Nossal

with best regards
Jack Marchalonis

COMMENTARY

BURNET AND NOSSAL: THE IMPACT ON IMMUNOLOGY OF THE WALTER AND ELIZA HALL INSTITUTE

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INTRODUCTION

THE WALTER AND ELIZA HALL Institute of Medical Research in Melbourne, Australia is probably the world's best known research center devoted to the study of immunology. This recognition was gained under the leadership of its third director, Sir Frank Macfarlane Burnet, who headed the Institute from 1944 to 1965. Subsequently, the Institute has shown explosive growth under the leadership of its present director, Sir Gustav Nossal (1966 to present). The two individuals differ markedly in personal characteristics, but both made major and unique contributions to the definition of immunology as a modern science. Two recent publications have brought the Hall Institute to general attention: the first is *Life among the Scientists: An Anthropological Study of an Australian Scientific Community* (Charlesworth et al., 1989). The second is *The Seeds of Time* (1991), a biography of Sir Macfarlane Burnet by Christopher Sexton. The overall perspectives of the two books are quite distinct.

The first has the stated purpose of attempting "to understand how a small group of scientists at a particular research institute, and in a specific scientific field, do science, as distinct from what the received scientific mythology *says* they do and what philosophers of science and other science watchers *suppose* they do" (p. 1). For this study a group of anthropologists used interviews and techniques of anthropological analysis to characterize a group of scientists as if they were a separate subculture working within the context of its own historical, sociological and mythological milieu. Charlesworth et al. write from an avowedly Marxist perspective, and address too many issues facing contemporary science to do justice to any single one or to give a coherent picture of the subject. The volume is interesting because it states many of the issues that have currently been brought to the front in various popular criticisms of science and analyses them within the philosophical context of the authors' beliefs and within the framework of interviews with scientists working in a single research institute. It should prove useful to historians of the Hall Institute and Australian Science and to future sociological or anthropological studies of the scientific subculture.

Sexton's book is a well-constructed biography of the life of Sir Macfarlane Burnet starting with the immigration of his father, Frank Burnet, to Australia in 1880 and ending with Burnet's death in 1986. The biography makes extensive use of interviews with Burnet, his writings, and interviews of individuals closely associated with him. I found it to be a fascinating book that provided an overall perspective of Burnet's life and times.

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My association with Burnet began in 1967, after he had stepped down as director of the Hall Institute and no longer had an active role in experimental research. Previously, as an undergraduate, I had been impressed with his book, *The Clonal Selection Theory of Acquired Immunity* (1959), and the desire to work with him gave impetus to the decision that brought me to the Walter and Eliza Hall Institute as a postdoctoral fellow. I had the opportunity to work with Gus Nossal as his first postdoctoral fellow, and then, with Sir Mac's urging and help, joined the staff; my association with Nossal continued for eight years. My view of Burnet was comparable to that of a grandson. Burnet showed great interest in my research on evolution and lymphocyte receptors. He was not directly involved, however, and we worked in a spirit of mutual friendship that was free of the tensions expressed by Nossal, who saw him as a stern, aloof, and somewhat unsupportive taskmaster. Thus I did not see him in the role of the distant and extremely dedicated scientist that he played during his active research and administrative years.

Burnet showed a strain of toughness that persevered throughout his life. In May 1984, he and I were seated out in the intense South Carolina sunshine while he was waiting to be awarded an honorary degree from the Medical University of South Carolina. Another honorary degree recipient, Clare Booth Luce, was overcome by the heat and humidity and moved back into the shade. I asked Mac whether he wanted to move back out of the sun. He shook his head emphatically "No," refusing to show any weakness whatsoever. In retrospect, this becomes more impressive because he must have known he was suffering from the cancer that would soon take his life.

Sexton develops and points out threads of Burnet's personality that were recognized by many of his associates and which shaped his contributions to both science and society. Burnet and Nossal have had wide-reaching international impact, and I felt that a major weak point of Charlesworth et al.'s book was the attempt to analyse the Hall Institute as an Australian phenomenon, rather than placing it in its international context. I welcome this opportunity to use these two volumes as a springboard to comment on the Walter and Eliza Hall Institute and its most dominant directors.

By international standards, the Hall Institute is a relatively small operation, but it has had an enormous impact on the development of immunology. Furthermore, under Nossal's leadership, it has provided a shining example of growth and support for research, while maintaining stability for individual investigators—and accomplishing this without becoming excessively entangled with industrial concerns. Past books on the Hall Institute have devoted a good deal of attention to research contributions. I will not consider these in detail, but instead will focus upon Burnet's contributions to the intellectual growth of the Hall Institute and on the development of Australian science, as distinct from that of England, and upon Nossal's transformation of the Institute from a small group of medical scientists working with relatively meager resources to a leading research center well equipped to carry out state-of-the-art studies in molecular biology, modern cell biology, and immunology. The following references provide additional information regarding the Walter and Eliza Hall Institute and many of the personnel described here: Burnet, 1971; Nossal, 1978; Wood, 1984; Fenner, 1990; Baskin, 1991.

BURNET: HIS CHARACTER AND IMPACT

Burnet seems to have been basically a shy individual whose diffidence was misinterpreted as arrogance during the heyday of his scientific career. He grew up in the Australian bush country, where he developed a strong interest in nature that continued throughout his life. Although he preferred to collect beetles, he took pride in winning a place on the crew at Melbourne University in order to win his father's approval. Burnet's background in amateur naturalism predisposed him toward the "Darwinian view of immunology," for which he served as an apostle throughout his life. The ingrained commitment to integrity that characterized his scientific life was developed early when he expressed dissatisfaction with shady real estate development policies supported by his father, a banker. Burnet had a long and fruitful life that encompassed major political changes within the context of Australia, the British Empire, and the world. His thinking and his contributions were shaped by these political changes. In the first place, Burnet saw himself as an Australian rather than as a displaced colonial Englishman. His father set the example here. The elder Burnet served successfully as a bank manager in Traralgon, Victoria, and was offered the prestigious opportunity to return to the U. K. to open the first London office of the bank. He declined, having made the decision to remain and raise his family in Australia.

