)[3]. I això únicament ho permet la recerca experimental d'alt nivell. A més, Doherty, que es confessa també influït per les tesis de Thomas Kuhn, sap que el canvi d'un paradigma vigent demana un nou paradigma, sòlid, ben contrastat i de major valor explicatiu[4]. I a aquesta tasca dedica tots els seus esforços.

Probablement, és també aquesta atracció per la complexitat la que el va conduir, a principis dels anys setanta, al camp de la immunologia, en aquells moments en plena eclosió. Molt pocs sistemes biològics tenen la complexitat del sistema immunitari. Recordo com em va impressionar la capacitat del sistema immunitari de reconèixer un nombre il·limitat de molècules. Aquest immens univers molecular immunitari em feia pensar en la famosa Biblioteca de Babel de Jorge Luis Borges, en la qual es trobaven tots els llibres possibles; escrits en totes les llengües, totes les estructures verbals, totes les variacions dels signes ortogràfics; amb sentit i sense. Una biblioteca il·limitada i periòdica. Una meravella de ficció que el genial Borges ignorava que existia de debò en els sistemes vius[5].

En aquest sentit, val a dir que les investigacions més rellevants i conegudes del Dr. Doherty versen, específicament, sobre el problema del reconeixement immunitari; en especial sobre el reconeixement de les cèl·lules infectades per virus. I, malgrat que es tracta de treballs de caràcter indubtablement fonamental, les seves aplicacions a la medicina i a la veterinària han estat nombroses i d'una enorme importància. Una enèsima prova que la bona ciència bàsica acaba engendrant la millor ciència aplicada.

I podríem seguir posant exemples i lloant la carrera del nou membre d'aquesta universitat; però, sincerament, penso que el més important ja s'ha dit.

El seu coratge per acceptar l'aventura de la investigació amb totes les seves conseqüències i la seva inquietud i capacitat intel·lectuals fora del comú han de ser exemple i estímul per a la nostra comunitat acadèmica. Gràcies per mostrar-nos el camí, Dr. Doherty.

Notes

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3. POPPER, K. R. *La lógica de la investigación científica*. Madrid: Tecnos, 1997.
4. KUHN, T. S. *La estructura de las revoluciones científicas*. Mèxic: Fondo de Cultura Económica, 1997.
5. BORGES, J. L. «La Biblioteca de Babel». A: *Narraciones*. Madrid: Cátedra, 1992.

DISCURS
DE
PETER CHARLES DOHERTY

My childhood was spent on the outskirts of the sub-tropical city of Brisbane. I have a younger brother, Ian, and we grew up as part of a traditional, extended family that was very much influenced by the values of our two grandmothers. The one was a devout Methodist, the other a lapsed Quaker who was born in England and embraced the informal Australian life style with great enthusiasm. My parents (Linda and Eric) were first and second generation Australians, the various elements of the family coming from County Louth (in the 1840's), Lancashire and Essex. Eric Doherty, a clever and entertaining man, trained initially as a telephone mechanic and was an administrator involved in the planning of telephone services. His mother had been left in straitened financial circumstances when my grandfather succumbed to pneumonia during the 1919 influenza epidemic. My father communicated his frustration at not having received an adequate formal education and, with his strong encouragement, the desire to learn and understand became the major focus of my life. Linda Byford was a piano teacher who, with her two brothers, spent much of her youth on the tennis court. After marriage she cared for her family, played Chopin, Debussy, and Beethoven, and grew roses. She gave me an appreciation, and emotional need for, classical music, but did not pass on the genes for tennis. The Byfords were devastated by the death of the eldest son, who was captured at the fall of Singapore and lost in a Japanese transport torpedoed by an American submarine. I remember my other Byford uncle shivering with recurrent malaria that he contracted during the fighting in New Guinea. I share Alfred Nobel's conviction that war is the greatest of all human disasters. Infectious disease runs a good second.

My Irish genetic heritage gave me a very fair skin, making me totally unsuited for life in a city that is known as the melanoma capital of the world. This limited my participation in the outdoor-oriented Australian way of life, and caused me to spend a great deal of time reading anything and everything. Even so, the Australian landscape was at our back door, there were adventures with home made canoes, I played tennis and Australian Rules football, and the extended family went to the beach for at least three weeks each year. The two things that I miss most when living out of Australia are the bush and the Pacific coast, especially fishing in the surf at night! My father had a workshop and I learned to be a carpenter, a skill that has resulted in the manufacture of some very substantial coffee tables and a fair amount of time working on houses. My most ambitious project as a teenager was the construction of a photographic enlarger and darkroom, but all the photographs

that I took at that time seem to have been lost after my father's early death (in 1961) and the selling of the family house.

I went to the local public schools and Methodist church. The commute to the high school involved daily trips on a steam train. I played basketball, and was a sergeant in the army cadet corps. Physics and chemistry came easily, but my natural inclinations were towards literature and history. Growing up without much money, however, also left me with the conviction that I needed to get some sort of reasonable job. An older cousin, Ralph Doherty was a brilliant scholar who was in the process of establishing himself as a leading viral epidemiologist. What he was doing seemed fascinating, but my contacts with the local general practitioners left me with no great enthusiasm for the idea of following his path to medical school. A visit to an "open day" at the University Veterinary School was my first real contact with biology in the formal sense: the subject could only be studied by girls in the Queensland public schools of that era. Another major influence at the time of my matriculation, was that I was reading Aldous Huxley, Jean Paul Sartre and Ernest Hemingway simultaneously. I decided to be the man of action rather than the philosopher, and resolved to graduate in veterinary science and pursue a research career. At this stage I was just 17 years old, and would probably have made a very different decision if I had been more mature.

The then vice-chancellor of the University of Queensland pursued a policy of open admission, from the conviction that matriculation results bore little relationship to later academic performance. As a consequence, the veterinary school had a number of mature students who had worked in the bush, while more than 50% (mostly school leavers) did not make it past the examinations at the end of the first year. This was one of two veterinary schools in Australia, and the survivors were joined by a spectrum of students from other states, New Zealand and south-east Asia (under the Colombo plan) at the beginning of year two of the five-year program. Being exposed in this milieu, together with spending the long vacations employed on sheep and cattle properties and seeing practice with rural veterinarians, caused me to grow up quickly. I soon discovered that I had little interest in small animal medicine or surgery, but retain a sense of nostalgia for the satisfaction and physical challenge of working with large domestic animals.

The veterinary school was staffed by a fairly young group of teachers, many of whom had strong research backgrounds. Courses in the physical sciences, zoology, botany and biochemistry were taught from the science faculty, and physiology in the medical school. I was introduced to the principles of ecology in first year zoology, with the commitment of my professor to marine biology almost causing me to switch to that discipline. Infectious disease was taught by John Francis, who communicated great enthusiasm for research, and immunology by the parasitologist, J.F.A. Sprent. Another course that influenced me strongly was population genetics given by Glenorchy MacBride. I also read F.M. Burnet and R.M. Stanley's books on viruses, some of Burnet's writings on immunology and cancer and wrote a final year thesis on the UV-induced squamous cell carcinoma (cancer eye) of Hereford cattle. Burnet's

teleological Darwinism, the idea that the body is a set of ecosystems and the realisation that good science involves quantitation have stayed with me from those early days.

When I graduated, I was contracted (under the terms of a "bonded" scholarship) to work for several years in the Queensland Department of Agriculture and Stock. I expressed enthusiasm for laboratory-based research, so the Department immediately sent me to the country as a rural veterinary officer. I spent some months driving large distances to postmortem cattle and pigs that had died of unknown causes, and to survey cattle for various venereal diseases. This resulted in the diagnosis of Trichomoniasis in an area where it was thought that complete eradication had been achieved. Realizing that I was a danger to their regulatory effort, the Department quickly brought me back to the state veterinary laboratory, the Animal Research Institute (ARI), Yeerongpilly. My task was to conduct a large-scale, externally-funded experiment on the epidemiology of bovine leptospirosis. This project involved injecting several cows with *Leptospira pomona*, then watching the spread of the disease throughout the herd. I became adept at dark-field microscopic analysis of urine for spirochetes, the histology of the bovine kidney and the serological test for the organism. This work was submitted for a master's thesis and published in local journals. I was also involved in the diagnostic veterinary pathology service.

The ARI was in the process of establishing a facility for diagnostic virology, and had employed a very attractive young microbiology graduate, Penny Stephens, to develop the laboratory. We married in 1965. Knowing of my interest in virology the ARI Director, Les Newton, sent me to Melbourne for six weeks to learn basic techniques. I worked with Toby St. George in the Commonwealth Scientific and Industrial Research Organization (CSIRO) laboratory of Dr. E.L. French, spent time in the virology group at the Commonwealth Serum Laboratories and (en route) visited F.J. Fenner's Department of Microbiology at the John Curtin School of Medical Research (JCSMR), Canberra. The latter was motivated by the desire to meet C.A. Mims, whose work on viral pathogenesis had considerably influenced my thinking about disease processes. On returning to Brisbane, I realised fairly quickly that I am an experimentalist at heart. A career as a diagnostic virologist was not for me!

I tried for a Ph.D. scholarship to work with Cedric Mims, but was told to apply again later because he already had a "scholar" and would take only one student at a time. At about the same time I got to know J.A. Roberts, who had done an excellent series of experiments with Mims on the ectromelia model and had recently returned from Cornell to a position as a research parasitologist in the CSIRO laboratories on the Yeerongpilly site. John Roberts told me that he had been very impressed by a visit that he had made to the Moredun Research Institute in Edinburgh, where there was a major research effort on scrapie, the then enigmatic "slow virus" disease. The Moredun also trained graduate students, who were affiliated with the University of Edinburgh. The following week a job in the Department of Experimental

Pathology at the Moredun was advertised in *Nature*. We sailed for Britain in early 1967, on a very slow and cheap ship.

