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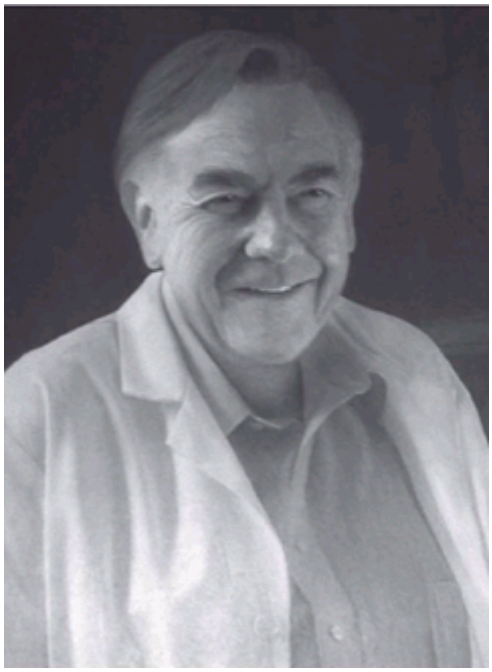

D. Bernard Amos

April 16, 1923 – May 15, 2003

By Edmond J. Yunis

D. BERNARD AMOS WAS one of the most distinguished scientists of the genetics of individuality of the twentieth century. He shares with K. Lansteiner and Peter O. Gorer the discovery that serologically detectable differences of individuals and transplantation specificities are related in nature. Discoveries of Gorer and Amos of the serology of the H-2 genetic system of murine histocompatibility and the subsequent discovery in both mouse and human (HLA system) that the transplantation antigens are controlled by closely linked loci with polymorphic alleles were fundamental in the development of clinical transplantation and the understanding of the genetics of the immune response. Amos ' s research for more than 35 years was seminal to the knowledge of the T-cell repertoire and the role of major histocompatibility complex (MHC) gene products in the immunology of restriction—self versus nonself—that are the basis of modern immunology.

Bernard, as he preferred to be called, was born on April 16, 1923, in Bromley, Kent, England. He was the only child of Vera (née Oliver) and Benjamin Amos. His family background was relatively humble, to the extent that no one could have predicted his outstanding place among the great scientists of the world. His father was a car mechanic, his mother a teacher. As a child he was a good student but was mischievous. At the Bromley School he once produced a contact explosive that burst as the instructor walked to the board. He was known for experimenting with chemicals and enjoyed lively dancing. He also attended Sir John Cass Technical Institute and worked as a technician at Burroughs Wellcome.

From 1940 to 1945 he worked for Dr. Macfarlane at Ratcliff Infirmary, Oxford. During this time he was assistant scoutmaster to children evacuated from London. In 1946 he returned to London and worked as a technician in Harley Street for D. Scott Jones. He attended Chelsea Polytechnic and obtained an M.B. degree before entering Guy ' s Medical School in 1947. During his studies he was awarded the Golding Bird Prize in Bacteriology and the Leonard Lubbock Gold Medal. He graduated in 1951 with M.B. and B.S. degrees. A postgraduate M.D degree for research was awarded to him in 1963.

In 1949 he married his first wife, Solange Labesse (medical student at Royal Free), and the first two children, Sue and Martin, were born in 1951 and 1953, respectively. He was appointed a postdoctoral fellow and pathology trainee at Guy ' s hospital from 1952 to 1955. From 1955 to 1962 was appointed a senior research scientist at Roswell Park Memorial Hospital in New York state. During that time three more children—Chris, Nigel, and Renee—were born. From 1962 to 1992 he was the James B. Duke Professor at Duke University and the Division of Immunology head. His wife, Solange, died in 1980. In 1984 he married Kay Veale, who had been widowed in 1980; he had met her while he was working for Dr. Macfarlane before Bernard became a medical student. Bernard Amos died on May 15, 2003, in Durham, North Carolina. At the time of his death he was the James B. Duke Emeritus Professor of Immunology and Experimental Surgery at Duke University Medical Center. He leaves his wife, Kay; daughters, Susan and Renee; sons, Martin, Christopher, and Nigel; and their families.

It has been 50 years since he was in the laboratory of Peter A. Isaac Gorer at Guy ' s Hospital in London and reported his method of agglutination of white blood cells against what is known today as MHC antigens (1953). His mentor had discovered

the genetics of individuality in 1934, including the genetics of tissue antigens that are involved in the rejection of allografts. Subsequently they demonstrated that skin allografts and intradermal injection of lymphocytes elicit antibodies to murine MHC antigens (1954) and the use of immunization against tissues of different strains of mice and analysis of serologic activity against tissues by cross-absorption with tissues to define what is today called the H2-D, H2-K, and H2-B haplotypes, with the first definition of more than one locus in the MHC region (1955).

