



**Baruj Benacerraf**

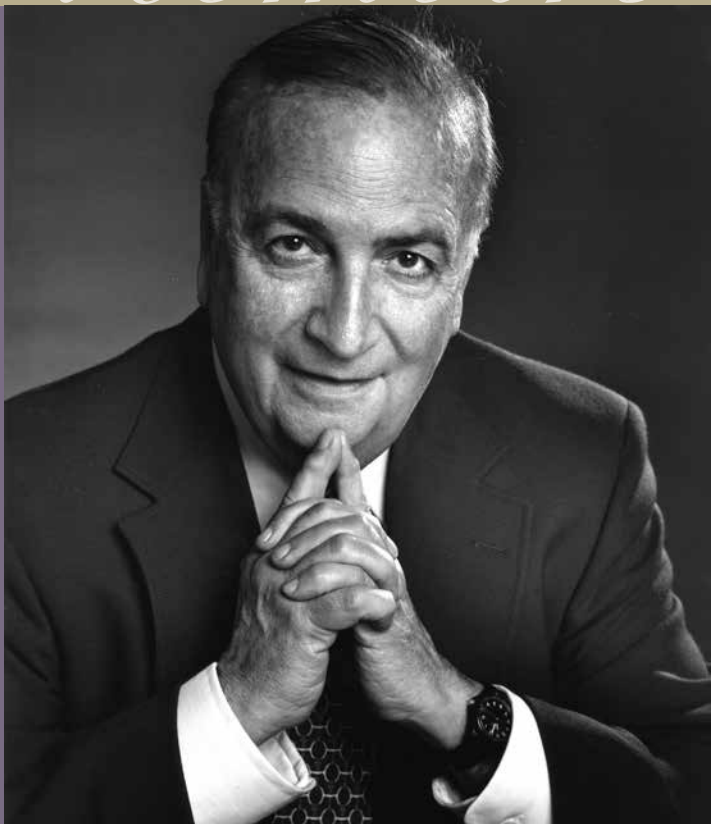
1920–2011

BIOGRAPHICAL

*Memoirs*

*A Biographical Memoir by  
William E. Paul*

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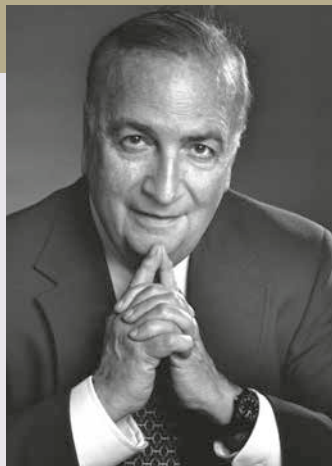
# BARUJ BENACERRAF

October 29, 1920 - August 2, 2011

Elected to the NAS, 1972

Baruj Benacerraf was a remarkable scientist, educator, and administrator who had an immense impact on biology and medicine through his path-breaking scientific achievements, his training of a generation of immunologists, and his leadership of biomedical research enterprises.

Baruj was born in 1920 in Caracas, Venezuela, to Sephardic Jewish parents. His father, Abraham Benacerraf, was a successful businessman who had emigrated to Venezuela from Morocco. In Caracas the elder Benacerraf had great success in the textile importing business and in finance. Baruj's mother, née Henriette Lasry, was raised in Algeria with a strong French cultural influence. When Baruj was five the family moved to Paris, where he received a rigorous French education. He attended the *Lycée Janson de Sailly*, located in the 16th arrondissement and generally considered one of the most prestigious *lycées* in Paris. His brother, Paul Benacerraf, born in 1931 in Paris, is a noted philosopher of mathematics and a professor at Princeton University, where he also served as provost of the university and chairman of the Department of Philosophy.



*Baruj Benacerraf*

By William E. Paul

In anticipation of the outbreak of the Second World War, the Benacerraf family returned to Venezuela in 1939, just before Baruj would have taken the final exams for his baccalauréat. They moved to New York City the following year so that Baruj could complete his education. He took the *baccalauréat* after study at the Lycée Français in Manhattan and was then accepted as a pre-medical student in the School of General Studies of Columbia University, from which he graduated in 1942. At Columbia he met and wooed the great love of his life, Annette Dreyfus, a student at Barnard College who had fled France with her family at the outset of the war. Annette's family was indirectly related to Captain Alfred Dreyfus and more closely to Eugene Meyer and his daughter Katherine Graham, the publishers of the *Washington Post*. Annette's aunt Odette was the wife of the great French molecular biologist Jacques Monod.