The experimental pathology position at the Moredun required that I do research and help to run the diagnostic neuropathology program that the institute operated for the Scottish Veterinary Investigation Service. I learned neuropathology from the head of the department, R. M. Barlow, and from Hugh Fraser who was doing seminal studies with Alan Dickinson defining the genetics of the scrapie mouse model. Dick Barlow also taught me to write clear, concise English. My initial intention was to work on sheep scrapie, but I quickly realised that this was not a good project area for an experimentalist. My abiding interest in infectious disease caused me to focus on the tickborne flavivirus, louping-ill virus, which was then regarded as problematic because of concerns about the safety of the vaccine, first developed at the Moredun many years previously. I enroled as a part-time graduate student at the University of Edinburgh medical school and, after I had been working with the virus for some time, developed a collaboration with another young veterinary graduate, H.W. Reid. Hugh Reid did the virology and serology aspects of the ensuing sheep experiments, while I concentrated on light and ultrastructural pathology. Part of Hugh's role was to test my blood for the presence of virus and antibody when I injected myself in the finger, an inadvertent human experiment that I later wrote up for the *Lancet*.

We greatly enjoyed living in Edinburgh. Penny worked with E.C.R. Reeve at the Institute for Animal Genetics until the birth of our two sons, James and Michael. The Edinburgh Festival and the Traverse Theatre were high points and, for the first time in my life, I could spend the whole day outside without the penalty of sunburn. Our long vacations were used for camping holidays in Europe, including our first trip to Scandinavia and Stockholm with a young child in the back of a Volkswagen van. I went to veterinary research and neuropathology meetings, and we came very close to staying permanently in Britain.

Eric French visited the Moredun, and raised the possibility of a permanent appointment in the veterinary virology group at the CSIRO laboratories in Melbourne. At about this time I heard a seminar by Mel Greaves at the Metchnikoff Club, an Edinburgh group organized by Spedding Micklem and Angus Stewart, that convinced me I had no real understanding of contemporary immunology. Cedric Mims also came through and talked about the work that he and R.V. Blanden had been doing on T cell responses in virus infections. Shortly afterwards a junior academic appointment was advertised in the Department of Microbiology at the JCSMR, with a job description that seemed to fit me reasonably well. Fenner's successor as head of the department, G.L. Ada, had actually written it for Bob Blanden, but offered me the only other position that he had available, a postdoctoral fellowship to work with Cedric Mims. I left my permanent research position, and turned down the offer of another, to take this opportunity to learn basic immunology. My long-term intention was to return to veterinary research. My only formal involvement in the veterinary world since then has been to serve (1987–1992) on the board of the International Laboratory for Research In Animal Diseases,

Nairobi, Kenya. This was an enormously broadening experience, and I learned a great deal from (in particular) my African colleagues.

We moved from Edinburgh to Canberra in December 1971. Cedric Mims had by then decided to take the Chair in Microbiology at Guy's Hospital Medical School so, though we overlapped by six months or so, we did not ever formally work together. At first I studied the pathogenesis of Semliki Forest virus infection in the mouse, then switched to the lymphocytic choriomeningitis virus (LCMV) model which was a much more powerful tool for immunological analysis. I first met Rolf Zinkernagel when he arrived to work with Bob Blanden in 1973, and Gordon Ada (for space reasons) moved him into the laboratory with me. We also lived in the same university housing complex, and shared rides to the JCSMR with a physicist from Trondheim, a Japanese pharmacologist, and a biochemist (Bob Gerdes) who is now working at the Karolinska Institute. The story of our scientific interaction through that time is told in the accompanying articles, and in an account that we wrote jointly some time back that is yet to appear in "Immunology Today". We were then (and have remained) good friends, though we don't always agree on everything.

The basis of the "single T-cell receptor altered self" hypothesis was fairly much worked out by the time of the Second International Immunology Meeting in Brighton, England. I traveled through the United States and gave the same talk in about 20 institutions. Among my hosts were Alan Rosenthal at NIH, Bethesda, and David Katz at Harvard. I also met Gene Shearer, who had results comparable to ours with haptenated cells. This was probably the first time that the immunology establishment became fully aware of what we were saying. Our ideas both contradicted the accepted North American model for the role of immune response genes, and turned the perception of the transplantation system on its head. Many people have told me years later that they heard this seminar, came away with the sense that the findings were significant, but did not fully grasp the import. Evidently some were also infuriated by what we were saying. Rolf traveled more extensively through Europe, and I also visited a number of institutions in England and traveled to Stockholm to speak to Göran and Erna Möller's group at the Wallenberg Laboratory in Lilla Frescati.

Despite the fact that we had made a major breakthrough, the rigidities imposed by the excessive use of tenured contracts through the earlier years at the JCSMR had made any prospects of long-term appointments there fairly remote. Rolf accepted a faculty position at the Scripps Institute, and Hilary Koprowski called on my 34th birthday to offer me an Associate Professorship at the Wistar Institute. I had visited Hilary, who was a good friend of Cedric Mims, during my publicity tour en route to Brighton earlier that year. We moved to Philadelphia in 1975, and I quickly became involved with the outstanding Immunology Graduate Group headed by Darcy Wilson and Norman Klinman at the University of Pennsylvania. The Wistar/Penn axis was a highly interactive, and very open, intellectual environment. I collaborated extensively with Walter Gerhard on the influenza model, did some experiments

with the late Tad Wiktor in Hilary Koprowski's rabies program and was part of a large, campus-wide multiple sclerosis research effort. I talked a lot with Jon Sprent, the son of my parasitology professor in Brisbane, who taught me how to do lymph duct cannulation in mice. Penny went back to school, and developed a new career in the area of drug information. I wrote grants, was a member of the immunology circuit, worked with outstanding graduate students and became an established scientist and academic.

My self confidence was such that I made the major mistake of accepting an offer to return to the JCSMR as Head of the Department of Experimental Pathology, intending to build a vital program comparable to that Gordon Ada had been able to create in the early 1970's. However, the era that this was possible had passed, and my decision was made on emotional grounds rather than on the basis of what was actually being offered. The less said about this time (1982–1988) the better, as I am still trying to get the overall experience in perspective. The most positive aspect was my interactions with some excellent colleagues, particularly Jane Allan and Rhodri Ceredig. With the passage of the years, the retirement of many of the tenured staff, the adoption of a more flexible appointment structure, and the return from Denver of Kevin Lafferty as Director, things at the JCSMR are now greatly improved. At the stage that I was there the situation looked hopeless. I decided to move back to a scientific world that I knew I could handle.

The opportunity to rebuild my research career came with the resources offered to me by J.V. Simone, then the Director of St. Jude Children's Research Hospital (SJCRH). I had first visited SJCRH during my swing through the USA in 1974. At that stage it was still a small institution, with a strong virology department headed by Alan Granoff. My contact was via Rob Webster, who had trained with Stephen Fazekas de St. Groth in Frank Fenner's program at the JCSMR and remains a close colleague of the JCSMR virologist, Graeme Laver. Alan and Rob engineered my move to Memphis, and Rob has been an outstanding friend and collaborator. This is a superb, open, research environment, that is extremely well funded. The two problems are that there is too much sunshine, and that we are too far from the Pacific Ocean. Such is life!

My characteristics as a scientist stem from a non-conformist upbringing, a sense of being something of an outsider, and looking for different perceptions in everything from novels, to art to experimental results. I like complexity, and am delighted by the unexpected. Ideas interest me. I was influenced early on by reading Arthur Koestler and Edward de Bono, and more recently by the writings of Karl Popper and Thomas Kuhn. My research career has been highly unconventional, and I have not been a full-time student in the academic sense since I was 22 years old. I have never had a powerful mentor who saw me as the product (or continuation) of his program, a situation that probably helped to determine the outcome of my two attempts to return to Australia. Intellectually, I march to the beat of my own drum and have little interest in competing in "races." There are too few people working in the area of viral pathogenesis and immunity, too little funding, too many problems and too little time.

CELL MEDIATED IMMUNITY IN VIRUS INFECTIONS

Nobel Lecture, December 8, 1996

by

PETER C. DOHERTY

St. Jude Children's Research Hospital, Memphis, Tennessee 38104, USA

INTRODUCTION

Many key concepts concerning the nature of immunity have originated from the very practical need to control virus infections. This year, 1996, has been designated the "Year of the Vaccine" commemorating the 200th anniversary of Edward Jenner's vaccination of James Phipps with cowpox virus, and subsequent challenge with smallpox virus. Insight into the nature of viruses, and how viruses interact with mammalian cells, has evolved since the turn of the century. Our concepts of immunity developed concurrently, beginning with Pasteur's treatment of Joseph Meissner with "aged" rabies virus. Antibody-mediated protection conferred by attenuated, live yellow fever virus won the Nobel Prize for Max Theiler in 1951. Perhaps the most exciting area of immunology when I graduated from the University of Queensland Veterinary School in 1962 was the nature of virus neutralization (1), a topic that is still being resolved with the monoclonal antibody (mAb) technology originated by Georges Köhler and César Milstein (Nobel Prize 1985). Crystallographic analysis of influenza virus neuraminidase-mAb complexes, and variants of neuraminidase selected by mAbs, led to the clear demonstration that Ig molecules normally bind to tertiary structure on proteins (2).

The present award is for our discovery (3–6) from experiments with lymphocytic choriomeningitis virus (LCMV) that the nature of T cell-mediated immunity (CMI) is essentially different, focusing on the recognition of cell-surface major histocompatibility complex (MHC) glycoproteins that have been modified as a consequence of infection. My intention here is to place these findings in historical context, and to develop some aspects to the present day in the context of viral immunity and pathology.

