AMERICAN SOCIETY OF TRANSPLANT SURGEONS

PRESIDENTIAL ADDRESS

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It has been my great fortune to be elected the 32nd President of the American Society of Transplant Surgeons. I am grateful to all of my colleagues for the privilege of serving as the spokesperson for our more than 1,000 surgeons, physicians and scientists for the past year. Certainly, one of the greatest honors an individual can receive is to be selected by his peers to a leadership position in an international society of such prominence. With the receipt of such a responsibility, the first question that crosses one's mind is: "How can I help to maintain this Society's traditions of leadership, education, and camaraderie?" This is closely followed by: "What can I possibly say in my Presidential Address that is worth saying?" Typically, Presidents seem to reminisce regarding their own lifetime experiences or those of previous giants in their field. I have chosen to recall for you the four Nobel Prizes in Medicine that have been awarded to eight physician-scientists who were recognized for their contributions to the field of transplantation (Table 1). Although several other Nobel Prizes have been awarded for more broadly inclusive medical discoveries that have proved to benefit transplant patients as well, these will not be reviewed here. Such prizes are the 1984 Award to Jerne, Kohler, and Milstein for their production of monoclonal antibodies and the 1988 Award to Black, Elion, and Hitchings for drug treatment discoveries, including some of the cytotoxic drugs that have been used for immunosuppression of allograft recipients.

THE NOBEL FOUNDATION

The Nobel Foundation was established when Dr. Alfred Nobel, a Swedish engineer and inventor prepared his will in 1895. The pertinent provision stated that:

"…The whole of my remaining realizable estate shall be dealt with in the following way: The capital shall be invested in safe securities by my executors and shall constitute a fund, the interest on which shall be annually distributed in the form of prizes to those who during the previous year, shall have conferred the greatest benefit to mankind…" (1)

The award was to be divided into five equal prizes, recognizing the most important discovery in the fields of chemistry, physics, literature, fraternity between nations (peace), and physiology or medicine. A sixth prize for economics was instituted in 1968 by the National Bank of Sweden.

The responsibility for selecting the annual awardees was directed to several institutions with the prize for medicine to be awarded by the Karolinska Institute in Stockholm, Sweden. Until 1977, the process was handled by the Institute's entire professional medical staff which initially numbered only nineteen members. However, with the growth of the medical faculty, it became difficult to conduct the complicated discussions that are required for the selection of Nobel Laureates. In addition, new Swedish laws were being introduced at that time that made documents of state institutions, which include the Karolinska Institute, open to the public. This would have made it impossible to keep secret the deliberations of the Nobel Committee. For both of these reasons, a new organization, the Nobel Assembly was instituted in 1977. Though this Assembly is strongly connected with the Karolinska Institute, it is legally and financially independent of the Institute itself as well as of the State.

The initial Nobel Prizes were awarded in 1901. Since then, 184 Nobel Laureates in Medicine have been named. Before reviewing the contributions of the eight extraordinary individuals who were awarded the Prize in our field of transplantation, it is of interest to recall a bit of the life of Dr. Nobel himself.

ALFRED NOBEL

Alfred Bernhard Nobel was born in 1833 in Stockholm. He was educated primarily by tutors in Leningrad where his father worked as an engineer and inventor. Around 1850, he left Russia and ended up working in the United States for several years under the direction of another Swedish engineer, John Ericsson, who incidentally is best known for having built the ironclad Civil War ship "USS Monitor".

Alfred Nobel is primarily remembered for his invention of dynamite. Unfortunately, as with many scientific projects, his preliminary results were not as anticipated, resulting in his factory blowing up causing five deaths, including Alfred Nobel's youngest brother. At this point, the Swedish government forbade rebuilding the factory and Nobel became dubbed "a mad scientist". Nevertheless, he stubbornly resumed his work on a barge in a nearby lake. Eventually, he was able to perfect the development of dynamite (a discovery undoubtedly worthy of a Nobel Prize itself) and subsequently other even more powerful explosives. The worldwide demand for this novel discovery, plus his shrewd investments in the Baku oil fields of Russia brought this creative inventor an immense fortune, the bulk of which was left to the establishment of the Nobel Prizes.