Baruj and Annette were married in 1943, the year he became a U.S. citizen. Their marriage, which spanned 68 years, was a remarkable pairing of two exceptional people. They were virtually always together. In later years, Annette accompanied Baruj on almost all of his scientific travels, and she could usually be found in his lab, especially at tea time.

Baruj's applications to U.S. medical schools were not successful, probably because of his educational background being so different from the usual U.S. applicant and possibly representing the still active anti-semitism in some academic circles. Through the help of George Bakeman, the father of a close family friend, he was granted an interview at the Medical College of Virginia, where he was accepted and from which he received his M.D. After internship at Queens General Hospital in New York City, he served in the United States Army from 1945 to 1948 as a physician in military hospital in Nancy, France.

### **With Elvin Kabat at Columbia**

Baruj's first serious adventure in research began in 1948, when he joined the laboratory of Elvin Kabat at the Columbia University College of Physicians and Surgeons. Kabat was a towering figure in immunochemistry and carbohydrate biochemistry and a most rigorous mentor. He was notable for his insistence on methodologic accuracy. No student or post-doc could begin experiments in the Kabat lab until he or she had mastered the measurement of protein nitrogen using a micro-Kjeldahl apparatus. The test was to carry out a precipitin analysis with a sample of an anti-pneumococcal polysaccharide anti-serum prepared many years earlier by Kabat's Ph.D. supervisor at Columbia, Michael Heidelberger, often regarded as the father of immunochemistry.

Only when one achieved a result within 1 or 2 percent of Heidelberger's was one "certified" to actually work in Kabat's lab. Baruj received and internalized the lesson of the absolute importance of applying quantitative analysis to biologic phenomena. Indeed, he subsequently applied the "Heidelberger test" to his own post-docs. I can personally attest to having achieved a result close enough to Heidelberger's to allow me to carry out experiments in the Benacerraf lab many years later. In Baruj's work with Kabat he examined the quantitative requirements for the induction of immunopathologic responses, including anaphylactic and Arthus reactions. The emphasis on quantitation of *in vivo* phenomena was to characterize much of his subsequent research. During Baruj's tenure at Kabat's lab, he and Annette celebrated the birth of their daughter, Beryl, in 1949. Beryl later did her undergraduate work at Barnard College, like her mother, and

went on to Harvard Medical School. She is now a leader in the use of sonography for prenatal diagnosis of congenital abnormalities and served as the editor-in-chief of the *Journal of Ultrasound in Medicine*.

### **Return to Paris**

In mid-1949, the Benacerrafs returned to Paris, where Baruj joined the laboratory of Bernard Halpern, a leader in the study of allergic disorders and anti-histamines. While in Paris, Baruj became deeply involved in managing his family's business interests in Venezuela, as his father had been incapacitated by a stroke.

At the Hôpital Broussais, where Halpern's lab was located, Baruj embarked on a series of studies of the phagocytic system, using experimental animals. Based on his understanding of the importance of quantitation in the analysis of biologic phenomena, he applied rigorous technology to the study of what was then designated the reticuloendothelial system (RES). Carefully measuring the clearance of particulate matter, he formulated the equations that describe this process. Much of this work was done in collaboration with Guido Biozzi, who became a lifelong friend.

### **NYU days: lymphocyte specificity, immunoglobulin function, Fc receptors and Ir genes**

By 1956 Baruj was feeling the constraint of the French biomedical research system, where he, as a "foreigner," found it difficult to win acceptance. When Louis Thomas, one of the great biomedical scientists of that era, offered him an independent position at the New York University School of Medicine, he seized the opportunity. Thomas and his colleagues at NYU were intent on establishing an international center of immunology at the medical school. Their recruitment of Baruj proved to be a key to their success. NYU developed a remarkable immunologic faculty, including, in addition to Thomas and Benacerraf, Jonathan Uhr, Edward Franklin, Michael Heidelberger (in his second post-retirement position), Zoltan Ovary, Jeanette Thorbecke, Victor and Ruth Nussenzeig, Kurt Hirschhorn, Robert McCluskey, Jerry Lawrence, Michael Lamm, and Gregory Siskind. Baruj became the intellectual leader of this remarkable group. His 12 years at NYU were perhaps the highlight of his scientific career. During this period, other than seeing to his family business responsibilities, he could devote himself full time to research.