THE AUSTRALIAN SCHOOL OF VIRAL PATHOGENESIS AND IMMUNITY

The strengths in both virology and immunology at the John Curtin School of Medical Research (JCSMR) where we did the LCMV experiments were a direct consequence of themes developed in Australia by F.M. (Sir Mac) Burnet. Over a period of more than 20 years, Sir Mac built the Walter and Eliza Hall Institute (WEHI) in Melbourne into a major international center for virus

(particularly influenza) research. In the late 1940's the only person working there on another virus disease was Frank Fenner, who at Burnet's suggestion studied the epidemiology and pathogenesis of ectromelia (mousepox). Following Burnet's demonstration that ectromelia could be titrated by pock assay on chick chorioallantoic membrane, Fenner did careful quantitative studies of virus distribution in a range of tissues (7). His conclusion was that the virus replicated initially at the site of inoculation in the dermis, then the regional lymph nodes, then generalized via the liver and spleen, and again to the skin, where it produced a smallpox-like rash. He also noted that delayed type "allergy" appeared earlier than serum antibody. In 1949 Fenner became head of the Department of Microbiology in the JCSMR at the Australian National University, which had just been formed largely as a consequence of initiatives taken by Sir Howard (later Lord) Florey (Nobel Prize 1945). Fenner built a very strong center for virology research.

In 1957, having just enunciated the clonal selection theory (8), Burnet abandoned virology and re-directed the work of the WEHI to basic immunology, a focus continued with great distinction by his protégé G.J.V. Nossal. Nossal recruited J.F.A.P. Miller, who established a strong program in T-cell immunology that was to have major influence both locally and on the international scene. Some of the WEHI virologists joined Fenner's department in Canberra. One of the few remaining in Melbourne was G.L. Ada, who switched to immunology. Gordon Ada then moved to Canberra in 1968, replacing Fenner who had become Director of the JCSMR. By the time that I arrived, the microbiology department in Canberra had a strong research effort in immunology, interfacing with the virologists remaining from the Fenner era.

Fenner's ectromelia model was subsequently pursued at the JCSMR in two ways that were to influence our discovery. The first was that C.A. Mims made extensive use of fluorescence microscopy to define patterns of virus growth in different organ sites (9), helping to keep the general area of whole-animal viral pathogenesis alive through the 1960's, when most virologists (following Ender's, Weller and Robbins, Noble Prize 1954) turned their attention to *in vitro* tissue culture systems. Fenner's final contribution to experimental viral immunology was to recruit R.V. Blanden back to Australia from the Trudeau Institute, where he had been working with George Mackaness (a Florey trainee and former JCSMR scientist) on CMI in bacterial infections (10). Bob Blanden applied the approaches that he had developed with Mackaness to the ectromelia model, using both adoptive transfer experiments and depletion with anti-thymocyte serum to show the crucial role of T lymphocytes in controlling the infection (11–13).

I had followed Mim's papers for many years, and returned to Australia from Edinburgh at the end of 1971 to work with him. He had warned me that he might be moving to a Chair in Microbiology in London, and left before the end of 1972. I inherited his laboratory, his technician (Gail Essery) and the LCMV model that had been brought to Canberra some years before by Fritz Lehmann-Grube. Rolf Zinkernagel arrived in 1973, to work with Blan-

den on CMI in Salmonellosis. Due to space requirements, Gordon Ada moved Rolf into the laboratory with me, which is how our collaboration started. Rolf was later to use our experimental data for his Ph.D. thesis but, though I helped him with the writing, the relationship was always as equal colleagues rather than supervisor and student.

EARLY EXPERIMENTS WITH LCMV AND THE DISCOVERY OF MHC RESTRICTION

My initial focus with the LCMV model was to combine contemporary T-cell immunology approaches with the capacity to quantitate inflammatory pathology (14) by counting cells in mouse cerebrospinal fluid (CSF), using a CSF tap technique that I had learned from R.I. Carp (15). This proved to be a very powerful approach (Fig. 2), providing strong support for the theme developed initially by W.P. Rowe and J.E. Hotchin (and later by D. H. Gilden, G.A. Cole and N. Nathanson) that clinical LCM is an immunopathological disease (16–18). The most visually satisfying experiment done at this time was to use Evan's blue injection to show that the virus-immune T-cells were causing a total breakdown of the blood-brain barrier to protein, an experiment that reaches back to the dye studies of Paul Ehrlich (Nobel Prize 1908). Much of this work never appeared in the primary literature, and was only published (3) in an article that G. Möller requested for *Transplantation Reviews*. This also carried the first, tentative description of the MHC-restriction finding.

The formal collaboration with Rolf Zinkernagel started when I suggested that we might look to see if the CSF cells that I was obtaining (Fig. 2) from clinically affected mice could be shown to have cytotoxic T lymphocyte (CTL) activity. Having worked in Lausanne, he was very familiar with the ^{51}Cr release assay that was being used so effectively by J.-C. Cerottini and K.T. Brunner (19) to study alloreactivity and had tried (unsuccessfully) to apply the approach to the *Salmonella* model. The CTL assay had already been used with spleen cells from LCMV-infected mice by M.B.A. Oldstone, O. Marker, M. Volkert and colleagues (20,21). Fortuitously, we were using H-2^k- compatible CBA/H mice and L929 fibroblasts (L cells) as a source of T lymphocytes and virus-infected targets respectively. The first experiment worked beautifully, and we were able to show that the lytic activity was mediated by Thy-1 positive cells (22).

At about this time, the very active group of cellular immunologists that made up Gordon Ada's weekly "bible class" had been discussing recent publications on immune response (Ir) gene effects from B. Benacerraf (Nobel Prize 1980) and D.H. Katz at Harvard , which used a very complex *in vivo* mouse model of T-cell/B cell collaboration (23). We later read of the experiments of E. Shevach and A. Rosenthal at NIH, Bethesda, who were looking at the Ir gene question using *in vitro* stimulation of guinea pig T-cells (24). The paradigm (25) in this East Coast USA immunology axis was that the Ir genes, which had been mapped to the I-region (now MHC class II) between the loci for the "strong" transplantation antigens (H-2K and H-2D, now MHC class I),

encoded all (or part of) the "enigmatic" T-cell receptor (TCR). This interpretation would probably have quickly been revised when it became apparent that the Ir gene product (Ia antigen) was expressed on macrophages (26).

We then saw a report by H. McDevitt, G.R. Mitchell and M.B.A. Oldstone that there was an "Ir gene" effect in the LCM immunopathology model (27). This stimulated us to accumulate all the mouse strains that were available (CBA/H, BALB/c, and C57BL/6J) in Canberra to see if we could correlate the level of CTL activity with H-2 type. The big surprise was that only the H-2^k T-cells were lytic for the MHC compatible, LCMV-infected L cells (3,4). We had no appropriate H-2^b or H-2^k cell lines available, so used primary peritoneal macrophages (28) to provide a source of LCMV-infected targets to demonstrate reciprocal exclusion of T-cell recognition. The next important experiment was with the H-K^kD^d A/J mouse strain (29) , establishing that CTL recognition mapped to H-$2D^d$ and (perhaps) to H-$2K^k$. Later studies on immunodominance hierarchies (30,31) were to show us how lucky we had been to have a system available where both the H-2K and H-2D alleles were associated with a potent LCMV-specific CTL response. The basic findings with LCMV were rapidly replicated for ectromelia by Bob Blanden's student Ian Gardner (32). Bob also used his contacts as a more established immunologist to bring in a range of H-2 recombinant and mutant mouse strains over the next 12–18 months that were used (with both the LCMV and ectromelia models) to map virus-specific CTL effector function to the MHC class I alleles (33,34). The more detailed description of the actual experiments, the preceding history of the MHC and the way that the TCR repertoire develops during ontogeny are being covered in the accompanying article by Rolf Zinkernagel (35).

THE "SINGLE TCR ALTERED SELF" HYPOTHESIS

Right from the time that we made the discovery (3–6), we considered that there might be two possible explanations for our findings (Fig. 1). The first was based on the "TCR" type hypothesis of Katz and Benacerraf, which was formulated as the various dual recognition models proposed through the 1970's and early 1980's. The second was that the virus was in some way modifying the MHC molecule (4–6), either by complexing with it on the cell surface or by inducing some other (perhaps allosteric) change. This idea of an "altered self" molecule recognized by a single TCR seemed reasonable for virus-infected cells, though we were a bit perturbed when the recognition of "minor" histocompatibility antigens was later shown to obey the same rules (36,37). Evidence against the dual recognition model as originally stated (like-like interaction) came from adoptive transfer studies, where we showed that LCMV-primed T-cells from H-2 heterozygous mice ("AxB" F1) which would kill virus (v) infected A and B targeT-cells partitioned into "clonotypes" lytic for A+v alone or B+v alone following further stimulation in irradiated, virus-infected mice of type A or B, respectively (5). Later variants of "two recep-

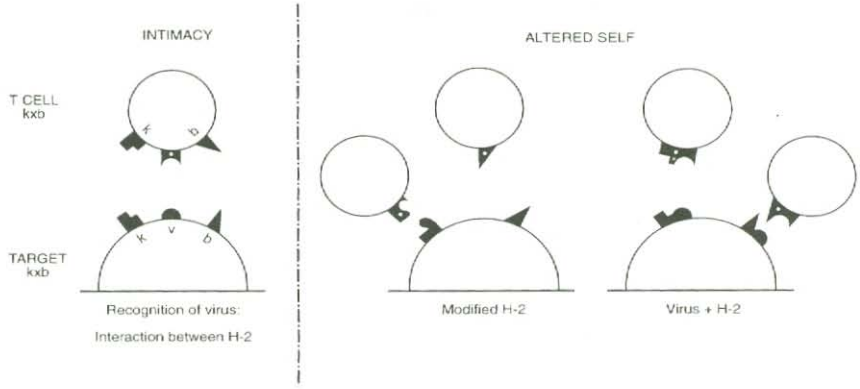

Figure 1. This formulation of the "single T-cell receptor altered self" hypothesis was published in the second article that appeared in *Nature* (4), about a year after the initial experiment showing MHC restriction of CTL activity. In this paper we discredited the "intimacy" model, which argued that there might be some form of "like-like" interaction between H-2 glycoproteins expressed on the T lymphocyte and the target cell. The experiments, and the intellectual context, are dealt with in much greater detail in the accompanying article by Rolf Zinkernagel (35).

tor" models got around this problem by arguing that the postulated recognition molecules seeing A or B molecules were themselves clonally excluded.