ALEXIS CARREL

In 1912, Alexis Carrel became the first "transplant surgeon" to be awarded the Nobel Prize **"for his work on suturing of vessels and transplantation of organs"**. Carrel was born near Lyons, France in 1873. He went to medical school at the University of Lyons graduating in 1900 (2).

Carrel's interest in vascular surgery was initially stimulated by his observation as a student in 1894, of the care of Sadi Carnot, President of the French Republic. An assassin's knife had severed Carnot's portal vein whereupon the best surgeons in France had concluded that it would be impossible to repair the vessel. The young Carrel voiced his opinion that Carnot's life could be saved, if surgeons had perfected blood vessel suturing techniques, a view that hardly endeared him to his surgical superiors.

In 1903, Carrel witnessed another dramatic event that proved to play a significant role in his subsequent career development. While attending to the sick making pilgrimages to the Shrine at Lourdes, he encountered a woman dying of tuberculous peritonitis. The following day, after being anointed with water from the pool, the woman made a remarkable recovery and went on to live another 34 years. When Carrel reported this apparent miracle to his surgical colleagues, he was ridiculed for his gullibility; and he was subsequently failed twice in his exams for a full faculty appointment to the surgical staff. Frustrated by this lack of acceptance at his own alma mater, Carrel left France in 1906 and moved to the Rockefeller Institute of Medical Research where he pursued his studies over the next 33 years.

The first contribution acknowledged in Carrel's Nobel Prize introduction was his perfection of a reliable method of suturing vessels, using the famous triangulation technique in which he

> *"..enlarged the opening using three retaining stitches located at equidistant points which converted the round opening into a trianglular one… This method proved to be reliable and effective insofar as it protects against post-*

> *operative hemorrhages and embolisms, but its greatest merit was that <u>it did not produce any stricture</u>…"*

Carrel immediately recognized the potential of his newly perfected suture methods and went on to transplant whole organs (initially thyroid gland and kidney) as either autografts or allografts. He even extended these studies to limb reimplantation. These discoveries were recognized as well in his Nobel Prize award.

Carrel later summarized his observations (3), as he had in his Nobel acceptance speech, as:

> *"…concerning homoplastic transplantation of organs such as kidneys, I have <u>never found positive results to continue after a few months</u>, whereas in autoplastic transplantation, the result was always positive. The biological side of the question has to be investigated very much more and we <u>must find out by what means to prevent the reaction</u> of the organism to a new organ"*

His insight in recognizing the failure of the transplant as rejection of non-autologous tissues would have to wait 30 years for the Nobel Laureates, Medawar and Burnet (see below) to clarify the nature of these biologic events resulting from the host's immunologic response and 40 years for the first successful transplantation of homoplastic organs (allografts). (see J. Murray, below).

Carrel remained at the Rockefeller Institute until his forced retirement in 1939 at age 65. Angered by this, he returned to France where he hoped to establish a new Research institute. France, unfortunately, was occupied by the Germans one year later; and when Carrel continued his plans for the Institute with the consent of the pro-Nazi

Vichy government, he was accused of collaboration with the enemy. Following the liberation of France by the allied armies, Carrel was relieved of his position at the Institute. He died shortly later on November 5, 1944, having been unable to clear his name.

PETER BRIAN MEDAWAR and FRANK MACFARLANE BURNET

The next Nobel prize in medicine for contributions to the field of transplantation was awarded jointly in 1960 to Drs. Medawar and Burnet **"for the discovery of acquired immunological tolerance".**

Medawar was born in 1915 in Rio de Janeiro. At the age of only 17, he went to Magdalen College, Oxford, to study zoology. He immediately became interested in research in several fields of biology related to medicine, including tissue culture, regeneration of peripheral nerves, and mathematical models of the changes that occur during development. However, it was the outbreak of the Second World War that proved to be the catalyst for his most important observations. At that time, Medawar was asked by the Medical Research Council to investigate why skin from one human being would not form a permanent graft when placed on another (4).

Medawar, together with Rupert Billingham and Leslie Brent, in a series of incisive studies of normal tissue grafting, was able to show that the graft reaction is an immunologic response similar to the tuberculin reaction and that the cellular immunological pattern is an expression of the individual's genetic constitution. Their observations of dense lymphocyte infiltrates in the allografted tissue ushered in the era of cellular immunology. The most significant contribution was the demonstration that allograft rejection was completely prevented in mice if living cells from the future allograft donor were introduced into the recipient during foetal or neo-natal life. This was the first clear demonstration that the immune system is not pre-programmed to distinguish between self and non-self, but learns to do so as a result of exposure to self antigens during early development. Most importantly, the immunological barriers to the transplantation of foreign tissue and organ grafts - till then thought to be insurmountable - could be overcome by immunological interference, which opened up a vast field of scientific endeavor.