Burnet's growth in science and his period of leadership of the Hall Institute coincided with the time during which Australia grew in stature and self-confidence to become a strong and independent nation, rather than a British colony. Consistent with his Australian pride, he commented rather sarcastically on the first official director of the Hall Institute, Sidney Patterson, M. D., who spent three years as director before taking a prestigious clinical practice at Duff House (Ruthin Castle), a private clinic for wealthy invalids in North Wales. Burnet noted that Patterson "came and he went," having little impact on the subsequent development of the Institute. The first named director, Gordon C. Matheson, M. D., unfortunately never served because he was mortally wounded at Gallipoli in World War I, shortly after the decision was made to offer him the position. Burnet speaks quite highly of the second Director, Charles Kellaway, who "set Australia on a new path to achievement in medicine." Burnet feels that Kellaway gave it the best 20 years of his professional life and "got it going" (Burnet, 1971).

Burnet's Australian patriotism and respect for the elitism of achievement and ability caused him to turn from the tired class-directed approaches of Britain to the positive egalitarian successes shown then in the United States. For example, Burnet spoke highly of Harvard Medical School "as probably the best in the world," and sought to further academic ties with the United States, as opposed to the preoccupation with England expressed by his predecessors. This spirit is illustrated in his pride that his hand-picked successor, Nossal, had spent two years at Stanford in Lederberg's department and built a first-class reputation in America. In Burnet's words, he had adsorbed the American approach that demands "the right tools for the job," rather than carrying out postdoctoral studies in England prior to taking up the directorship.

Burnet took particular pride and vigorously defended his uniqueness in his application of Darwinian principles to immunology. Immunology began in an applied and clinical setting. Even today, the vast majority of studies are carried out either on humans or on common laboratory rodents, and studies with lower vertebrates are looked upon as unimportant. Burnet pioneered in the view that much could be learned from studying lower animals such as protochordate tunicates, or even from attempting to understand recognition and defense mechanisms of plants. Moreover, Burnet put his ideas into practice.

One example of his broad interests is recorded in a photograph taken in 1975 in the garden of the School of Botany at Melbourne University (Fig. 1); it shows the core speakers at a widely significant conference on self/nonself discrimination that was put together largely because of Burnet's inspiration. Burnet was instrumental in attracting R. Bruce Knox to the School of Botany because of his interest in the biochemistry and genetics of nonself recognition in plants and in establishing collaborations between Knox and me because of my interest in the molecular evolution of immune recognition. Burnet's ability to see common biological problems across disciplines is reflected in the individuals in this photograph who represent botany, immunology, and physical chemistry. The spirit of Burnet's attempt to get people together who would give a final synthesis to common problems of defense and differentiation relating to self/nonself recognition continues today with international meetings held in Europe and the United States, the latest of which was "Primordial Immunity," held at the Marine Biological Laboratory, Woods Hole, Massachusetts in May 1993. These conferences are dedicated to the general appreciation of the fact that basic defense and recognition mechanisms are broadly shared among living animals. Further illustrating the generality of his perspective, Burnet took great pride in the fact that he had been instrumental in bringing the pioneer ethologist Konrad Lorenz to the attention of the Nobel Selection Committee.

FIG. 1. SPEAKERS IN THE SYMPOSIUM ON BIOLOGICAL RECOGNITION HELD AT THE SCHOOL OF BOTANY, UNIVERSITY OF MELBOURNE, JULY 31ST, 1975

The participants are from left: Sir Macfarlane Burnet, John J. Marchalonis, John Heslop-Harrison (Director, Royal Botanical Gardens, Kew, England), R. Bruce Knox (School of Botany, University of Melbourne), and Sir Rutherford Robertson (Research School of Biological Sciences, Australian National University). The symposium reflected Burnet's broad approach to the crucial biological problem of recognition; viz, self and nonself in plants (Heslop-Harrison), the evolution of biological recognition (Burnet), membrane biochemistry (Robertson), molecular aspects of lymphocyte membranes (Marchalonis) and the interaction of plant proteins with human cells (Knox).

Despite his shyness, Burnet held many strong opinions and was not afraid to state them. The question of whether Burnet would have been capable of leading the Hall Institute through its modern period of growth has been asked. He probably would not have been able to do so. Despite his enormous intellectual contributions, today's society would see Burnet as someone who is not "politically correct." He had an absolute commitment to scientific truth, and would not alter his opinions to meet political circumstances. He was an unashamed elitist, with the qualification that his respect was for individual ability and achievement. During his years of leadership, he made his views quite clear; he maintained that serious research could not be carried out at a university or medical school, and he had as little to do with faculty committees as possible. David White of the Department of Microbiology commented that "presumably he [Burnet] assessed his priorities and quickly concluded that his principal responsibility was to administer the Hall Institute and conduct his own research. Moreover, he had no liking for the cut and thrust of university politics, let alone the desire to waste precious hours battling committees for a larger share of the cake. I think history has shown his decision to be correct" (p. 130). Burnet's commitment was to the development of the Hall Institute and to his own research. He resisted opportunities to integrate the Institute fully into the academic institutional structure of the University College of Medicine, and became unpopular in the process for his lack of collegiality. In fact, at the time of his retirement, Burnet took some pride in his unpopularity with the general University faculty.