In 1955 Bernard joined Ted Hauschka ' s cancer research group at Roswell Park, where he continued his pioneering work in tumor immunity. While there he documented the earliest demonstration of tumor immunity using antibodies (1959,1). He described the first sex-linked histocompatibility antigen and developed expertise in skin graft models of tissue rejection in mice and humans (1959,2).

He was recruited to Duke University in 1962 as a professor of experimental surgery, and remained at Duke University for more then 40 years. One of his many contributions demonstrated the use of lymphocytes for typing the MHC antigens to match donors and recipients for organ transplantation. As a matter of fact, the first kidney transplant between a recipient and a living related donor who was selected on the basis of MHC matching was performed at Duke University Medical Center in 1965, resulting from his fundamental research (1965,1). The 1962-1965 period saw advances in his ability to define antibodies to be used for matching histocompatibility. At first they depended on small volumes of sera and serum procurement from multiparous women or from transfused individuals. Then his original efforts to study the genetics of antigens were combined with the use of functional assays. Before 1967 the most widely used methods were the normal lymphocyte transfer test (NLT) of Brent and Medawar (Brit. Med. J. 5352[1963]:269) as adapted to man by Gray and Russell (Lancet 2[1963]:863) and the third man-skin-graft procedure of Rapaport et al. (Ann. N. Y. Acad. Sci. 99[1962]:564). In the NLT, live lymphocytes were injected intradermally.

Positive reactions were characterized by erythema and induration appearing at 24 to 72 hours. When Bernard ' s group carried out the NLT tests, they found that the subjects tested could provide an excellent supply of novel antibodies. By serendipity they found that when the test was performed weeks later in the same individuals, the reactions could not be reproduced; their reactions diminished or did not occur. Serum samples were tested and cytotoxic antibodies were found; there was a good correlation between reduced reactivity and antibody production (1965,2).[1]

During the late 1960s skin grafts were used to match donor and recipients for kidney transplantation together with serological results; two HLA identical pairs rejecting each other ' s skins several days later than haploidentical (half identical) or HLA different siblings. Such contributions established the foundations for the importance of HLA typing in allotransplantation (1966,2; 1967,1; 1978,1).

He with other pioneers defined the role of public and private epitopes in the MHC antigens as well the concept of shared epitopes by HLA alleles to explain cross-reactivity (1955; 1969,2; 1972,2).[2] It is remarkable that he and his collaborators made the discovery of both the first H-2 recombinants and the first HLA recombinants (1966,1; 1969,1), which prepared him to understand before others in the field the concept of linkage (haplotypes) and, at the population level, nonrandom association of HLA alleles.

With Fritz Bach he discovered MHC-controlled reactivity, using the mixed leukocyte reaction, later used as a tool for matching in organ and bone marrow transplantation; HLA identity resulted in the lack of MLC reactivity. Since skin grafting and serotyping were well advanced at Duke and mixed lymphocyte culture reactions and access to large families were available at the University of Wisconsin, the two schools had a productive collaboration that resulted in the demonstration that HLA controlled MLC reactivity, serologically detectable leukocyte antigens, and skin graft reactivity (1967,2; 1967,4). The degree of stimulation was related to the difference in the number of haplotypes shared. Subsequently the map order of HLA-A, HLA-B, and HLA-DR was established in family studies with Frances Ward, Janet Plate, and Edmond Yunis (1971,2; 1971,3). These results were confirmed in investigations of large Amish families using serology and MLC testing (1974,1) and in a three-generation family study (1974,2).

Bernard was a pioneer in cellular immunology. The mixed lymphocyte test was used routinely, together with serology, for many years to match transplantation antigens (1967,3; 1970,2). Further, his laboratory demonstrated a major role for cellular immunology not only in transplantation but also in cancer, with the characterization of cytotoxic lymphocytes against tumors, in collaboration with Gideon Berke and Karen Sullivan (1971,4; 1972,1), and also against Class I gene products (1978,2). He was also involved in the early studies of immunological enhancement (1970,1).

He was one of the first to recognize the value of studying different ethnic populations in order to understand polymorphisms in the evolution of the MHC. Such interest gave him the opportunity to do research and teach in Asia and South America. He personally helped to establish clinical histocompatibility laboratories in the United States, Chile, Brazil, Argentina, Peru, Thailand, and India. He established the association of histocompatibility genes with various disease states, such as iron storage (1980), and the first documentation of MHC allelic loss during malignant transformation (1971,1).

His contributions were many and he took pride in teaching, which for him was more important than the many awards he received. He had the skill to bring together leaders and make things happen. He organized the First International Histocompatibility Workshop, in Durham, North Carolina, which in an unprecedented manner stimulated international collaboration and led to competitive studies that define the MHC (HLA) complex (Publ. no. 1229, National Academy of Sciences and National Research Council, Washington, D.C., 1965). There have been 13 of these international workshops. The genetic diversity detected in different ethnic populations has been the topic of these workshops, influenced by many of his pioneer efforts.