Baruj thrived in the NYU environment. When he first arrived, he continued and extended his studies of clearance of antigen/antibody complexes by the RES and of the

immunopathologic consequences of immune complexes. But he quickly developed a whole new set of interests. Among them was the analysis of the distinctive specificity of cellular and antibody-based immunity, a study that morphed into an analysis of the relative specificity of T and B lymphocytes. That work began with a long-lasting collaboration between Baruj and Philip Gell, professor of immunology at England's University of Birmingham. Gell was one of the giants of British immunology, then in its heyday.

Together, Benacerraf and Gell showed that when hapten-carrier conjugates were used as immunogens, the antibodies that emerged and the immediate hypersensitivity reactions they induced were specific for the hapten alone. Stated more precisely, conjugates of the hapten, used in the immunization protocol, with proteins other than that used for immunization could provoke an immediate hypersensitivity reaction. By contrast, cellular immunity, as exemplified by delayed hypersensitivity, was intensely carrier-specific. For example, if guinea pigs were immunized with a hapten conjugate of guinea pig albumin (so there was no response to the unconjugated carrier), only the immunizing conjugate would provoke a response. Later, when I joined Baruj's laboratory in 1964, I continued this line of work under his supervision, now measuring antibody specificity and affinity by physical methods, analyzing cellular immunity by *in vitro* responses of lymphocytes (T lymphocytes, although we did not know that at the time) in proliferation assays, and validating the fundamental difference between the specificity of T and B cells nominally directed at the same antigen.

The work on specificity proceeded apace with the analysis of the distinctive functions of different classes of antibodies. Here Baruj was fortunate to have the collaboration of Zoltan Ovary, a remarkable man who had developed the passive cutaneous anaphylaxis test for antibodies mediating immediate hypersensitivity. With Ovary and his post-doctoral fellows Kurt Bloch and François Kourilsky, Baruj showed that guinea pig IgG1 antibodies mediated immediate hypersensitivity and anaphylaxis while guinea pig IgG2 antibodies were responsible for complement fixation and the opsonization of microorganisms in preparation for their phagocytosis. Not only did this work unequivocally establish that different classes (or subclasses) of immunoglobulins mediated distinct functions, it also led to work with his post-doc Arthur Berken establishing that a receptor existed on phagocytic cells for the Fc portion of antibody that was critical for the phagocytosis of antibody-coated bacteria. This description of Fc receptors laid the foundation for an entire field of immunology.

But the crowning achievement of the NYU era was the discovery of immune response (*Ir*) genes. Baruj had undertaken a series of experiments with Gerald Edelman, then at the Rockefeller University, on the structural basis of antibody specificity. Reasoning that they would have the best chance to see differences in mobility of L chains from antibodies directed to distinct antigens if the immunogens were simple, Baruj and his post-doctoral fellow Bernard Levine examined the immunogenicity of 2,4-dinitrophenyl (DNP) conjugates of homopolymers of L-lysine (poly-L-lysine, or PLL). Unexpectedly, they observed that of a population of outbred guinea pigs, only 40 percent responded to DNP-PLL. Although inbred guinea pigs were not available to Baruj at that time (they did become available later), interbreeding studies revealed that the responsiveness segregated as if it were controlled by a single genetic locus. Furthermore, the capacity to respond to DNP-PLL extended to other hapten conjugates of PLL as well as to the co-polymer of glutamic acid and lysine, although animals immunized with one PLL immunogen did not respond to challenge with another of the PLL conjugates, indicating that the *Ir* gene was not simply controlling the lymphocyte receptors for antigen that recognized the hapten-PLL conjugate.

Perhaps most importantly, transfer experiments that Baruj and Ira Green, a post-doc and life-long friend, carried out revealed that delayed hypersensitivity to a hapten-PLL conjugate could be transferred to naïve recipients by lymphocytes from an immunized donor only if the recipient itself possessed the responder allele at the *Ir* locus. This clearly argued that the site of action of the *Ir* gene products was in a cell that was essential to generate an immune response but not in the lymphocyte mediating the response. Perhaps a vigorous follow-up of this experiment would have revealed that the guinea pig *Ir* genes were histocompatibility genes, although so little was known of the guinea pig major histocompatibility complex (MHC) that this would have probably proved very difficult. It was left to Hugh McDevitt at Stanford to show, in an elegant experiment, that mouse *Ir* genes were encoded in the MHC, and eventually it would be recognized that the *Ir* gene products were the histocompatibility antigens themselves.