Despite his diffidence, Burnet became a very effective scientific debater. A vignette recounted by Edward A. Boyse, FRS, describes an encounter in 1958 between Burnet and Boyse's mentor, Peter Gorer, one of the founders of immunogenetics. Gorer felt that Burnet was quite "off the mark" in his ideas regarding immunology and cancer, and resolved to attend his London appearance and take him to task. Gorer was a dreadful speaker, so when he very much wanted to make a point, he would prepare himself by coming in, repeatedly, to rehearse and polish what he would say—in this case, at question time. Boyse knew Gorer's points exactly, and wondered earnestly how Burnet would be able to respond to them. In the actual confrontation, Gorer stated that he had some difficulty with Burnet's results and made his case with considerable force and clarity. Burnet, however, was able to sidestep the issues adroitly by responding "Yes, Dr. Gorer, I can see your difficulty," and signaled for the next question.

Burnet's strongly stated general views often caused considerable ruckus. In 1966 Burnet wrote a position paper for *Lancet* entitled "Men or molecules? A tilt at molecular biology." Here, following his retirement, he made statements of such extremity that rebuttals are still being written. In essence, Burnet wrote that molecular biology and cell biology had not contributed anything positive to the advance of medicine, and that their further pursuit might even be an evil thing. Although one can argue that molecular biology is not even a discipline, much less a religion, the extremity of Burnet's parting shots is indefensible. In 1989 Sydney Brenner wrote a strong rebuttal to Burnet's editorial, arguing that "today we are all molecular biologists," and indeed we are.

In his last book, *Endurance of Life*, published in 1978, Burnet develops a theory of aging based upon the accumulation of damage to DNA and considers the social implications of various aspects of aging and natural selection. His characteristic genius and ability to integrate diverse material shines in his approach to, paradoxically, the molecular basis of aging (see Bernstein and Bernstein, 1991 for a recent discussion of DNA repair in aging). Furthermore, he makes extrapolations to social philosophy that he knows are politically contentious. Among these are advocacy of abortion when there is a known risk of serious abnormality in the infant either from genetic causes or resulting from toxicity or infectious diseases, the advocacy of voluntary euthanasia for individuals suffering from incurable diseases, and the conviction that individuals of "low intelligence and slovenly habits," should be restrained from having excessively large numbers of children. Burnet was aware of the unpopularity of these views among both the general public and many academics, yet felt that the issues had to be addressed.

Burnet had a love of science that underlies all his achievements. This is best articulated by his statement that "science to me is the finest sport in the world." In our unceasing contemporary quest to obtain increasingly more targeted grant funds and to deal with a skeptical public, we tend to emphasize the importance of science to the cure and prevention of disease and to the improvement of the general human condition. Furthermore, we tend to get lost in the minutiae of limited projects that provide short-term research support and offer realistic short-term payoffs. These drives and pressures are indeed real, but the outstanding scientist is motivated by the enjoyment of facing new challenges and conquering them.

Burnet stated that the Hall Institute was "his life for 42 years," beginning with his humble appointment as a pathology registrar and culminating with his 21 years of service as director. During his years as a research fellow, Burnet developed a reputation for complete dedication to science, an unflinching commitment to scientific integrity and personal ethics, and a lack of toleration for academic manipulation and political cant. Although these are ideal qualities of an intellectual leader, or a "tribal god figure," they are not the qualities required of an administrator who must deal with university and governmental politics in order to ensure the growth and recognition of his institute. This perception of Burnet was shared by Kellaway, who felt that even though Burnet was the obvious choice to become the third director, based upon his scientific achievements and international recognition, it might be a personal disservice to burden him with the political responsibilities of serving in that role. In Burnet's words "his [Kellaway's] view was that I was probably near my peak as an investigator and that I should go on at the bench and remain shielded by someone else from the administrative responsibilities which I would obviously find difficult and frustrating" (p. 54). Burnet, however, was quite firm on impressing to Kellaway that he did want the directorship, and Kellaway finally gave his blessing. Burnet feels that the Board of Directors most probably shared Kellaway's doubts, but their confidence in him was increased when Burnet was invited to give the Dunham Lectures at Harvard.

Burnet assumed the directorship and brought the Hall Institute to a position of international prominence in immunology. He changed the focus of the Institute from an interest in general infectious disease problems with particular service in times of crises to an institution devoted to the study of immunology. He recruited many leading scientists who either remained at the Institute and achieved international renown, such as Ian Wood, the Chief of Clinical Research and a leading gastroenterologist; Gordon Ada, head of the Biochemistry Unit, who went on to become Professor of Microbiology at Australian National University; John Cairns, a virologist who went on to become Director of The Cold Spring Harbor Laboratory of Quantitative Biology; Donald Metcalf, who remains at the Hall Institute as a leading scientist in cell biology and cancer; and G. J. V. Nossal, who joined the Institute in 1957. In addition, Burnet put together an administrative staff, two members of which continued to provide valuable service long into the Nossal years. One is Margaret Holmes, who ran the extensive animal facility and supervised the training and job performance of the technical staff, where she served admirably as mentor and counselor. The other is Arthur Hughes ("Hughsie"), who served as General Manager for the Physical Operations of the Institute. These people continued to provide valuable assistance to the new director and also helped faculty and visiting postdoctoral fellows.

Burnet thus left for his successor an intellectual legacy and a cluster of dedicated scientists, as well as a helpful staff. He did not, however, leave a well-funded or well-equipped institution. All of the sources describing the Hall Institute in those days complain of a lack of resources, particularly of equipment. Burnet's research was strong in ideas. He focused upon experiments that could be done with simple tools such as a microscope, petri dishes, and the Pasteur pipette. My time at the Institute was spent during the transition years, and I personally can attest to the lack of biochemical equipment needed to bring the Institute into technological parity with the world's leading research centers at the time. Another aspect of the contradictions shown by Burnet is in his attitude toward equipment and new technology. Despite deemphasizing these aspects of science, he wrote wistfully in the Foreword to my monograph, *Immunity in Evolution*, that "he [Marchalonis] has been able to make use of all the more refined biochemical and radiochemical techniques which *my own generation lacked*" (my italics) (p. xx).