When the Prize was awarded to Medawar and Burnet in 1960, it was noted that (5):

> *"This observation has now been amply confirmed and expanded in various directions. Experimentally produced tolerance has developed into a biological research tool of great usefulness. Application in practical medicine is still in its very early stages. Naturally it has been close at hand to attempt to apply the laboratory experience gained in the field of surgery, where the problem of <u>substitution of defective or damaged, vitally important organs</u> not infrequently presents itself…The <u>first successful operations</u> of this kind were <u>recently reported</u>, and there are reasons to await the future development with confidence…"*

How prophetic was this prediction, as we now witness thousands of successful transplants being performed worldwide every year.

Medawar had been named Professor of Zoology at University College. London, in 1951, at the age of 36. In 1962, shortly after receiving the Nobel Prize, he became Director of the National Institute for Medical Reseach. He continued his studies, either personally training or greatly influencing the careers of many of our transplant community. Unfortunately, at the age of only 54, while reading the lesson during Sunday services at the cathedral, he suffered a massive cerebral vascular accident which left him seriously handicapped for the rest of his life. Nevertheless, he remained extraordinarily active, continuing to pursue his research, now more in the field of cancer, and to publish a widely-read stream of books and essays such as "Advice to a Young Scientist" in 1979 and his widely acclaimed autobiography: "Memoirs of a Thinking Radish" in 1986, only one year before his death (4).

MacFarlane Burnet was awarded the Nobel Prize in 1960 jointly with Medawar. Burnet was born in Victoria, Australia in 1899. At the age of 24, he went to the Walter and Eliza Hall Institute of the University of Melbourne where he worked essentially continuously for the rest of his life. Burnet's early research was primarily in the field of viral infections and the host response to the virus which provided a naturally occurring phenomenon to study immunologic reactions. He is credited with first speculating on the concept of "self" vs "non-self" and for developing a unifying hypothesis regarding the overall nature of the immune response as a major defence mechanism for survival of the species and of the controlling reactions that prevent autoimmunity (6). He concluded that allograft rejection resulted from the same immune response as that directed to viruses and postulated that individuals could be treated in order to accept grafts as self. As noted above, it was Medawar, then, who proved the validity of this speculation. Thus, the Nobel Committee recognized Burnet together with Medawar for the discovery of tolerance, making Burnet the first Australian to receive a Nobel Prize. Like Medawar, Burnet continued his prolific research, producing numerous scientific publications almost until the time of his death in 1985.

GEORGE D. SNELL, JEAN DAUSSET, AND BARUJ BENACERRAF

The third Nobel prize awarded for contributions to transplantation science was in 1980 when Drs. Snell, Dausset, and Benacerraf were cited **"for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions"**. In the presentation speech for their award, it was noted that "starting from three different directions", their individual studies led to an understanding of the major histocompatibility complex (MHC) and its importance as a surveillance system for the preservation of the species (7).

Dr. Snell was born in Bradford, Massachusetts in 1903. He became interested in genetics while studying at Dartmouth College, an interest that led to his lifelong work. In 1935, he joined the staff of the recently founded Jackson Laboratories in Bar Harbor, Maine, where the world's first inbred strains of mice had just been produced. Over the succeeding 30 years, Dr. Snell manipulated these unique experimental models to determine the role of genetic factors, initially in the acceptance or rejection of cancers; but soon afterwards he extended his studies to the rejection of normal tissues. Snell concluded that the immunologic response against non-cancerous tissues was regulated by what he termed "histocompatibility genes" and he identified the MHC of the mouse to be the H-2 region (8).