In 1969 he organized, with Dr. David Hume, the first regional organ-sharing program in the United States, later known as the

South-Eastern Organ Procurement Foundation (SEOPF). This organization continues and was fundamental to the establishment of UNOS, which is the national center for organ allocation in the United States. He was the main force in organizing the Transplantation Society in 1967 and was its first past president.

Bernard also organized the first World Health Organization Nomenclature Committee, which has been responsible for the naming of HLA specificities and alleles since 1967. Through his contact with the National Institutes of Health, he facilitated support for several laboratories involved in transplantation research in the United States and abroad. He was the chairman of the task force on immunology and disease for the National Institute of Allergy and Infectious Diseases, the first chair of the National Institutes of Health committee on transplantation and immunity, and established a repository of reference reagents for histocompatibility testing laboratories worldwide.

He was the first chair of WHO HLA Nomenclature Committee and was a member of the Organizing Committee of the First International Congress of Immunology. In addition, he served as president of the American Association of Immunology from 1980 to 1981. Bernard ' s scientific contributions and his importance to the world were the reasons for his many awards, including his election to membership in the National Academy of Sciences and the Institute of Medicine, the Rose Payne Award presented by the American Society for Histocompatibility and Immunogenetics, and the 3M Life Sciences Award. He was pleased that SEOPF/Sandoz gives an award annually in his name to an outstanding young scientist for research in transplantation. He was proud to have been the first editor of Human Immunology. Upon his retirement as editor in chief of the journal Human Immunology, which he cofounded, he was honored in a special issue with tributes by his colleagues and students. The XIV International Congress of the Transplantation Society recognized him for his contributions (Transplantation Proc. Dedication of the XIV International Congress of the Transplantation Society—the Jean Hamburger Memorial Congress—and citations, pp. 4-6, 1993).

On February 21, 2000, members of Duke ' s original transplant team and current members gathered to celebrate the future of the program, and a graduate scholarship was endowed, the Bernard Amos Training Fellowship for Immunology to honor Duke ' s first immunologist.

Recently, and in connection with the last international histocompatibility workshop, many friends and colleagues contributed written statements of experiences concerning their friend and mentor (" A Tribute to Bernard Amos. " Clin. Transplant.16 [2002]:75-91). Such a tribute is the best way to remember him and to honor him as a scientist who was loved by the many he trained or influenced.

Helping new laboratories develop research and clinical programs in histocompatibility testing and immunogenetics, whether in the United States or abroad, was always one of Bernard ' s major interests. He invited investigators to his laboratory, sent technologists and junior faculty to various places to help set up labs, brought them into national and international workshops, and sent supplies, reagents, books, and equipment to those in need.

My own experience with Bernard lasted 35 years and began by chance at the annual meeting of the Federation of American Societies for Experimental Biology in Atlantic City in 1967. Even though I had been trained in blood groups, I did not understand his lecture. Months later I was asked to establish a tissue-typing facility. Bernard Amos became my mentor. Space in his laboratory was limited, and it was generous of him to give me a corner of a bench and a desk. " BC " was the immunized donor in our studies of cross-reactivity of antigens (1969,2; 1972,2)

Family studies included a Minnesota family, which together with the studies of the HLA genetics and mixed lymphocyte reaction of Bernard ' s own family, demonstrated that there was a separate genetic locus from HLA-B. It was important because the dogma at the time was the belief that MLC reactivity was explained by the difference of HLA phenotypes in unrelated individuals (1971,2). His poem written in 1992 explained the discovery.

Soon came Janet, Fran and you
Observing how mixed cells react
In culture, Martin, Ni, and Sue
The Schlagel sibs, we made a pact.
To understand the many genes
Upon one haplotype arranged
In order, this became our theme
And with MLR-R and MLR-S we played

The map order was confirmed in a large three-generation family, which included the genetic transmission of a recombinant haplotype (1974,2). In addition, Bernard suggested that MLR would have alleles in linkage disequilibria with HLA-B alleles and that their incompatibility would result in graft versus host disease and that genes in the HLA region (now Class I) were involved in the rejection of allotransplants. These conclusions were related to the lack of MLR reactivity in some HLA identical unrelated individuals that were unreactive, and the analyses of skin graft rejections. He once described the early period of transplantation genetics, times of unselfished cooperation to define the genetic basis and the definition of many loci and their alleles in HLA, when he and others adopted the concept of the haplotype, which appears to be greater than the sum of the parts. He said, " For me the two great unknowns were and are how to measure the immunogeneity of a haplotype and how to measure the host response to an incompatible haplotype. "

He was proud to have been honored by many of his students who are presently in research and teaching, as was apparent by the participation of many of them from the United States and abroad in celebration of his eightieth birthday (including the

unveiling of the portrait shown in this memoir) at Duke one month before his death. He was hospitalized at the time and was not able to attend. A memorial service was held at the Duke chapel on May 24, 2003.