NOSSAL'S DIRECTORSHIP AND THE GROWTH OF THE INSTITUTE

Burnet realized that he had made his contributions and that someone with a new outlook and personality was required to provide the resources necessary to catalyze and sustain the material growth of the Institute. Just as Burnet was Kellaway's handpicked successor, Nossal was Burnet's. Nossal took over the directorship at the age of 34. He was a friendly, outgoing and likeable individual who was not reluctant to enter the academic and governmental political fray. Rather, he actually relished the interactions. The point comes across in the Charlesworth et al. book that the ghost of Burnet is still a powerful presence at the Institute, and that his example reminds today's scientists that "small can be both beautiful and successful." By contrast, Nossal is "not seen so much as a role model for the budding young scientist in the Institute, but as a skilled administrator and entrepreneur." Many of the comments in the Charlesworth et al. book remind me of the gossip I heard on almost a daily basis when I was a member of the Institute. In addition, there was considerable jealousy expressed toward Nossal by faculty members at other research centers and universities, who felt that the Hall Institute was obtaining a disproportionate share of Australian research funds. Possibly this sort of criticism is inevitable to a "front-runner," but due credit has not been given to Nossal's scientific achievements. It should also be stressed that he was extremely generous in providing support to young investigators. His approach was, and still is, unusual because he ensured that even postdoctoral fellows had technical and resource support, and he did not feel that it was necessary to put his name on every paper. On the research front, Burnet provided the concept of clonal selection, and it was Nossal who has fought the battles that continue to this day in defending various aspects of it. I will return to this point later.

One can find fault with details of Nossal's leadership, but there is no question that he took an extremely small research operation and turned it into a large center that is intellectually and technologically competitive with major international centers in immunology, cancer research, immunopathology, molecular immunology, and autoimmunity. It is instructive to analyse the budgetary growth of the Hall Institute as a function of time and to correlate this with changes in staff and publications. Despite the inherent limitations of this type of analysis, it is also worthwhile to compare the Hall Institute data with corresponding data from other institutions. The Institute started with a modest annual bequest from the Walter and Eliza Hall Foundation that amounted to £2500 a year (approximately $5000). The total income of the Hall Institute in 1926 as estimated by Burnet was $13,275, and in 1965 it was $358,600. During Nossal's first five years, this amount doubled and subsequently (Fig. 2) grew with an average rate of 18% per year until 1991.

The data shown here are taken from the Hall Institute Annual Reviews for the period 1987 through 1992, and are not corrected for inflation. The growth of the Institute largely reflects the results of a productive ongoing partnership with the Australian Government.

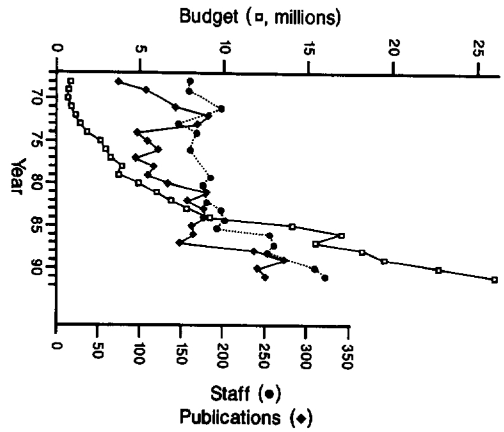

FIG. 2. GRAPH SHOWING THE ANNUAL BUDGET (IN MILLIONS OF AUSTRALIAN DOLLARS), THE NUMBER OF STAFF, AND THE NUMBER OF PUBLICATIONS GENERATED BY THE WALTER AND ELIZA HALL INSTITUTE FOR 1967 THROUGH 1991

Data were taken from the Annual Reports of the Hall Institute covering that time period.

In order to ensure stability of the Institute research operation and to allow the possibility for necessary growth, Burnet recognized the need for obtaining a "special relationship" with the National Health and Medical Research Council (NHMRC). Burnet was unsuccessful in attaining this goal, but Nossal established a working relationship with the NHMRC in 1968 that ensured that staff salary and much of the research expenses were covered by that federal agency. He also negotiated an arrangement with the State of Victoria that covered the operating expenses of the Institute, such as maintenance of the plant and facilities—those activities that scientists in the U. S. think of as covered under "indirect costs." In 1991–1992, the Australian Federal Government contributed 42.9% of the operating revenue and the State of Victoria contributed 8%. Australian grants and fellowships contributed 10.2%, whereas "other Australian sources" generated 14.9%. Industrial grants and contracts generated 12.1% and 11.9% was contributed by overseas grants and fellowships. This balance is of interest, because the Hall Institute has grown without developing a special relationship with any particular industry, unlike the

TABLE 1

Growth of funding for WEHI and NIAID from 1988 through 1993

Data for the Walter and Eliza Hall Institute (WEHI) were taken from the Annual Reports for the corresponding years. The data for National Institute of Allergy and Infectious Diseases (NIAID) were kindly provided by Kristin Adamson, Budget Analyst at that Institute.

	WEHI*		NIAID	
Year	$$ (millions)	% increase	$$ (millions)	% increase
88	14.9	8.4	638,800	17.1
89	15.9	6.5	744,152	16.5
90	16.4	3.3	843,745	13.4
91	18.4	11.9	906,251	7.5
92	20.5	11.7	960,082	5.9
93	Not available		979,471	2.0

* The monetary values for WEHI are given in Australian dollars, $1 Australian = 0.7 $U.S.