This brief description of the NYU days does not do justice to the intellectual excitement and the insights that characterized the Benacerraf lab in those days, but I hope it gives at least a glimpse of the remarkable 12-year period that Ron Germain and I called the Benacerraf *wunderjahre*.<sup>1</sup>

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1 Germain, R.N., and W. E. Paul. Baruj Benacerraf (1920-2011). *Nature*. 2011; 477:34.

## Baruj as a banker

Meanwhile, during this period Baruj continued to represent his family's business interests in New York City, which involved acting as a director of the Colonial Trust Co., a New York City-based bank, and later as a consultant to the Meadowbrook National Bank after its purchase of Colonial Trust. Baruj's experiences in banking and in managing the family's business interests prepared him for his later responsibilities at the Dana-Farber Cancer Institute as well as in his day-to-day interactions with colleagues, trainees, and administrators.

Baruj and Annette had a wide circle of friends in New York City, many from the upper echelons of the émigré scientific community, including Leo Szilard and André Cournand.

## Living in Manhattan

Baruj and Annette had a wide circle of friends in New York City, many from the upper echelons of the émigré scientific community, including Leo Szilard and Andre Cournand. The Benacerrafs lived in an elegant apartment on a high floor of Tower East, a striking Manhattan building designed by the architectural firm of Emery Roth and Sons and located at East 72nd Street and 3rd Avenue, where they entertained extensively. I recall that Baruj's rent for his parking space at Tower East was not very much less than my annual salary as a post-doc in his lab.

## The NYU days end badly

Although Baruj did not always get on well with those in authority, often because he felt he could do their jobs so much better than they, he had the highest regard for Lewis Thomas, and those feelings were reciprocated. Thus, Baruj was unprepared for a fiasco that led to his departure from NYU and from his days of running a small lab where he could oversee every experiment in minute detail.

Lewis Thomas was chairman of the Department of Pathology at NYU when he recruited Baruj but then moved to become the chairman of medicine. In 1966/67 Thomas was appointed dean of the medical school and proposed to Baruj that he apply for the position of chairman of anatomy, which had been vacant for an extended time. This possibility appealed to Baruj, as it would allow him to achieve a sorely needed expansion of his lab and to find positions for his junior colleagues (including me). He believed that the department required modernization and had proposed that it be retitled Cell

Biology. To the consternation of Baruj (and those of us who were in the lab at the time), the search committee did not recommend him for the position; instead, a proposal was made that he head a section of immunology that consisted essentially of the resources he already had. Deeply embarrassed by these events, he resolved to leave NYU, and he let it be known that he would be available for recruitment. Many opportunities presented themselves, although the one Baruj had hoped for, the chair of pathology at Harvard, did not—a result, it turned out, of unfortunate timing.

### **The Laboratory of Immunology: first effort to build a center**

Failing the Harvard position, Baruj's most attractive opportunity was the leadership of the Laboratory of Immunology (LI) at the National Institute of Allergy and Infectious Diseases (NIAID). Among its attractions were resources of space, positions, and funds sufficient for him to develop an integrated attack on the scientific problems that interested him the most. Also, very importantly, it gave him easy access to the two inbred strains of guinea pigs that were available in substantial numbers at NIH but virtually nowhere else in the world. More particularly, the two strains differed in the allelic forms of the *Ir* genes they possessed, making a serious analysis of the mode of action of the *Ir* gene products feasible. Baruj also found at NIH an administrator whom he truly admired, John Seal, scientific director of the NIAID Intramural Research Program.

Upon accepting the position of LI Laboratory Chief, Baruj discovered that while the lab had had an excellent beginning when it was founded in 1957 under the leadership of Jules Freund, after Freund's death, in 1960, things had not gone well. There was a small nucleus of excellent scientists, including Rose Lieberman, a pioneer in the study of mouse immunoglobulin genetics; Rose Mage, who was a leader in the study of rabbit immunoglobulin allotypes; and Ralph Reisfeld, an outstanding immunochemist. But others in the lab did not meet the Benacerraf standard. Such was the power of his name that many of these individuals chose to leave the LI, giving him leeway to initiate the subsequent flourishing of the Lab. With Ira Green, me, and a new crop of outstanding post-docs, Baruj continued his detailed analysis of the mode of action of *Ir* genes and embarked on insightful studies of T cell/ B cell collaboration.