We do not want to interrupt
the silence of our friendship.
Why destiny build such unions
to destroy them?
It is time without repair
as we remain with memories.
Let ' s for a sustained moment
continue without losing what we lost.

Let ' s remember his enjoyment of life
with family, students and friends
near the ocean, the sea that we loved
and the mountains so near.
And, above all the need to be with children
that will carry his torch,
his pride!

He cried, our eternal friend
with perseverance, without time,
with tears of stone
and thorns of crystals.
Yes, he cried and also we did
but most we laughed
and kept the smile
to see the birth and growth
of many that are present
and others in our thoughts!

– –Edmond Yunis

His memory is imprinted not only in our minds but also in generations to come, because he was one of the outstanding scientists of the twentieth century. He was one of the selected pioneers of modern immunology, particularly cellular immunology, cancer immunology, and immunogenetics. Of course, he is one of the central figures in the success of allotransplantation, especially in the development of the methods to match MHC antigens. His studies were important in the discovery of H-2 haplotypes, HLA alleles and haplotypes, the genetic order of the HLA loci, the significance of histocompatibility antigens in skin graft rejection as a test for histocompatibility, and in the outcome of kidney allografts. He was the first to use histocompatibility data to select sibling donors for kidney transplantation. He was one of a small international group of scientists, which included Rose Payne, Jean Dausset, Ruggiero Ceppellini, Paul Terasaki, Roy Walford, and Jon Van Rood, to produce what became HLA serology. This international collaborative effort led to the identification and definition of alleles of the different loci used in research of immune responses, disease association, and transplantation.

In the interview given by Bernard to Floyd Rogers in 1990 (Floyd Rogers ' s article of April 15 in Tarheel Sketch. " Bernard Amos. " Winston-Salem Journal.), Bernard said that he learned immunology from Gorer in the pub (Gorer would order a scotch—and he a beer—and discuss his results). He said that " Gorer ' s idea was that if you knew something about the body ' s normal tissue, you could build on that to learn something about cancer, to find something else that was special to the cancer. From the standpoint of immunology, cancer research and transplantation research are two sides of the same coin. " He was asked about the Nobel Prize. " You can never evaluate yourself. I never saw that as a serious possibility. The Nobels are good for science, but can have negative effects when investigators don ' t fully disseminate their findings for fear of helping a competitor. I think you realize that we ' re none of us in isolation. We must talk to each other; must read. And so, consciously or unconsciously, we take somebody else ' s ideas, and a little bit of this idea and a little bit of what that one says, and they may simmer in your mind for six months or one year and you meld them like making cheese balls. A little of port wine goes there and a little cheese, and it gets mixed together and soon nobody can identify the cheese ball. "

Perhaps his most endearing quality was his altruism, which combined with his humility, showed an aspect of his life that was unusual; for most of the time after 1990 he with his wife, Kay, volunteered weekly with the Meals on Wheels program in Durham. They took meals to many poor families and they continued even when he was in poor health during the last months of his life.

D. Bernard Amos made an impact on scientific knowledge in several areas: in immunogenetics, tumor immunity, and transplantation immunology. He was a pioneer in the studies of genetics of individuality and a leader in founding important national and international scientific organizations. He trained a number of prominent scientists and established pioneering clinical and basic research programs worldwide, including developing countries. He was altruistic and ready to help not only his students but also others who needed help.

SEVERAL INDIVIDUALS provided important help in preparing this manuscript. They include Fran Ward from Duke University, Chris Amos (Bernard ' s son) from the University of Texas, Kay Amos (Bernard ' s wife), Janet Plate from Rush Medical School, Jeffrey

Dawson from Duke University, and Floyd Rogers in his article in the *Winston-Salem Journal* cited above.

NOTES

[1] Only two months before his death I asked him about a research problem I had encountered testing individuals exposed to tuberculosis that have a negative skin test. He remembered his NLT work of 40 years earlier and suggested that I look for antibodies to Class II and antibodies to tuberculin that could prevent delayed hypersensitivity reactions tested by intradermal inoculation of tuberculin.

[2] In this regard it is important to mention that experiments performed during the last histocompatibility workshop using a panel of monoclonal antibodies and cells typed at the allele level formally established, without cross-absorptions, that there are epitopes shared by alleles as well as private epitopes and that such epitopes are amino acid sequences recognized by antibodies.

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