Basel Institute for Immunology, which is a subsidiary of Hoffman-LaRoche, or the Scripps Institute, which has received 300 million dollars in research support from Sandoz. The continuing growth of the Hall Institute, despite bad economic times in Australia as well as the United States, is reflected in Table 1. This table compares the growth of the Hall Institute with that of the National Institute of Allergy and Infectious Diseases (NIAID) in millions of dollars and in percentage increase in the years from 1988 through 1993. In the first place, it is clear that the Hall Institute has an extremely small budget by comparison with NIAID. It is a large budget by Australian standards, however, where the Institute now receives approximately 7% of the NHMRC budget. The striking feature of this table is that the operating budget of the Institute continued to increase until 1992, whereas that of the NIAID has been declining since 1988. Nossal has informed me that the Institute is not immune from budgetary stagnation, and he expects the 1993 research spending figure to be approximately equal to that for 1992.

An extremely serious issue with respect to U. S. funding is seen in 1992, when the percentage increase fell below the rate of inflation. This trend continues with the U. S. scientific community facing catastrophe, even though as Nossal states "the absolute level of medical research funding in the United States is still the envy of the whole world" (pers. commun.). Science and medicine in the United States are under attack from all sides, and similar attacks are occurring in Australia, as reflected in Charlesworth et al.'s book. The trend shown for NIAID, coupled with increasing political pressure on federal grant agencies either to fund the "political priority of the month" or to prepare for cuts, signals a crisis for research in immunology (and science in general), unless immediate steps are taken to remedy the situation.

Charlesworth et al. are correct in pointing out that science is a social phenomenon and one that reflects perceived economic realities. I would disagree with the Marxist analysis, however, and emphasize that science is an extremely challenging and essential aspect of human endeavor that does not have a stable funding base. In the United States, it is possible to obtain relatively large short-term funding to carry on research, but these funds confer no stability to the effort. Projects that have begun to make great progress are terminated after three years because there is insufficient funding to continue them. This is irrespective of the progress they have made and the quality of the people involved. It reflects predominantly short-term perceptions of financial needs, scientific trends, or political directions. Nossal is to be commended for developing a unique nongovernmental institution (the Institute is incorporated in Victoria as a Company) that allows individuals the stability to pursue research that does not produce immediately marketable or clinically relevant ends. One of the major aspects of Nossal's philosophy that impressed me as a postdoctoral fellow and subsequently a faculty member, was that these individuals were allowed both technical and research support, irrespective of their generation of particular grants. It was expected, of course, that the individuals would apply for extramural funding, if their Institute-funded initiatives were successful.

In the 1970s, the junior faculty at the Institute were extremely successful in competing for funds from U. S. agencies, including the National Institutes of Health and the National Cancer Institute. Their competitiveness was predicated on, first, their ability to generate critical primary data because of in-house support and, second, on the fact that the Hall Institute did not ask for indirect costs on the U. S. federal grants. This was a very attractive selling feature, since U. S. universities can ask for add-ons of more than 100% of the direct or research part of the grant. The stability provided by this kind of in-house support is characteristic of the Hall Institute and also of the Basel Institute for Immunology. It has enabled the initiation and development of projects that could not be funded in a short-term peer-reviewed mechanism. The need for this stability was recognized by Burnet and incorporated into a central feature of the Hall Institute under Nossal's leadership.

Figure 2 also includes annual data on the number of staff and on publications generated. The current staff numbers 270, plus 44 postgraduate students. Analysis of the graph indicates that the number of staff remained relatively constant from 1966 to 1986, when the new enlarged Institute building came online, after which the staff size approximately doubled. The number of permanent faculty at the Institute is relatively small (35), and there is a large number of postdoctoral fellows and support staff representing technicians, people involved in the animal facility, secretaries, and other service capacities. Technical support and individuals involved in running the animal facility are essential to the successful operation of the Institute, with its particular focus on research in mice. The relative constancy of staff size in the years 1966 through 1985, coupled with a generally small budget from 1966 through 1980, raises some amusing issues when annual publications are considered. Each year at the public board meeting the chairman of the board, Sir Colin Syme, the CEO of Broken Hill Propriety Ltd., would begin his remarks by saying that when he dealt with his stockholders in the mining industry, he knew how to analyse productivity, but when it came to reporting on what the annual productivity of the Hall Institute was, he was at a loss. Thus, he would refer to the number of publications as an indication of productivity. The data show that there were essentially three "bubbles" of generation of papers. The first was from 1969 through 1972, which was essentially independent of staff size and budget. The second was from 1980 through 1984; it correlated with a large increase in budget. The most recent one in the late 1980s corresponded with both budgetary and staff increases.

The move to the new building in 1986 afforded the possibility of expanding the graduate student and postdoctoral population considerably, as is evident in the bubble. The first publication bubble of the Nossal years reflects a time of great excitement at both the Institute and with immunology throughout the world. Miller and Mitchell had recently initiated their forays into the function of the thymus, and a nucleus of advanced technology in cell culture and molecular immunology was growing at the Institute, allowing it to make new explorations into the nature of receptors for antigens on B and T cells and on mechanisms of T and B cooperation. Everything we did was new and exciting and generated general interest, as evidenced by publication in quality journals and by invitations to present the data at international meetings. It was the initiation phase of a new field, which was subsequently followed by a consolidation phase in which investigators from other institutions became involved and paradigms were continually being reexamined.