The "single TCR-altered self" hypothesis allowed us to assign a biological role to the strong transplantation antigens, and to explain alloreactivity, Ir gene hierarchies, and the extreme polymorphism of the MHC. We believed from the outset that we had found the mechanistic basis of immunological surveillance of self, though we used the term in a somewhat different context (5,6,38,39) from that employed by Lewis Thomas and Burnet in their discussion of susceptibility to cancer (40). Many people did not accept the "altered-self" idea, including some of our colleagues in the JCSMR group (34). It was to remain controversial, and regarded as heretical by most T-cell immunologists for the next 10 years or so (discussed in, 41,42). The "two receptor" models that were generally favoured continued, however, to have the problem that they offered no satisfactory generalization that would accommodate alloreactivity and the Ir gene mechanism.

The resolution of the dilemma came with the finding of A.R. Townsend, A.J. McMichael and colleagues that the class I MHC molecules are presenting viral peptides processed via the "endogenous" pathway (43). This, together with the publication of the 3-dimensional structure of a class I MHC molecule by P. Bjorkman, J. Strominger and D. Wiley (44), and the definition of the two chain TCR by M. Davis, S. Hedrick, T. Mak, J. Allison, P. Marrack, J. Kappler, S. Tonegawa and others (45), put the final nail in the coffin of the various "dual receptor" TCR models. The recent characterization of the tertiary structure of the TCR provides a very satisfactory conclusion to the debate that started with the "altered self" hypothesis (46,47).

THE LCMV MODEL AND T-CELL TARGETING *IN VIVO*

The MHC-restriction of CTL effector function indicated from the outset that the virus-immune T-cell must interact directly with the virus-infected target cell. This had already been obvious for alloreactivity, but no one had suggested that the strong transplantation antigens were in any way involved in the immune response to pathogens. Thinking about CMI in infectious diseases had been very much constrained by experiments with *Listeria monocytogenes*, which emphasized the need for T-cells in macrophage recruitment and activation (10). The numbers and the status (in terms of heat shock-protein mRNA expression) of monocyte/macrophages that localize to the lungs of mice infected with an influenza A virus are, for example, clearly a function of the concurrent $CD4^+$ and/or $CD8^+$ T-cell response (48). Macrophages activated during the T-cell-mediated elimination of LCMV or ectromelia virus can rapidly destroy *L. monocytogenes* (49).

The MHC-restriction findings with *in vitro* CTL assays were quickly translated into the *in vivo* situation. One of the reasons that the LCMV model was so powerful was that we had a very clean *in vivo* system for analysing an inflammatory process. Unlike many viruses, LCMV causes little damage and the levels of "background" cellular infiltration independent of the T-cell response (3,50) are low (Fig. 2). Combining this with the capacity to quantitate

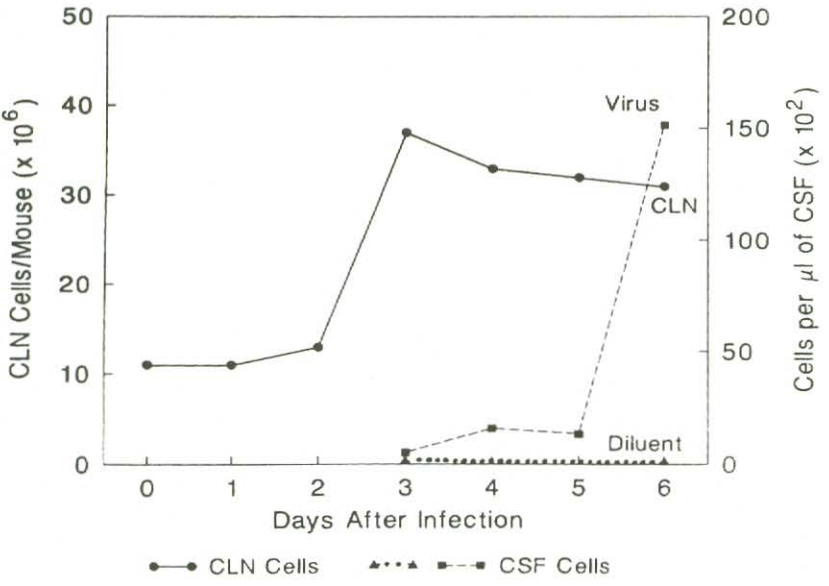

Figure 2. The finding that led to the discovery of MHC-restriction was the demonstration that the inflammatory population recovered from the CSF of mice with clinical LCM contains potent CTL effectors (22). The data shown are from a much later experiment (50), which illustrates the massive influx of cells (dotted line) into the CSF accompanying the onset of CTL activity between days 5 and 6 after infection of the central nervous system. Also shown (solid line) is the preceding increase in cellularity (4-fold) of the cervical lymph nodes (CLN).

very accurately by counting cells in the CSF allowed us to determine rapidly by adoptive transfer experiments that the same rules apply for T-cell recognition *in vitro* and *in vivo*. This was shown for differences in MHC haplotype, particular MHC class I alleles and for H-2 mutant mice (34,51,52).

The interpretation that the T-cell must bind directly *in vivo* to the virus-infected target rather than just to an appropriate antigen-presenting stimulator cell has, however, continued to be subject to challenge. The alternative idea is that cytokines released as a consequence of such interactions are the key effector molecules, an idea that seems to work for the control of a hepatitis virus transgene by interferon-mediated mechanisms (53). So far, this hepatitis model seems to be unique. Adoptively transferred LCMV-immune T-cells only caused severe meningitis in virus-infected, chimeric mice when the appropriate MHC restriction element was present on virus-infected epithelial cells in the brain. Neither secondary stimulation of the virus-specific CTL populations in lymphoid tissue, nor interaction with inflammatory monocyte/macrophages in the site of pathology, were alone sufficient to cause the massive cellular extravasation characteristic of LCM (54–56).

Perhaps the final indication that the LCMV-immune effector CTL must interact directly with virus infected CNS epithelia *in vivo* has come from experiments with perforin -/- mice, which failed to develop the classical symptoms of T-cell-mediated immunopathology (57). Cytokine-mediated mechanisms may, however, be responsible for the chronic wasting disease (58–60) that develops in LCMV-infected CD8 "knockout"(-/-) mice and $CD8^+$ T-cell-deficient mice (61) that are -/- for β2-microglobulin (β2-m), the light chain of the MHC class I glycoproteins. Both these genetically- manipulated mouse strains mice are unable to clear LCMV, leading to a persistent confrontation between virus-infected stimulators and the immune $CD4^+$ population. The studies with LCMV, and other experiments with respiratory viruses (see below), indicate that the effector mechanisms used by $CD4^+$ and $CD8^+$ T-cells to deal with viruses are fundamentally different.

THE NON-SELF COMPONENT: ANALYSIS WITH RESPIRATORY VIRUSES

The division of labor in the LCMV experiments at the JCSMR was that Rolf Zinkernagel did the *in vitro* CTL analysis, while I was responsible for the *in vivo* immunopathology experiments and for writing the manuscripts with, of course, the benefit of his immediate and constant critique. I thus used respiratory infection with the parainfluenza type 1 virus, Sendai virus, to develop a facility with the CTL assay (62), and to confirm that MHC restriction was true for more than LCMV and the poxviruses (27, 32, 63). I returned to the Sendai model (64, 65) years later at St Jude Children's Research Hospital, principally because of the molecular virology expertise available in the laboratory of A. Portner.

When I moved to the Wistar Institute in mid-1975, it quickly became apparent that the animal facility was not sufficiently secure to allow extensive experimentation with LCMV, which can easily induce clinically "silent" infections

We thought that, by using serologically distinct variants such as the H1N1 and H3N2 viruses which do not cross-neutralize, we would be able to map CTL activity to H or N, both of which are expressed on the plasma membrane of the virus-infected cell. The aim then was to use "drifted" variants to map fine specificity. The initial experiments were done by my first graduate student, R.B. Effros and were later pursued by my second student J.R. Bennink. Much to our surprise, Rita found that the CTL response for these two viruses was almost totally cross-reactive (67,68). Though we were unaware of it at the time, similar findings were being recorded in B.A. (Ita) Askonas' laboratory at the National Institute for Medical Research in London (69). Our findings with LCMV had induced Ita to drop her long-term studies of the B cell responses to concentrate on virus-specific T-cell mediated immunity. Her laboratory was to make an enormous contribution over the next 10 years.

Though we failed at this stage to define the nature of the antigenic entity recognized by the influenza specific CTL, these early experiments further supported the conclusion from the MHC restriction analysis that the specificity profiles of T and B lymphocytes are fundamentally different (34,70). In addition, we quickly established that exposure to any one influenza A virus will prime T-cell memory for a secondary response (Fig. 4) to any other in-

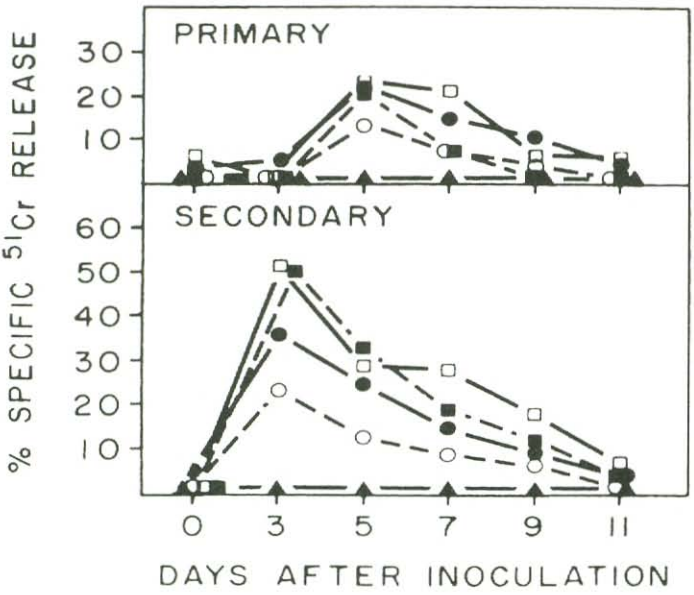

Figure 4. Immunologically naive (primary) CBA/J (H-2^k) mice, or mice that had been infected with the PR8 (H1N1) influenza A virus 52 days previously (secondary), were challenged with the HKx31 (H3N2) influenza A virus (68). Spleen cells were assayed (100:1) at the intervals shown on H-2 compatible targets infected with a range of influenza A viruses, or with an influenza B virus (triangles). Both the enhanced kinetics and potency of the recall response are very apparent. Later experiments with HKx31 infection of C57BL/6J (H-2^b) mice have shown very little CTL activity in lymphoid tissue following primary exposure (98).

fluenza A virus (68,71). This meant that infection with a "drifted" or "shifted" influenza A virus in an adult person is likely to be proceeding in the context of a secondary CTL response and a primary humoral response. The albeit imperfect protection conferred by influenza-specific memory T-cells (72–74) probably explains why young to middle-aged adults are generally much less likely to die from influenza than are small children or elderly people. These results were quickly confirmed for other viruses which had, after the influenza experiments, also been found to induce CTL specificity profiles that were not predicted by serological analysis (75).