Baruj also formed a deep friendship with Sheldon Wolff, the head of the NIAID clinical lab and an outstanding physician who had organized a remarkable clinical research center. Shelly (as he was universally known) mentored both Anthony Fauci and Charles Dinarello.



Baruj suffered from Familial Mediterranean Fever (FMF), and Shelly, having with his clinical colleagues demonstrated the efficacy of colchicine in the treatment of FMF, became Baruj's physician. Their relationship continued when they both moved to Boston, Baruj as chairman of pathology at Harvard Medical School and Shelly as chairman of medicine at Tufts.

Although Baruj truly enjoyed his days at LI and believed it was the optimal environment for doing research without distractions and with the stimulation of superb colleagues, he and Annette did not find Washington a very hospitable place to live, particularly after their glory years in Manhattan. When the opportunity to lead the Department of Pathology at Harvard Medical School presented itself in the spring of 1969, Baruj, with Annette's enthusiastic assent, accepted the chair of pathology and in July 1970 took up the position and the attendant Fabyan Professorship of Comparative Pathology.

### **Building experimental pathology and immunology at Harvard**

The Harvard Pathology Department in that era consisted of a "basic science component" located in the main quadrangle on Longwood Avenue and the divisions of pathology in the Harvard-affiliated hospitals. As chairman, Baruj was installed in building D2 of the quadrangle, where he built a first-rate faculty and at the same time filled the hospital pathology division directorships, which had almost all become vacant. In typical Benacerraf style, with his sure judgment of individuals, he made several outstanding appointments, including Ramzi Cotran at the Brigham and Women's Hospital, Robert McCluskey (his former NYU colleague) first at the Children's Hospital and later at the Massachusetts General Hospital, and Hal Dvorak at the Beth Israel Hospital.

In the quadrangle he had the benefit of an outstanding cell biologist already in residence, Morris Karnovsky. His first major recruit was Emil Unanue, then a young scientist at the Scripps Institute who had just returned from postdoctoral training with Brigitte Askonas at the National Institute for Medical Research in London. Emil would later go on to complete the line of work Baruj had started by demonstrating that class II MHC molecules could directly bind immunogenic peptides and to show that this binding event determined whether a molecule would be an immunogen or not. Baruj and Emil took joint responsibility for the organization of immunology in the Pathology Department and their influence was felt throughout the medical school as a whole. Indeed, the flowering of immunology at Harvard can largely be dated to Baruj's appointment. Before his arrival, there were individual areas of excellence, but they were not integrated. Baruj was able to bring together these disparate groups into a cohesive program with a single and

strong graduate program, a common and exciting seminar series that became the most heavily attended at Harvard, and collaborations among the various groups. During the Benacerraf years and extending to today, Harvard has been an immunologic powerhouse.

Baruj's move to Harvard completed the evolution of his research lab experience from a small group, usually numbering no more than four post-docs and two technicians at any one time in the NYU days, to an intermediate-size research group at NIH, to a large and integrated group at Harvard. His Harvard years were marked by work with some outstanding individuals, many of whom he trained himself. David Katz, who had been a post-doc with him at NIH, came to Boston as a junior faculty member and together they did several elegant experiments clearly demonstrating that the locus of action of Ir gene products was in cells expressing class II MHC molecules, not in the T cells.

Among students and post-docs trained in Baruj's laboratory in the Harvard days, the most notable were Steve Burakoff, now director of the Mount Sinai Cancer Center; Ron Germain, Chief of the NIAID Laboratory of Systems Biology; Mark Greene, a professor at the University of Pennsylvania School of Medicine; Bob Finberg, chairman of medicine at the University of Massachusetts School of Medicine; Ken Rock, chairman of pathology at the University of Massachusetts School of Medicine; and Normal Letvin, now deceased, who as a Harvard professor had been a leader in the study of T cell responses to HIV.