Dr. Dausset was born in Toulouse, France in 1916. As with many of his generation, Dausset's discoveries were, in large part, related to his experiences in the Second World War. While assigned to the fighting forces in North Africa, he observed that recipients of multiple blood transfusions often developed leukocytotoxic antibodies that reacted with donor white blood cells, but not with their own. This initial observation led to his intensive post war studies in Paris, as well as at Children's Hospital in Boston, in the rapidly developing field of immuno-hematology. Although he couldn't pursue his studies in an elegant inbred model as was available for Dr. Snell's work, Dausset began extensive family analyses. From these, he concluded that the immune response to incompatible white blood cells was determined by a single gene complex, the first product of which he identified in 1958 and is now known as HLA-2. Dausset's studies emphasized that the MHC of man, which he initially termed Hu-1 and was ultimately named Human Leukocyte Antigen locus A or HLA, was analagous with H-2 in the mouse (9).

The dissemination and application of Dausset's observations rapidly required the establishment of histocompatibility laboratories for support of clinical transplant centers around the world in order to help select compatible donor-recipient combinations.

Meanwhile, Dr. Benacerraf was pursuing a different line of investigations that would lead to definition of another important MHC locus, the immune responsiveness or IR complex of genes.

Dr. Benacerraf was born in Caracas, Venezuela in 1920. His initial education was in France, but the outbreak of the Second World War forced his family's return to Venezuela, and then New York. Amazingly, despite his excellent academic record and his ultimate accomplishments, he always reported that he had some difficulty in gaining admission to medical school. He entered the Medical College of Virginia in 1942 from which he graduated three years later. After a two-year Army Medical Corps tour in post-war France, Dr. Benacerraf returned briefly to Columbia University, then back to Paris in 1949, and ultimately to New York University. It was here that his studies led to the seminal observations that outbred animals, all immunized to the same antigen, appeared to segregate into responder or non-responder groups (10).

Benacerraf postulated that the intensity of an individual's immune response to a particular antigen is controlled by specific genes which ultimately have come to be termed immune response (Ir) genes. Over the next 15 years at New York University and later at the Laboratory of Immunology of the NIAID in Bethesda, Benacerraf's studies systematically clarified how the area of the MHC containing these genes regulates immune responsiveness.

The individual studies of Snell, Dausset, and Benacerraf, therefore, all led to a single region on one chromosome in mice and man. These observations served to identify and clarify the biological system (MHC) that is responsible for cell recognition, immune responsiveness, and transplant rejection. As such, their combined work was recognized as an indivisible discovery by the Nobel Assembly in 1980.

Dr. Snell retired in the mid-1980's, 50 years after the discovery of H-2; and he died in June of 1996. Dr. Dausset has continued his extensive studies of the polymorphism of the HLA complex and is still Chairman of the France Bone Marrow Grafts. Dr. Benacerraf was President of the Dana-Farber Cancer Institute until 1992 and continued his active research and publication career until the early years of this century.

JOSEPH E. MURRAY and E. DONNALL THOMAS

The most recent Nobel Prize for transplantation was awarded in 1990, jointly to Drs. Murray and Thomas **"for their discoveries concerning organ and cell transplantation in the treatment of human disease".** Dr. Murray was born in Milford, Massachusetts in 1919. He received his Medical Degree from Harvard Medical School in 1943. Following an abbreviated nine-month surgical internship at Peter Bent Brigham Hospital (PBBH), he was assigned to active duty in the army at Valley Forge General Hospital in Pennsylvania. At that hospital, skin allografts from family members or cadavers, were sometimes being used as temporary dressings on extensively burned soldiers, an approach that stimulated Dr. Murray's interest in the biology of tissue transplantation. He was particularly intrigued by the unusually slow rate of rejection of some allografts in these critically ill patients. His Chief, Dr. James Barrett Brown, had speculated that more rapid destruction of the skin graft was associated with increasing genetic differences between donor and recipient. He also advised Dr. Murray that he had observed skin grafts exchanged between identical twins to survive indefinitely. That observation proved to be a prophetic event that would lead to the first successful human renal transplant between identical twins less than a decade later.

When Dr. Murray joined the surgical faculty at PBBH in the early 1950's, he was encouraged by his Chief, Francis Moore, to work with the already active team that Dr. David Hume had assembled to perfect the operation of kidney transplantation in dogs with the goal of treating renal failure in humans (11).