Other significant experiments that were done with the influenza model at about this time were the extension of MHC-restriction to the rat model (76) and, most importantly, the clear demonstration by A.J. McMichael (from the Askonas laboratory) that this is also true for humans (77). Further pursuit of this unpredicted cross-reactivity for the influenza viruses led to A. Townsend's (again from the Askonas laboratory) seminal finding (43,78) that MHC class I restricted T-cells are responding to a peptide derived from the influenza nucleoprotein (NP), which finally explained the molecular mechanism underlying our "altered self" hypothesis (Fig. 1) and started the whole field of antigen processing in the "endogenous" compartment. Analysis at the Wistar Institute by Jack Bennink and J.R. Yewdell with recombinant vaccinia viruses also showed that much of the CTL recognition in the influenza model is directed at internal components of the virus (79).

Latterly, the non-lethal respiratory infections have emerged as the experimental system of choice for analysing localised, transient viral infections (80–83). These models have the advantage that it is easy to obtain both the regional lymphoid tissue, and the inflammatory cells from the pneumonic lung by bronchoalveolar lavage (BAL). There is also no obvious way that either the virus or the viral genome can persist after infection with such negative strand RNA viruses (84), which is important when we are considering the difficult area of T-cell memory (85).

Some recent experiments addressed again the question of T-cell targeting *in vivo* that we had analysed earlier with the LCMV model (Fig. 2). Using adoptive transfer protocols and bone marrow radiation chimeras made between β2-m -/- and +/+ mice, we showed that the clearance of Sendai virus depends on the $CD8^+$ effector T-cells interacting directly with virus-infected, MHC class I^+ respiratory epithelium (86). The opposite conclusion was reached concerning the capacity of $CD4^+$ T-cells (87–89) to control influenza virus infection in the absence of the $CD8^-$ subset: expression of the MHC class II glycoproteins that target the $CD4^+$ T-cells is not essential in the respiratory tract (90). More recent experiments performed by David Topham are confirming the theme developed by Walter Gerhard (91) that complete clearance of the virus by $CD4^+$ T-cells requires the concurrent presence of antibody-forming cells.

QUANTITATING INFLAMMATION AND T-CELL-MEDIATED IMMUNITY

The essence of the virology-based approach to pathogenesis has always been quantitation, a theme that was started by Mac Burnet with his various plaque assays and continued by Cedric Mims for the fluorescence microscopic localization of virus-infected cells in different organ sites (9). Measuring the inflammatory process that is the consequence of CMI has, however, traditionally been (at best) semi-quantitative, The classical delayed-type hypersensitivity foot-pad swelling assay is a very blunt instrument.

Analysing inflammation

My early experience in ultrastructural pathology and immunocytochemistry (92,93) resulted in an intense curiosity concerning the nature of the lymphocyte populations that invade into tissue sites of virus growth (Fig. 5). The

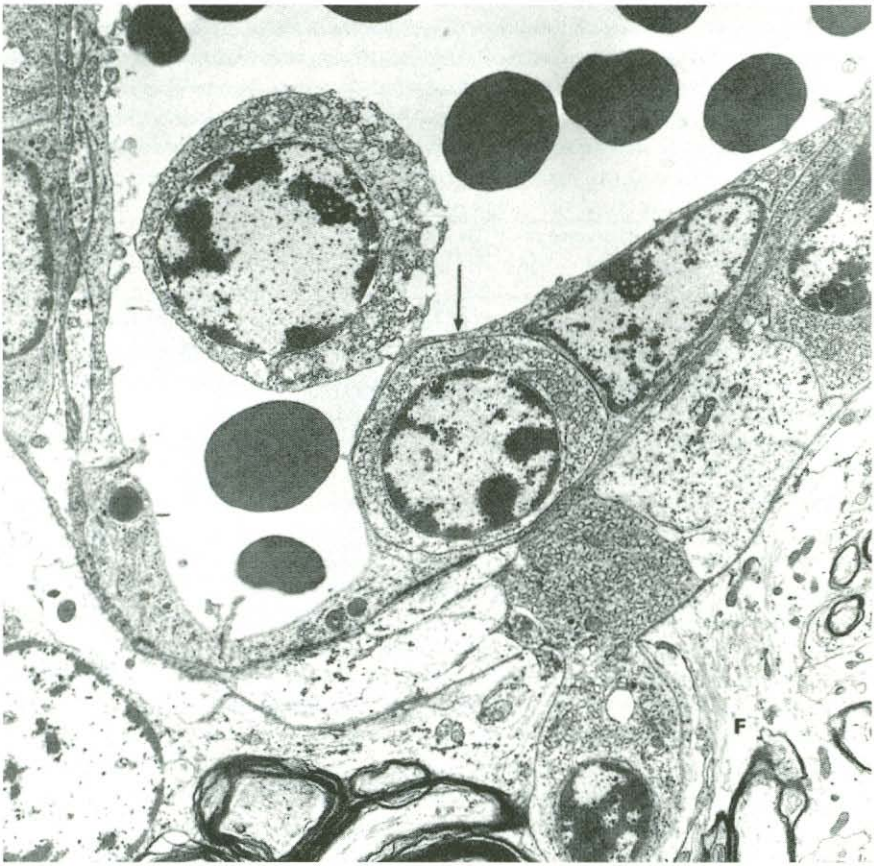

Figure 5. My interest in the nature of virus-specific CMI was stimulated by the experimental studies of louping-ill encephalomyelitis that Hugh Reid and I did with sheep at the Moredun Research Institute, Edinburgh (92–94). The electron micrograph shows cells of undetermined identity extravasating from a capillary into the brain parenchyma. Lymphocyte invasion into tissue sites of virus growth is the central feature of CMI.

experiments that H.W. Reid and I did with the sheep louping-ill (tick-borne flavivirus) model at the Moredun Research Institute in Edinburgh led to the conclusion that antibody forming cells were extravasating into the CNS and were responsible for a substantial, *in situ* virus-specific Ig response (92, 94). Much later studies by D.E. Griffin have shown that such locally-produced antibody controls Sindbis virus infection of mouse brain (95).

The dual frustrations with morphological approaches are the lack of functional analysis and the difficulty of quantitation, though my current perception is that there is a great need to focus more attention on the anatomical localisation of events in immunity that is only possible with microscopy-based protocols. My early attempts at quantitating inflammatory pathology caused me to seize on the CSF tap technique that Richard Carp (15) had developed to look for enzymatic activity in CSF from scrapie-infected mouse brain and apply it to the study of viral meningitis (Fig. 2). Experiments with this simple model induced us to develop the LCMV-specific CTL assay, and allowed the later *in vivo* dissection of MHC-restricted T-cell effector function. The capacity to measure statistically significant differences for quite small effects enabled us to operate with unique sensitivity in the *in vivo* situation (3, 34). However, because the approach was technically demanding and only really useful with the LCMV model, nobody else adopted this analytical system. The other, great advantage of being able to obtain inflammatory cells directly from the CSF (or from the lung by the BAL) is that the lymphocytes do not need to be freed from tissue by enzymatic techniques. This has been of great benefit for later experiments concentrating on flow cytometric analysis and FACS separation to define functional T-cell subsets (56, 96, 97), experiments that were first started for LCMV (with R. Ceredig in Canberra) and have been a major focus of the respiratory infection studies (98,99) in Memphis (Fig. 3).

Measuring the T-cell response

Though the *in vitro* ^{51}Cr release CTL assay provides numbers, the precursor (p) frequencies that give comparable levels of lytic activity (both during the course of *in vivo* infection or as a consequence of *in vitro* culture) can vary enormously (100,101). The potency of the $CD8^+$ CTL set in the BAL population from mice with influenza pneumonia is, for example, apparently equivalent by day 10 after infection for $CD4^+$ T-cell deficient MHC class II -/- mice and for MHC class II +/+ controls (101,102). However, the CTLp numbers in both the BAL and regional lymph nodes are much lower for the MHC class II -/- mice, and virus clearance may be slightly delayed. The much smaller CTLp pool in the MHC class II -/- mice is almost totally consumed to provide the level of CTL effector function needed to deal with the infection. A conclusion based on the CTL data alone that the absence of the $CD4^-$ set does not greatly modify the magnitude of the $CD8^+$ T-cell response would thus be misleading. Careful, kinetic analysis is essential in these *in vivo* pathogenesis studies.