Nonetheless, the impact of publications by Hall Institute workers during that time period was large on an international scale as reflected by citations of publications, and the fact that many of the concepts and presentations of the time either are generally accepted or are still being actively debated. In *Contemporary Classics in the Life Sciences* (Vol. 1), which covers cell biology including immunology, publications by the following Hall Institute investigators were given status as "citation classics": Gordon Ada, Anthony Basten, Alistair Cunningham, John Marbrook, John Marchalonis, Don Metcalf, J. A. F. P. Miller, Graham Mitchell, Gus Nossal, Ken Shortman, and Alex Szenberg. This short list of Institute personnel during the early Nossal years illustrates contributions by individuals who remained at the Institute through the whole of their research careers (Miller, Shortman, and Szenberg), and the contributions of individuals who trained at the Institute and went on to other positions and careers (Basten, Cunningham, Marbrook, Marchalonis, and Mitchell). We would agree with a disclaimer by Nossal that it is easier to publish papers in cellular immunology than it is in other areas, such as biochemistry or molecular biology, so that the number of papers alone should not be taken to reflect the entire productivity or quality of the Institute. The papers by the investigators cited here, however, range from cellular immunology to techniques for the analysis of antibody-secreting cells, the separation of lymphocytes, and to biochemistry. Thus a small group of investigators generated a relatively large burst of papers that stimulated general interest. Many of the points of view and findings were controversial and generated intensive debate, which continues today. This is another feature of science as a social entity that was alluded by Charlesworth et al. but, unfortunately, was not developed. It would be an extremely interesting and insightful exercise to analyse in sociological and individual terms some of the major immunological debates in which the Hall Institute plays major roles. Two areas that merit in-depth analysis are the determination of the nature of the antigen-specific receptor on T lymphocytes and the role of the major histocompatibility complex in the regulation of the immune system. Study of these key immunological issues would demonstrate how different positions are taken by smaller groups, as well as by larger groups representing national viewpoints, and how a definitive position is chosen.

Nossal took a relatively small institution that was poor in equipment and resources but rich in the quality of its few scientists and gave it both growth and stability to pursue novel or unpopular research that allowed it to be competitive in resources with leading institutions in immunology and molecular biology worldwide. As an example that illustrates the success in building the financial base of the Institute, Burnet reports that the endowment and working capital of the Institute in 1965 was $690,100. In 1992, Nossal reported that the total invested principal has a book value of $25,719,684.00 and a market value of greater than $40 million (Australian). The Institute is now housed in a modern building of seven floors (15,000 sq. meters) and includes a major animal facility.

The area of the Institute and the support generated do not reflect accurately the impact that the Hall Institute under Nossal's leadership has had on the development of immunology as a widely recognized independent discipline. From that standpoint, the real product is the people who were trained at the Institute and who went on to make contributions in the field and carry with them principles they learned during their period of training there. In the first place, the Institute was a magnet for some of the best people within the British Empire, and trained some outstanding individuals from the United Kingdom. A large number of individuals from the United States received training, beginning in Burnet's days and continuing to the present. There have also been times when numbers of Europeans (particularly French and Germans) and Japanese have trained either directly with Nossal or with other permanent faculty. The list is too long to even attempt to include everyone, but it is worthwhile mentioning a few individuals who have come to prominence outside of Australia. These include Erwin Diener (Canada), Noel Warner (USA), Harold Von Boehmer (Switzerland), Marc Feldmann (UK), Masaru Tanaguchi (Japan), Martin Rollinghoff (Germany), Gregory Warr (USA), John T. Boyer (USA), Robert E. Cone (USA), John Marbrook (New Zealand), and John Schrader (Canada). The impact of the Institute was large in the number of individuals trained. This is reflected in the content of immunology courses taught to graduate students, undergraduates, and medical students. Even here, at the University of Arizona, we have six individuals who received training at the Hall Institute (J. M. Decker, D. DeLuca, J. T. Boyer,

G. S. Boyer, M. Schumacher, and myself). This aspect of the Hall Institute as a training ground for future contributors to immunology deserves special attention because a small institution has imprinted its philosophies and modes of operation upon a large group of people, many of whom have achieved positions of leadership in areas of immunology and medical research.

CLONAL SELECTION: THE CONTINUING SAGA

By the late 1940s and the early 1950s, it was clear that mammals had the capacity to respond immunologically to a potentially limitless array of foreign antigens, including microbes, proteins, carbohydrates, and even small organic molecules termed haptens, in an extremely specific fashion. The structure of antibodies and even the nature of the cells producing them was not established, but a number of theories were proposed to explain how one individual could respond specifically to an extremely large set of foreign antigens. The problem was an intellectually challenging one and leading figures, including Linus Pauling and Felix Haurowitz, entered the fray that came up with instructive theories, but they missed the mark on a number of grounds. Niels Jerne (past director of the Basel Institute for Immunology; Nobel Laureate, 1984) recognized the importance of preexisting natural antibodies in the recognition of foreign antigens and proposed a selective theory based upon this interaction. Burnet built upon Jerne's theory but added a dimension, following from his experience as a microbiologist and naturalist, that allowed him to formulate what has proven to be the correct theory. Burnet had worked on bacterial phages, on viruses such as influenza, and on bacteria. His contributions in the area of infectious disease were widely recognized; for example, he was honored by having the causative agent of Q fever, *Coxiella burnetti*, named after him.

In solving the problem of the generation of specific antibodies, Burnet assumed that Darwinian principles of genetics must apply. He made the insightful prediction that the lymphocytes in the body were analogous to a population of microbes in a test tube, where individual variants were generated by spontaneous mutation and selective conditions could be set up for the particular mutants. A selective theory is in principle Darwinian, whereas instructive theories are Lamarckian. The microbial analogy for the lymphocyte population is depicted with Burnet's original diagram in Figure 3. The lymphocyte pool consists of a large population of individual cells marked a, b, c, . . ., on the basis of expression of a cell surface form of receptor immunoglobulin that can bind in a complementary manner to an antigen designated here by the capital letter C. Specificity is imparted because that antigen will interact only with one or a small number of the large set with sufficient affinity to initiate activation and clonal proliferation. The end stage is the production of plasma cells that secrete antibodies specifically reactive with antigen C. The system is Darwinian in that the antigen does not provide new information, but merely selects among the cells on the basis of interaction with a receptor encoded by an existing gene.