In the fall of 1954, a history-making sequence of events began to evolve. A patient with severe renal disease, who was referred to the PBBH for treatment, was found to have a healthy twin brother. In preparation for a possible precedent-setting transplant operation, the ethical issues involved were extensively debated and ultimately resolved. On December 23, 1954, many years of work by investigators all over the world finally came to fruition when Joseph Murray, at the age of 35, performed the first successful human kidney transplant. Good function was maintained in this patient for a subsequent nearly eight years at which point the original renal disease recurred, ultimately leading to the patient's death (12). Dr. Murray would subsequently recall:

"This spectacular success was a clear demonstration that

> *organ transplantation could be life saving. In a way, it was spying into the future because we had achieved our long-term goal by bypassing, but not solving, the issue of biological incompatibility"* (13)

Dr. Murray was recognized by the Nobel Foundation not only for this procedure, but also for performing in 1959 the first successful kidney transplantation between relatives that were not identical twins, using whole body irradiation as immunosuppression, and ultimately that between unrelated individuals, performed in 1962 using some of the cytotoxic drugs synthesized by George Hitchings and Gertrude Elion for immunosuppression.

Joseph Murray continued his research and dual clinical practice in transplantation and plastic surgery for nearly twenty years after that first successful transplant in 1954. In 1971, he resigned as Chief of Transplant Surgery at the now Brigham and Women's Hospital (BWH) to focus on his major surgical interest, reconstructive surgery. He continued his practice until 1986 when a cerebral vascular accident, from which he recovered completely, prompted him to retire from active clinical work. He, nevertheless, remains active, with reference to his publications regarding various aspects of clinical medicine; including transplantation, reconstructive surgery, and medical ethics, appearing in Pub Med even today.

Dr. E. Donnell Thomas was jointly honored by the Nobel Assembly in 1990 for his many contributions to the successful clinical application of bone marrow transplantation. Dr. Thomas was born in Texas in 1920. He received his M.D. from Harvard in 1946 and while continuing his post graduate training, he and Dr. Joseph

Murray became friends at the then PBBH in Boston. Dr. Thomas thus was present, as a medical resident, to help care for the first kidney transplant recipient described above.

Dr. Thomas began his lifelong investigation of bone marrow transplantation initially with Dr. Sydney Farber in Boston. He then worked for several years at Cooperstown, New York, but eventually settled in Seattle, Washington in the early 1960's (14). His ongoing attempts to establish allogeneic marrow engraftment in dogs and man while avoiding the usually encountered and often fatal graft-versus-host disease (GVHD) were greatly aided by the clarifications of the histocompatibility system that were being provided at the same time by Snell and Dausset (see above).

Dr. Thomas's team eventually settled in the Fred Hutchinson Cancer Research Center which became the leading bone marrow transplant center in the U.S. His contributions, particularly to the control of GVHD with judicious administration of cyotoxic agents, were credited by the Nobel Assembly as the foundation for the cure of thousands of patients with leukemia and other blood disorders.

Dr. Thomas retired from patient care about the same time that he was awarded the Nobel Prize, but he has continued to lecture and publish widely. He remains involved with the Fred Hutchinson Cancer Research Center activities, most recently as an ardent advocate for stem cell research.

CONCLUSION

The Nobel Prizes awarded to these eight individuals highlight some of the most remarkable achievements in the art, the science, and the practice of transplant medicine over the past century.

The important discoveries made by these pioneers were based upon a range of ingenious approaches and astute observations. As acknowledged by the Nobel

Foundation, these contributions do not "cover the whole story", but they should serve as a collective source of pride and inspiration for the entire transplant community. The vision, courage, and perseverance displayed by these giants emphasize that success is not an accident; and their enthusiasm for their work should serve as a source of inspiration and example for all investigators currently seeking to unravel the many remaining mysteries that limit the more widespread application of organ and tissue transplantation.

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Table 1

NOBEL PRIZE FOR CONTRIBUTIONS TO TRANSPLANTATION

LAUREATE	LIVED	AWARD	TOPIC
Alexis Carrel	1873-1944	1912	Vascular/Tx Surgery
F.M. Burnet P.B. Medawar	1899-1985 1915-1987	1960 1960	Fetal Distinction of Self vs Nonself
G.D. Snell J. Dausset B. Benacerraf	1903-1996 1916- 1920-	1980 1980 1980	MHC/Tissue Typing/Ir Genes
J. Murray E.D. Thomas	1919- 1920-	1990 1990	Organ and Cell Tx

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