We first realised this when we tried to quantitate the Ir gene hierarchy that we discovered for the MHC class I alleles $H\text{-}2K^k$, $H\text{-}2K^b$ and $H\text{-}2D^b$ with the in-

fluenza A viruses (30,31). The situation here is that the CTL response associated with H-2D^b +NP peptide is dominant in mice that express H-2K^b, but apparently absent when H-2K^k is present. The same thing happens with vaccinia virus. Jack Bennink and I tried hard to work out the underlying mechanism, using thoracic duct cannulation and negative selection *in vivo* to remove the alloreactive T-cells (103), a very tedious protocol that we learned from J.A. Sprent. The lack of any useful resolution is a good example of the fact that (though important insights can be generated) molecular mechanisms cannot ultimately be worked out by biological experiments. My current guess is that H-2K^k must greatly out-compete H-2D^b for binding some constant molecule involved in the MHC class I antigen processing pathway (104), though not to the extent that H-2D^b +NP peptide is no longer present at sufficient levels to be recognized by the appropriate effector CTL on an H-K^{k}D^b targeT-cell.

When J. A. Owen joined the laboratory in Philadelphia she took on the task of developing a quantitative limiting dilution analysis (LDA) for determining influenza virus-specific CTLp frequencies (105), an approach that has been central to my research program over the subsequent years. Judy Owen and Michelle Allouche then applied this technique to the H-2K^{k}D^b hierarchy problem and found that, for mice that had been primed a month or more previously, the CTLp numbers specific for influenza virus components expressed in the context of H-2K^k and H-2D^b may be fairly comparable (106). Recent experiments with this experimental system by R.A. Tripp in Memphis indicate that the reason that the H-2K^k-restricted CTL effectors are preferentially generated is that this component of the response emerges more quickly.

The rate problem in immunology

The preceding is a good example of one of the major difficulties that we face in developing a detailed understanding of immunity. How do we measure the true kinetics of responses in terms of lymphocyte generation and loss, and in the context of transit times through the various tissue sites that are sampled? A major insight developed from studies with superantigens was that the majority of the T-cells that proliferate following such stimulation die as a consequence (107,108). We initially thought that this was not the case for "conventional" antigens, such as influenza virus or Sendai virus epitopes, largely because sequential LDA studies indicated a remarkable constancy (Fig. 6) in CTLp frequencies (1:2–3,000 cells in a lymph node) from about day 7 after infection through to long-term memory (85,99,109). This was somewhat different from the situation that was concurrently being described for LDA studies with LCMV by Rafi Ahmed (110), but we agreed that the difference was probably due to the fact that systemic LCMV infection undoubtedly gives a much greater antigenic stimulus.

The thymidine analogue bromodeoxyuridine (BrDU) incorporates into the DNA of multiplying cells and causes the formation of toxic thymidine dimers following exposure to bright light, a protocol that was used many years ago to "suicide" *in vitro*-stimulated T-cells (111). Ralph Tripp found that load-

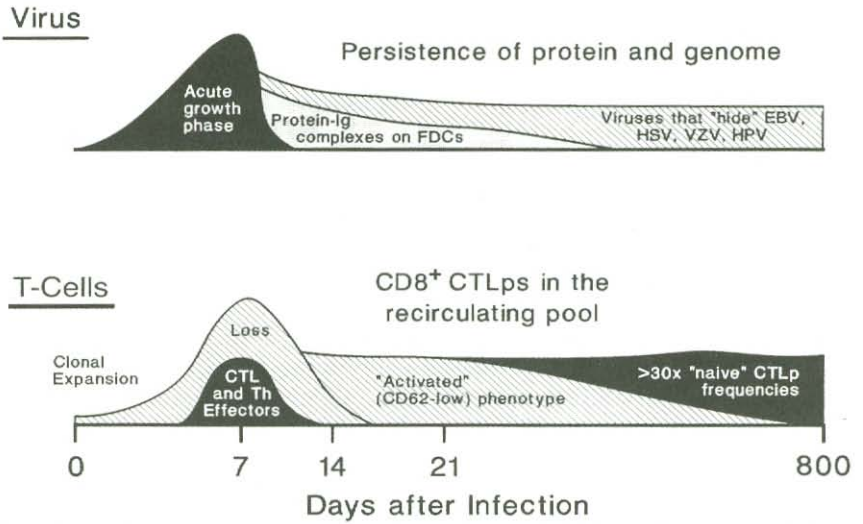

Figure 6. *Virus.* Replication of the negative strand RNA viruses is generally terminated by the immune response within 7–10 days (84,118), with the only trace of the infectious agent generally being the long-term maintenance of protein-Ig complexes on the surface of follicular dendritic cells (110). These do not seem to be necessary for the maintenance of influenza-specific $CD4^+$ T-cell memory (119), but are probably essential for B cell memory. Other pathogens, such as the herpes viruses, may persist in a latent form in neurons or B lymphocytes and periodically reactivate into lytic phase (120).

T-cells. Clonal expansion of the $CD4^+$ THp and $CD8^+$ CTLp during the acute phase of the response is greatly in excess of the numbers required to generate the cytokine-producing TH or effector CTL populations that deal with the infection. Many of the CTLp, in particular, either die or are excreted, and CTLp frequencies may remain remarkably stable thereafter for the life of a laboratory mouse. However, the activation phenotype of these T-cells may (as first shown by Sam Hou, 121) change with time.

ing proliferating T-cells with BrDU *in vivo* led to the same effect when the lymphocytes were exposed to the laser beam of the flow cytometer (112). Use of this protocol indicates that the CTLp numbers generated during the acute phase of the response to an influenza A virus are more than 10-fold in excess of what would be expected from estimates of CTLp frequencies (Fig. 6). Some of these T-cells will give rise to the CTL effectors that are found in the virus-infected respiratory tract, but it seems that many others are lost. Measuring a virus specific $CD8^+$ T-cell response by effector CTL assays takes no account of the CTLp numbers that are generated. However, the more extensive quantitation of CTLp frequencies shows only the balance between CTLp generation and loss, and does not give a true estimate of the real magnitude of an acute host response. This is less a problem with T-cell memory, where the cell populations are turning over at a much slower rate (113).

Homeostasis: on the edge of chaos?

The above experience, together with trying to understand the nature of T-cell memory, has left me with the conviction that the major challenge for cellular immunology is to develop a much clearer understanding of lymphocyte ho-

meostasis (114). In the past, many of us would have followed Burnet's insight that the balance between responsiveness and tolerance is the key question, but recent studies (particularly with transgenic mice) have clarified the issues, blurred the distinction and made the tolerance/response mantra less compelling (115). It could be argued that tolerance/response is simply a more refined statement of the homeostasis problem, but language conditions, perceptions and defining the area in this way focuses attention solely towards antigen and away from the more physiological mechanisms and quantitative considerations that are also likely to be enormously important.

An obsession with homeostasis is dangerous territory, as it has led in the past to some of the least useful and expensive efforts in immunology. Even so, it may be time for our experimentally- based discipline to take greater cognizance of the contribution that can be made by theoreticians, particularly those who are more mathematically inclined. A good example of the way that quantitative analysis can contribute to the development of better predictive models has been provided by recent determinations of the numbers of virus infected cells (116) in people infected with the human immunodeficiency virus (HIV). Influenza virus-specific memory $CD8^+$ T-cells seem to show a remarkable constancy in frequency over a very long period (Fig. 6). Is this an example (117) of a chaotic system? Now that we are starting to generate useful numbers, we need the help of people whose business is numbers.

CONCLUSIONS

The need to deal with pathogens has driven the evolution of the vertebrate immune system, so it should not be surprising that experiments with infectious agents have often illuminated key elements of the underlying mechanisms. The discovery of MHC restriction and the development of the single TCR "altered" self hypothesis is a classical example of how interfacing different scientific disciplines and ways of thinking, an inevitable consequence of studying viral pathogenesis, can lead to a major paradigm shift. The progress that was made over the subsequent 10 years, and the intellectual directions that were followed as a consequence of this simple, operational hypothesis tell us a great deal about the power of ideas. This is not to decry the importance of technology. Our success depended totally on the availability of the ^{51}Cr release CTL assay and inbred mouse strains, both of which had been developed to study alloreactivity. The experiments were done in the context of an experimental framework that was being used to dissect T-cell responsiveness, the immunopathology of LCMV infection, and the nature of CMI to *L. monocytogenes* and ectromelia virus. The local intellectual environment was strong, and heavily focused on the then current forefront of immunology research. Being isolated in those pre-FAX and e-mail days in Australia was a great advantage, as it allowed time to discuss and to think things through. We had outspoken and informed local critics, the freedom and resources to pursue our own ideas and were given full credit for our efforts. Those of us who

have senior roles in science need to do everything possible to ensure that comparable opportunities and environments remain available to young scientists.

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4. Zinkernagel, R.M., and P.C. Doherty. 1974. Restriction of in vitro T-cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. *Nature* 248:701.
5. Zinkernagel, R. M. and P. C. Doherty. 1974. Immunological surveillance against altered self components by sensitised T lymphocytes in lymphocytic choriomeningitis. *Nature* 251:547.
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11. Blanden, R. V. 1970. Mechanisms of recovery from a generalized viral infection: mousepox. I. The effects of anti-thymocyte serum. *J. Exp. Med.* 132:1035.
12. Blanden, R. V. 1971. Mechanisms of recovery from a generalized viral infection: mousepox. II. Passive transfer of recovery mechanisms with immune lymphoid cells. *J. Exp. Med.* 133:1074.
13. Blanden, R. V. 1971. Mechanisms of recovery from a generalized viral infection: mousepox. 3. Regression infectious foci. *J. Exp. Med.* 133:1090.
14. Doherty, P. C. 1973. Quantitative studies of the inflammatory process in fatal viral meningoencephalitis. *Am. J. Pathol.* 73:607.
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36. Bevan, M. J. 1975. The major histocompatibility complex determines susceptibility to cytotoxic T-cells directed against minor histocompatibility antigens. *J. Exp. Med.* 142:1349.
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38. Doherty, P. C. and R. M. Zinkernagel. 1975. Enhanced immunological surveillance in