Burnet assumed that by analogy with microbes the variation would occur by a sponta-

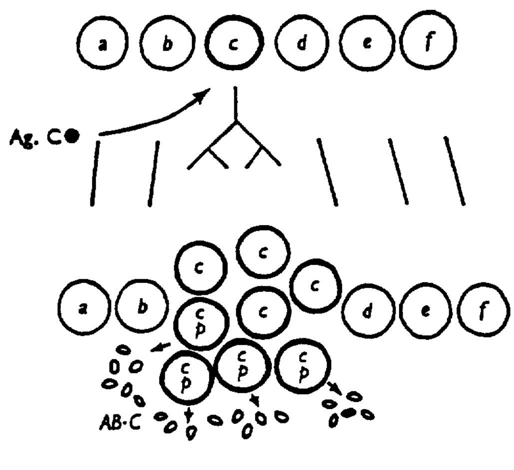

FIG. 3. BURNET'S ORIGINAL ILLUSTRATION OF THE CLONAL SELECTION THEORY OF IMMUNITY

He states that "contact of the corresponding antigenic determinant Ag.C with cells of clone c stimulates proliferation to antibody-producing plasma cells cp and non-producing type c" (Fig. 7 from Burnet, 1959, with permission of the Vanderbilt University Press and the Cambridge University Press).

neous mutation process that was essentially random in nature. Since this process is random, the likelihood of the surface antibody receptors reacting with self antigens would probably be just as great as their probability of reacting with foreign or nonself markers. In order to get out of this trap of autoimmunity or "horror autotoxicus," Burnet invoked the concept of "tolerance," in which an animal deletes cells capable of reacting with self when they arise early in the development of the animal and come in contact with self antigens. To account for the occasional occurrence of autoimmunity, he proposed that this was the result of the activation of "forbidden" clones directed against self antigens. In a sense, autoimmunity would reflect a failure of tolerance. This concept is elegantly simple and explained much of the phenomenology of immunology and also provided an intellectual holy grail as people applied increasingly sophisticated biochemical and recombinant DNA technologies to prove it and to explain it in molecular terms. For this concept and its implications, Burnet shared the Nobel Prize with Peter Medawar in 1960.

Nossal and many others devoted considerable effort to establishing clonal selection by showing that individual antibody-forming cells were indeed restricted in their capacity to respond to antigens, were monoclonal in the light and heavy chains of the antibodies they expressed, and finally, contained individual functional genes specifying immunoglobulin chains. In elegant molecular biological studies, Susumu Tonegawa and his associates showed that clonal commitment results from the selection of one variable region gene segment in the germ line and its recombination with a joining segment gene in B cell differentiation to form a rearranged gene capable of being translated into messenger RNA and eventually leading to synthesis and secretion of only that particular gene product by a particular cell. The diversity in the first instance is caused by the existence of large numbers of variable region gene segments and the clonal restriction follows from the selective usage of particular ones in individual cells. An example of the type of diversity that could be generated by this kind of mechanism would be 300 V_κ genes $\times$ 5 J_κ segments generates 1500 V_κ possibilities; 300 V_H segments $\times$ 10 diversity segments $\times$ 5 J_H segments generates 15,000 V_H possibilities. Since a combining site is formed by a V_HV_L interaction, this allows the formation of a possible 22.5 million combining sites that could be interpreted as the ability to recognize that many distinct antigens. Additional diversity comes from somatic mutation and variability caused by stabilized misreading of the D and J segment insertions. The clonal selection theory provided a major impetus to develop and apply new technologies to lymphocytes and antibodies and appears to have a solid place in history.

The primal formulation of clonal selection, however, is currently under strenuous attack. Challenges to the clonal selective theory come from two areas. The first attack stems from the observation that "forbidden clones" are not rare and found only in autoimmune diseases, but are extremely common and expressed by virtually all normal individuals. This questions the efficacy or existence of a clonal deletion or abortion mechanism and has raised possibilities that network type interactions in which antibodies recognize other antibodies by other combining sites and other control regions actually serve to regulate the system. Cohen (1992), for example, states that a "cognitive" rather than a "selective paradigm" is a more accurate theoretical description of the immune response. In a sense, the regulation of the immune system is depicted as being closer to Jerne's early model of interactions among natural antibodies, as opposed to Burnet's emphasis on a specific clonal mechanism dependent upon the binding of the immunoglobulinlike cell surface receptors to the target antigen, where specific regulation follows most readily from amplification or removal of appropriate clones.

A second area stems from the application of the techniques of molecular biology to immunoglobulin genes of primitive vertebrates. In particular, sharks are elasmobranchs that arose over 400 million years ago and have potent immune responses based upon IgM (immune macroglobulin) antibodies. Genes specifying light and heavy chains of immunoglobulins in at least two species of sharks are not arranged as described above for mammals, where there are large arrays of variable region gene segments and smaller arrays of joining (and diversity segments in some cases), with a few constant regions, the entire complex spreading over hundreds of kilobases. These complexes have been called translocons because of the need for rearrangement of at least the variable and joining elements. By contrast, the immunoglobulin genes in the elasmobranchs are arranged in little clusters, which in the case of light chains, are of only 3 kb in size and contain V, J, and C segments. Each cluster is different in the exact sequence of the V, J, and C elements, and there are many (hundreds or thousands) of these separated by large distances on the chromosome. Moreover, the V and J segments can be fused in register in the germ line (Hohman et al., 1992). Thus, diversity is generated in a different way than in mammals, but the capacity is there for expression of large numbers of immunoglobulin combining sites. If, for example, there are a minimum of 100 V_H and 100 V_L genes each, at least 10,000 distinct combining sites can be generated. The difficulty with respect to clonal restriction is that if these individual clusters act independently, a new mechanism must be developed to account for clonal restriction. To put the problem in perspective, if the individual clusters are separated by roughly 100 kb, the first and last cluster would be separated by an enormous germ line distance and would be unlinked to one another. If the first one is activated, how is the last one, or in fact any of the intermediate ones, to know this and not themselves be activated so that the cell would produce multiple immunoglobulin light or heavy chains? I believe that Sir Mac would be delighted to know that his theory is still generating this interest and even furor that may go on into the next century. My guess is that clonal selection will remain intact when the dust settles, but the use of recombination alone as a means of clonal restriction will fall by the wayside.