The Boston years were also ones of personal pleasure for both Baruj and Annette. They installed themselves in a beautiful apartment in Jamaicaway Towers, with an unrivaled view of the Boston skyline, and purchased a beach house in Woods Hole. They formed close personal relationships with many at Harvard and most particularly with the post-docs and students who were moving through the department and the Dana-Farber Cancer Institute (DFCI). Despite Baruj's considerable administrative responsibilities, he was immersed in his research program, and his trainees could expect calls from him at virtually any hour to discuss the implications of a new result and to plan the follow-on experiments.

### **The DFCI and the Nobel Prize**

Baruj's growing reputation as an outstanding scientist and administrator led to his being widely sought for very senior positions. In 1979, he was offered the presidency of the Memorial Sloan Kettering Cancer Center, a position that had just previously been held by his long-time friend and mentor, Louis Thomas. While Baruj was considering this

possibility, the leadership at Harvard asked him to take on the presidency of Harvard's cancer center, the Sidney Farber Cancer Institute, which was to be renamed the DFCI as a result of a major gift by philanthropist Charles A. Dana. Baruj accepted this new opportunity and the challenge of moving the Institute to a leadership position in cancer research.

Within a few months of moving into DFCI, word came that Baruj had been selected to share the 1980 Nobel Prize in Medicine or Physiology with Jean Dausset and George Snell, "for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions." This recognition was clearly for his discovery of *Ir* genes and for his elucidation of the



Benacerraf at the Nobel Prize ceremony, 1980. Below left, receiving the Nobel Prize from King Carl XVI Gustaf.



central role that they and their products, the MHC molecules, played in regulating T cell responses. Baruj was of course enormously honored, although he was disappointed that Hugh McDevitt did not share in the prize. His Nobel lecture, "The Role of MHC Gene Products in Immune Regulation and its Relevance to Alloreactivity," was a masterful summary of the sometimes painfully difficult process through which the earlier work on genetic control of immune responses had developed into the knowledge that illuminated how all T cell responses were controlled and the nature of the

immunogens recognized by T cells. Baruj donated the prize money itself to initiate the first fund-raising campaign of the DFCI, a move that would insure its success. Baruj's sure sense of leadership shone through.

Baruj continued to be the chairman of the Department of Pathology at Harvard until 1991, when he stepped down from that position; the following year he retired from the presidency of the DFCI. He maintained important ties to the DFCI serving as president of DFCI Incorporated and later as a trustee.

### **Family joys**

Baruj was justly proud of his daughter's accomplishments and those of his son-in-law, Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital and Mallinckrodt Professor of Medicine at Harvard Medical School. He delighted in his grandchildren, Oliver and Brigitte. Oliver was a 2003 graduate of Harvard College and is now a leader in a consulting firm that advises on energy, infrastructure and life sciences. Brigitte received her B.A. from Columbia (there is a continuing thread there) and her Ph.D. in classics from Princeton. She is now an Assistant Professor of Classics at Boston College.

As already noted, Baruj and Annette were inseparable from their earliest days as a couple until the end. My wife and I recalled visiting them in 2010 and 2011, when age had taken its toll, particularly on Annette. There they were, seated together on a couch, as we might have found them at an earlier time. Annette died on June 3, 2011, just a few days before her 90th birthday. I spoke to Baruj that day. He told me that he could not go on without her, and true to his word, as ever, he died on August 2, 2011.

Legacies are often hard to assess. What seem like great strides forward at the time often pale when looked at from a later vantage point. But I think enough time has passed since the Benacerraf glory years to be confident that the work that illuminated how T cells recognize antigens and how this determines immunogenicity will live on, although it is often sad to see that, while the consequences of the work are known to new entrants in the field, those who did that work are often forgotten.

### **Summing up**

Baruj Benacerraf was a remarkable and unique man, combining scientific creativity and rigor with a deep appreciation of how to deal with people and a remarkable talent for managing institutions. Superficially, he may not have seemed the most approachable of individuals. He was a formidable personality from the day I met him in 1962 to the very end of his life. But for those who knew him well, he was an enormously warm and caring individual, acting as a virtual father figure for many who were his trainees. He certainly fulfilled the injunction of Judaism of *tikun olam*, to perfect the world. He liked to point out that his name, Baruj Benacerraf, could be translated as Blessed Son of the Angel. No more need be said.

### **Acknowledgements**

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