1984. Cytotoxic T-cell recognition of the influenza nucleoprotein and hemagglutinin expressed in transfected mouse L cells. *Cell* 39:13.
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81. Openshaw, P. J. 1989. Flow cytometric analysis of pulmonary lymphocytes from mice infected with respiratory syncytial virus. *Clin. Exp. Immunol.* 75:324.
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83. Doherty, P. C. 1996. Immune response to viruses. p 535 in, *Clinical Immunology, Principles and Practice.* R. R. Rich, T. A. Fleischer, B. D. Schwartz, W. T. Shearer, and W. Strober eds, Mosby, St Louis.
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87. Eichelberger, M., W. Allan, M. Zijlstra, R. Jaenisch, and P. C. Doherty. 1991. Clearance of influenza virus respiratory infection in mice lacking class I major histocompatibility complex-restricted $CD8^+$ T-cells. *J. Exp. Med.* 174:875.
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93. Doherty, P. C. and H. W. Reid. 1971. Louping-ill encephalomyelitis in the sheep. II. Distribution of virus and lesions in nervous tissue. *J. Comp. Pathol.* 81:531.
94. Reid, H. W., P. C. Doherty, and A. M. Dawson. 1971. Louping-ill encephalomyelitis in the sheep. 3. Immunoglobulins in cerebrospinal fluid. *J. Comp. Pathol.* 81:537.
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96. Ceredig, R., J. E. Allan, Z. Tabi, F. Lynch, and P. C. Doherty. 1987. Phenotypic analysis of the inflammatory exudate in murine lymphocytic choriomeningitis. *J. Exp. Med.* 165:1539.
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98. Allan, W., Z. Tabi, A. Cleary, and P. C. Doherty. 1990. Cellular events in the lymph node and lung of mice with influenza. Consequences of depleting $CD4^+$ T-cells. *J. Immunol.* 144:3980.
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and proliferation of $CD8^+$ T-cells in respiratory virus infections. *J. Immunol.* 154:6013.
100. Hou, S., L. Hyland, K. W. Ryan, A. Portner, and P. C. Doherty. 1994. Virus-specific CD8+ T-cell memory determined by clonal burst size. *Nature.* 369:652.
101. Tripp, R. A., S. R. Sarawar, and P. C. Doherty. 1995. Characteristics of the influenza virus-specific $CD8^+$ T-cell response in mice homozygous for disruption of the $H\text{-}21A^b$ gene. *J. Immunol.* 155:2955.
102. Bodmer, H., G. Obert, S. Chan, C. Benoist, and D. Mathis. 1993. Environmental modulation of the autonomy of cytotoxic T lymphocytes. *Eur. J. Immunol.* 23:1649.
103. Bennink, J. R. and P. C. Doherty. 1979. Reciprocal stimulation of negatively selected high-responder and low- responder T-cells in virus-infected recipients. *Proc. Natl. Acad. Sci. U. S. A.* 76:3482.
104. Androwlewicz, M. J., and P. Creswell. 1996. How selective is the transporter associated with antigen processing? *Immunity* 5:1
105. Owen, J. A., M. Allouche, and P. C. Doherty. 1982. Limiting dilution analysis of the specificity of influenza-immune cytotoxic T-cells. *Cell. Immunol.* 67:49.
106. Allouche, M., J. A. Owen, and P. C. Doherty. 1982. Limit-dilution analysis of weak influenza-immune T-cell responses associated with $H\text{-}2K^b$ and $H\text{-}2D^b$. *J. Immunol.* 129:689.
107. Webb, S., C. Morris, and J. Sprent. 1990. Extrathymic tolerance of mature T-cells: clonal elimination as a consequence of immunity. *Cell* 63:1249.
108. McCormack, J. E., J. E. Callahan, J. Kappler, and P. C. Marrack. 1993. Profound deletion of mature T-cells in vivo by chronic exposure to exogenous superantigen. *J. Immunol.* 150:3785.
109. Tripp, R. A., S. Hou, and P. C. Doherty. 1995. Temporal loss of the activated L-selectin-low phenotype for virus-specific $CD8^+$ memory T-cells. *J. Immunol.* 154:5870.
110. Ahmed, R. and D. Gray. 1996. Immunological memory and protective immunity: Understanding their relation. *Science* 272:54.
111. Paul, W. E., E. M. Shevach, S. Pickeral, D. W. Thomas, and A. S. Rosenthal. 1977. Independent populations of primed F1 guinea pig T lymphocytes respond to antigen-pulsed parental peritoneal exudate cells. *J. Exp. Med.* 145:618.
112. Tripp, R. A., J. M. Lahti, and P. C. Doherty. 1995. Laser light suicide of proliferating virus-specific CD8+ T-cells in an in vivo response. *J. Immunol.* 155:3719.
113. Tough, D. F. and J. Sprent. 1994. Turnover of naive- and memory-phenotype T-cells. *J. Exp. Med.* 179:1127.
114. Freitas, A. A. and B. B. Rocha. 1993. Lymphocyte lifespans: homeostasis, selection and competition. *Immunol. Today* 14:25.
115. Matzinger, P. 1994. Tolerance, danger, and the extended family. *Annu. Rev. Immunol.* 12:991.
116. Perelson, A. S., A. U. Neumann, M. Markowit, J. M. Leonard, and D. D. Ho. 1996. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span and viral generation time. *Science* 271:1582.
117. Waldrop, M. W. 1992. "*Complexity: the emerging science at the edge of chaos.*" Simon and Shuster, New York.
118. Doherty, P. C. 1995. Immunity to viruses. *The Immunologist* 3:231.
119. Topham, D. J., R. A. Tripp, A-M. Hamilton-Easton, S. R. Sarawar, and P. C. Doherty. 1996. Quantitative analysis of influenza virus-specific $CD4^+$ T-cell memory in the absence of B cells and Ig. *J. Immunol.* 157:2947.
120. Cardin, R. D., J. W. Brooks, S. R. Sarawar, and P.C. Doherty. 1996. Progressive loss of $CD8^+$ T-cell-mediated control of a -herpesvirus in the absence of $CD4^+$ T-cells. *J. Exp. Med.* 184:863.
121. Hou, S. and P. C. Doherty. 1993. Partitioning of responder $CD8^+$ T-cells in lymph node and lung of mice with Sendai virus pneumonia by LECAM-1 and CD45RB phenotype. *J. Immunol.* 150:5494.

CURRICULUM VITAE

DE

PETER CHARLES DOHERTY

October 15, 1940; Australia
Department of Immunology
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105-2794
Telephone: (901) 495-3470
Fax: (901) 495-3107

ACADEMIC DEGREES

BVSc	1962	University of Queensland, Australia
MVSc	1966	University of Queensland, Australia
PhD	1970	University of Edinburgh, Scotland
DVSc (hc)	1995	University of Queensland, Australia
DSc (hc)	1996	Australia National University
DSc (hc)	1997	University o Edinburgh, Scotland
DSc (hc)	1997	Tufts University, Medford, Maryland
DMSc (hc)	1998	Rhodes College, Memphis, Tennessee
DPh (hc)	1998	Kyorin University
DSc (hc)	1998	Warsaw Agricultural University
DSc (hc)	1999	Latrobe University, Melbourne, Australia

PROFESSIONAL APPOINTMENTS

1963-67	Veterinary Officer, Animal Research Institute, Brisbane, Australia
1967-71	Scientific Officer, Senior Scientific Officer, Department of Experimental Pathology, Moredun Research Institute, Edinburgh, Scotland
1972-75	Postdoctoral Fellow (6 months), Research Fellow, Department of Microbiology, The John Curtin School of Medical Research, Australian National University, Canberra
1975-82	Associate Professor/Professor, The Wistar Institute, Philadelphia, Pennsylvania
1982-88	Professor and Head, Department of Experimental Pathology, The John Curtin School of Medical Research, Australian National University, Canberra
1988-	Chairman, Department of Immunology (Michael F. Tamer Chair of Biomedical Research), St. Jude Children's Research Hospital, Memphis, Tennessee
1992-	Adjunct Professor, Departments of Pathology and Pediatrics, University of Tennessee, Memphis, College of Medicine, Memphis, Tennessee

PROFESSIONAL SOCIETY MEMBERSHIPS

American Association of Immunologists
Australian Society for Immunology
American Association of Pathologists
Neuroimmunology Society
American Association of Veterinary Immunologists

LICENSURE

Royal College of Veterinary Surgeons, London, England

RESEARCH INTERESTS

Cell-mediated immunity
T cell recognition and repertoire
Immunological tolerance
Viral immunology
Immunopathology
Immune memory

HONORS AND AWARDS

Royal College of Veterinary Surgeons, 1999
Royal Australian College of Physicians, 1998
Royal Australian College of Pathologists, 1998
The College of Physicians of Philadelphia, 1998
Nafional Academy of Science, USA, 1998
Member, Australia's 100 Living National Treasures, Australia, 1997
Honorary Fellowship, Australian College of Veterinary Scientists, Australia, 1997
Australia Day Honours List, Australia, 1997
Nobel Prize for Physiology or Medicine, 1996
Albert Lasker Basic Medical Research Award, USA, 1995
Alumnus of the Year, University of Queensland, 1993
Fellow of the Royal Society of London (FRS), 1987
Gairdner International Award for Medical Science, Canada, 1986
Paul Ehrlich Prize, Germany, 1983
Fellowship of the Australian Academy of Science (FAA), 1983

GRANT SUPPORT

NIAID, 5 R37 AI 29579-10, Cell Mediated Immunity in Influenza, 04/01/95 - 03/31/00, -06 $149,927.00, -07 $155,922.10, -$175,393, 30% effort, Peter Doherty, Principal Investigator.

NIAID, 5 RO1 AI38359-04, T Cell memory to Respiratory Viruses, 04/01/96 - 03/31/01, $121,232, 20% effort Peter Doherty, Principal Investigator.

NIAID, 1 PO1 AI45142-01, P2, Single Cell analysis of a Multi-Tier AIDS Vaccine, $155,962, 10% effort, Peter Doherty, Principal Investigator.