THE INSTITUTE AND THE FUTURE

Burnet turned the Walter and Eliza Hall Institute from its rather broad interests in experimental medicine and infectious diseases to a focus on immunology, and brought international recognition to this Australian institution while laying the intellectual foundations for the emerging discipline. Nossal has been extremely successful in building a physical plant and obtaining resources allowing the Institute to be competitive with leading world centers. I have heard Nossal described as the "world's most visible immunologist." He holds fellowships in the Royal Society of the United Kingdom and the National Academy of Sciences of the USA, and has recently completed a term as president of the International Union of Immunological Societies. His scientific work, beginning with his training as a student in Burnet's laboratory, dealt originally with obtaining proof of the clonal selection theory and continues to this day with a strong program applying the principles of clonal selection to B cell memory and tolerance.

Two conclusions gleaned from the experiences of Burnet and Nossal are extremely pertinent to present day immunology and biological science, in general. The first is that in order for a research institute to be competitive, there must be a financial base and a philosophical commitment that allows for long-term support of promising investigators and projects. This conclusion is particularly relevant to the initiation of novel projects, to the pursuit of difficult areas that do not lend themselves to quick solutions, and to unpopular avenues that may prove to be correct. Science would not have progressed without these opportunities. One of the best examples is, of course, Burnet's clonal selection theory. The other is a fundamental scientific discovery that set the stage for the modern burst of molecular biology. Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty would not have been able to dedicate ten years to the arduous biochemical proof that DNA was the pneumococcal transformation (i.e., genetic) factor if it were not for the stability offered by The Rockefeller Institute for Medical Research. There is, thus, a need for stability allowing for the pursuit of unpopular and even controversial research. Burnet's strong advocacy of this position was clear in his advice given to me in 1976 in an attempt to dissuade me from leaving the Institute and returning to the U. S. He remarked that he had turned down chairs at Oxford and Harvard because he could be as controversial as he wanted to be, and could safely ride out the storms of response, at his Australian institute.

The second issue of contemporary concern is related to the first, and is shown in Burnet's repeated convictions that serious science cannot be done in a university or medical school setting. His argument is that an outstanding scientist must be totally committed to the pursuit of his research, whereas this is only a part-time occupation in the traditional academic environment. Furthermore, universities have other agendas and constituencies to satisfy. With one recent exception, all of the Australian universities are "state universities" and the downturn of the economy with its loss of tax revenues has most probably hit Australia. This downturn has already had a devastating effect on U. S. state universities. Major American universities have not only had their funding fall behind inflation but also have suffered numerical cuts. In this environment of decerebrate cost cutting, universities do not support research. Rather, they use research-generated funds to support underfunded instructional and accessory programs. Burnet chose not to become involved in formal instruction and in the university politics that would have ensued had the director of the Institute also become chairperson of the Department of Medicine. The Institute achieved the necessary stability by forming a special partnership with the Australian Federal Government and with the State of Victoria.

The Hall Institute and the much larger Rockefeller Institute (University) have been landmarks in both the development of new avenues of research and in maintaining continuity. Burnet clearly recognized the problem in the 1930s and 1940s and worked to strengthen his Institute. The fundamental problem was masked by the economic growth of the 1960s, 1970s, and 1980s, but as illustrated in Table 1 above, it is back with a vengeance. Was Burnet right in concluding that serious research could be carried out only at a research institute? The general attitudes of public skepticism or hostility as outlined by Charlesworth et al. indicate that today's scientist has a considerable barrier to surmount in convincing politicians that the biological sciences should be adequately supported.

Australia has a rigid policy that retirement is mandatory at age 65. Nossal is approaching retirement and rumors are already spreading among the international immunological community concerning the future of the Hall Institute. In particular, when a new director is chosen, will that person retain the emphasis in immunology or expand into new areas? Under Nossal's leadership, strong programs have been developed in parasitology, an area of major concern to the Third World, and in hemato-oncology, where Metcalf has spearheaded an internationally acclaimed program on colony stimulating factors and their identification as cytokines. Despite wrestling with various political crises tending toward cutting support for research, particularly in the early 1970s, Nossal has always maintained a strongly positive attitude in stressing the importance of immunology and medical sciences in general. Following his retirement as director, he will probably play an even greater role on an international scale in convincing governments and industry of the importance of supporting basic science. His legacy will not be the creation of a major scientific paradigm as was Burnet's, but it will be the major center he has built and, possibly more importantly, the large cadre of young scientists he imbued with enthusiasm and a commitment to immunology. The two men differed markedly in their attitudes toward their imminent retirements. Burnet made statements to the effect that everything of importance had been done and, in some ways, it might even be dangerous to apply new approaches, such as molecular biology, to human problems. The ramifications of this are still felt. His attitude has been characterized as a "Gotterdammerung" or an "aprés moi le déluge" attitude. Nossal, on the other hand, has stated that he "truly takes great joy in the observation that there are so many colleagues in their thirties who are so much brighter and more knowledgeable than I am and in whose very good hands one can leave the future of science and immunology!" (pers. commun.). Burnet was a complex and often contradictory figure. I would like to close with a perception that I believe captures the essential spirit of the man and underlies both his drive for success in science and his capacity for outrageous, but often correct, statements: "Science to me is the finest sport in the world. . . . The higher the animal the longer is the period of play and the more keenly it is enjoyed. There is something of Peter Pan in all of us and in good scientists more than most."

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