NCI, 2 P30 CA 21765-22, Cancer Center Support Grant (CCSG) - Composite, 03/02/97 - 02/28/02, -20 $2,661,958.00, -21 $2,528,085.00, -22 $2,585,844.00, -23 $2,645,328.00, -24, $2,706,599.00, TOTAL YEARS $13,127,814.00, Arthur W. Nienhuis, Principal Investigator.

CORE Major Program Leaders, 03/01/97 - 02/28/02, -22 $111,565 8% effort, 5. 10 % salary, Arthur Nienhuis, Principal Investigator.

PUBLICACIONS CIENTÍFIQUES

ORIGINAL ARTICLES (10 MOST CURRENT OF 231 PAPERS)

1. Stevenson, P. G., Doherty, P. C. «Non-antigen-specific B-cell activation following murine gammaherpesvirus infection is CD4~independent in vitro but CD4 dependent in vivo». *J. Virol.* 73: 1075-1079, 1999.

2. Flynn, K. J., Riberdy, J. M., Christensen, J. P., Altman, J. D., Doherty, P. C. «In vivo proliferation of naïve and memory influenza specific CD8 + T cells». *Proc. Natl. Acad. Sci. USA* 96: 8597-8602, 1999.

3. Stevenson, P. G., Belz, G. T., Castrucci, M. R., Altman, J. D., Doherty, P. C. «A y-herpesvirus sneaks through a CD8' T cell response primed to a lytic phase epitope». *Proc. Natl. Acad. Sci. USA* 96: 9281-9286, 1999.

4. Hamilton-Easton, A. M., Christensen, J. P., Doherty, P. C. «Turnover of T cells in murine gammaherpesvirus 68- infected mice». *J. Virol.* 73: 7866-7869, 1999.

5. Brooks, J. W., Hamilton-Easton, A. M., Christensen, J. P., Cardin, R. D., Hardy, C. L., Doherty, P. C. «Requirement for a CD40 ligand-mediated interaction between CD4+ T cells and B cells in an infectious mononucleosis-like syndrome». *J. Virol.* 73: 9650-9654, 1999.

6. Brown, M. P., Nosaka, T., Tripp, R. A., Brooks, J., van Deursen, J. M. A., Brenner, M. K., Doherty, P. C., Ihle, J. N. «Restoration of early lymphoid proliferation and immune function in Jak3-deficient mice by IL-3». *Blood* 94: 1906-1914, 1999.

7. Belz, G. T., Stevenson, P. G., Castrucci, M. R., Altman, J. D., Doherty, P. C. «Post exposure vaccination massively increases the prevalence of gamma-Herpesvirus-specific CD8+ T cells but confers minimal survival advantage on CD4-deficient mice». *Proc. Natl. Acad. Sci. USA* 97: 2725-2730, 2000.

8. Doherty, P. C., Christensen, J. P. «Accessing complexity: The dynamics of virus-specific T cell responses». *Ann. Rev. Immunol.* 18: 561-592, 2000.

9. Sangster, M. Y., Topham, D. J., D'Costa, S. D., Cardin, R. D., Marion, T. N., Myers, L. K., Doherty, P. C. «Analysis of the virus-specific and nonspecific B cell response to a persistent B-lymphotropic gamma-herpesvirus». *J. Immunol.* 164: 1820-1828, 2000.

10. Belz, G. T., Xie, W., Altman, J. D., Doherty, P. C. «A previously unrecognized H-2D^{b}-restricted peptide prominent in the primary influenza A virus-specific CD8+ T cell response is much less apparent following secondary challenge». *J. Virol.* 74: 3486-3493, 2000.

PUBLISHED INTERVIEW

Suzanne Vogle, «Discoveries Down Under». *Journal of NIH Research* (Re: Zinkernagel, R. M., Doherty, P. C. «Restriction of in vitro T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semi-allogeneic system». *Nature* [Lond] 248: 701-702, 1974) *Journal of NIH Research* 3: 68-72, 1991.

BOOK CHAPTERS AND REVIEW ARTICLES (10 MOST CURRENT OF 88 BOOK CHAPTERS)

1 DOHERTY, P. C. «The new numerology of immunity mediated by virus-specific CD8+ T cells». *Curr. Opin. Microbiol.* 1: 419-422, 1998.

2. WEBSTER, R. G., DOHERTY, P. C., TRIPP, R. A. «Influenza virus (orthomyxovirus) infection and immunity». In: Delves, P. J., ed. 2nd Edition. *Encyclopedia of Immunology*. Vol. 3. San Diego, California: Academic Press Publishers, 1998. P. 1385-1387.

3. DOHERTY, P. C., BELZ, G., FLYNN, K. J. «The continuing revolution in virus-specific CD8+ T cell-mediated immunity». *The Immunologist* 6: 173-177, 1998.

4. RIBERDY, J., DOHERTY, P. C. «MHC, functions of». In: Delves, P. J., Roitt, I. M., eds. 2nd Edition. *Encyclopedia of Immunology*, San Diego, California: Academic Press Publishers, 1998. P. 1703-1706

5. DOHERTY, P. C. «Hamessing science to solve global poverty and hunger: Flexibility and freedom of action are essential for rapid progress». *1998 Sir John Crawford Memorial Lectures*. Washington, DC: Consultative Group on International Agricultural Research (CGIAR) Secretariat Publisher, 1998. P. 1- 13.

6. DOHERTY, P. C. «Living in the Burnet Lineage». *Immunol. Cell. Biol.* 77: 167-176, 1999.

7. DOHERTY, P. C. «Viral studies illuminate the nature of immunity». *ASM News* 65: 340-344, 1999.
8. DOHERTY, P. C. «The terminology problem for T cells: a discussion paper». *Phil. Trans. R. Soc. Lond. B.* 355: 361-362, 2000.

9. RIBERDY, J., DOHERTY, P. C. «Cell mediated immune response». In: Webster, R. G., Granoff, A., eds. 2nd Edition. *Encyclopedia of Virology*, Academic Press Publisher, 1999. P. 813-824.

10. DOHERTY, P. C., RIBERDY, J. M., BELZ, G. T. «Quantative analysis of the CD8+ T cell response to readily eliminated and persistent viruses». *Proceedings to the Royal Society* (in press).

UNPUBLISHED THESES

«Studies in the experimental pathology of louping-ill encephalitis». Edinburgh, 1970.

«The epizootiolology of bovine leptospirosis». Queensland, 1966.

EDITORIAL

Parasite Immunology (1979-1982); *Journal of Neuroimmunology* (from 1980); *Journal of Immunology* (1980-1982) 1990; *Infection and Immunity* (1981-1984); *Journal of Veterinary Immunology and Immunopathology* (1983 -1986); *Journal of Virology* (1984-1986) (1996-1999); *Microbial Pathogenesis* (from 1985); *Archives of Virology* (1986-1989); *Virology* (1990); *Viral Immunology* (1994).

Editor for volume 4, No. 2 of *Seminars in Immunology.* 1992.
Editor for volume 6, No. 4 of *Current Opinion in Immunology.* 1994.

CONSULTANT ACTIVITIES

1977	Virology Task Force, NIAID, Washington, DC
1979	Informal discussion of African Swine Fever research needs, FAO, Rome, Italy
	Workshop in influenza B viruses and Reye's syndrome, NIH, Washington DC
	Etiology Workshop, National Conference on Diabetes, Reston, Virginia
1980	Immunology Task Force, National Institute of Allergy and Infectious Diseases, Washington, DC
1980-81	Member, Experimental Virology Study Section, NIH, Bethesda
1982-84	Consultant to Scientific Advisory Committee, ILRAD, Nairobi, Kenya
1982-87	Member, National Multiple Sclerosis Society of Australia Research Advisory Board
1983	Member, NH&MRC Quinquennial Review of the Walter & Eliza Hall Institute of Medical Research
1983-86	Temporary Adviser at WHO Peer Review Meeting on Dengue Vaccine Development, Bangkok, Thailand
1984	Member, New Zealand MRC Site Visit for Review of MRC Auto-immunity Research Unit, Dunedin
1985-88	Chairman, Australian Animal Health Laboratory (AAHL) Research Advisory Committee
1986-92	Board Member, Member, and Chairman of Programme Committee (1990-1992) for the International Laboratory for Research on Animal Diseases (ILRAD), Nairobi, Kenya
1990-94	Member, Experimental Virology Study Section, NIH, Bethesda

1991- Section Editor, Journal of Immunology
1994 Immunology of Aging Task Force, NIH, Bethesda
1994 Review Committee Member, National Multiple Sclerosis Society, New York
1994 Review Committee, Queensland Institute of Medical Research, Brisbane
1993-95 Co-Organizer, Keystone Meeting on Viral Immunity
1995-96 Nominating Committee Member, American Association of Immunologists

TEACHING

AAI seminar course in Advanced Immunology, Colorado Springs, 1991, 1995.

STUDENTS

The following have successfully completed Ph.D. theses while working with me:

1. R. M. Zinkernagel, March 1975 (ANU); Professor of Experimental Biology, University of Zurich, Switzerland.

2. R. B. Effros, June 1978 (Wistar Institute); Professor, University of California at Los Angeles.

3. J. R. Bennink, August 1978 (Wistar Institute); Chief Viral Immunology Laboratory, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

4. N. Greenspan, MD/Ph.D., July 1981 (Wistar Institute); Associate Professor, Department of Pathology, Case Western Reserve University, Cleveland, OH.

5. D. Schwartz, MD/Ph.D., December 1982 (Wistar Institute); Johns Hopkins University, Baltimore, MD.

6. N. Bowern, May 1986 (ANU); Commonwealth Department of Health, Canberra, Australia.

7. J. Dixon, September 1987 (ANU); Postdoctoral Fellow, Suny, Stonybrook, New York.

8. Z. Tabi, September 1988 (ANU); Research Associate, University of Queensland, Australia.

9. M. F. Uren, November 1988 (ANU); CSIRO Senior Research Scientist, Division of Tropical Sciences, Brisbane, Australia.