

Nobel Prize Winners Who Contributed To Transplantation



Przemyslaw Rutkowski^{1,3}, Janusz Ostrowski², Alicja Debska-Slizien³, Boleslaw Rutkowski³

¹ Department of the General Nursery, Medical University Gdansk, Poland,

² Department of History of Medicine, Centre of Postgraduate Medical Education, Warsaw, Poland

³ Department of Nephrology, Transplantation and Internal Medicine, Medical University Gdansk, Poland

Corresponding Author: Przemyslaw Rutkowski MD, PhD

Department of the General Nursery, Medical University Gdansk, Poland Debinki Str 7 | 80- 211 Gdansk , Poland

Tel: +48 58 349 2505, Mobile +48 664 479 338; e-mail: prut@gumed.edu.pl

ABSTRACT

The Nobel Prize in Physiology or Medicine, administered by the Nobel Foundation, is awarded once a year for outstanding discoveries in the fields of life sciences and medicine. It is one of five Nobel Prizes established in 1895 by Alfred Nobel. Idea of transplantation came from antiquity. The patron of modern transplantation are Damian and Cosma, monks who according to the legend, transplanted leg to the ill comrade. The modern transplantation required series discoveries before had achieved present level. Many, among these discoveries were such important that were acknowledged with the Nobel Prize. There is always open question were there other important people or/and breakpoint which should be also appreciate, but in presented paper only Nobel Prize winners were described. Alexis Carrel discovered how to connect vessels and described "Carell's patch". Sir Frank MacFarlane Burnet and Peter Brian Medawar described acquired immunological tolerance. Next milestone was discover role of antigens on the leukocytes surface independently by George Snell, Jean Dausset and Baruj Benaceraff. The first organ as well as bone marrow transplantation were performed despite lack of effective immunosuppression. Successful kidney transplantation was done by Joseph E. Murray, E. Donnall Thomas was pioneer in bone marrow transplantation. Present transplantation would not be possible without immunosuppressive drugs. Synthesis of azathioprine was breakthrough, and that was achieved by Gertrude B. Elion and George H. Hitchings. Thanks to Ralf M. Steinman we know and understand the role of dendritic cells in adaptive immunity. Transplantation is still developing, next breakthrough will come soon.

KEYWORDS: Nobel Prize, transplantation, immunology, immunosuppression

Introduction

The Nobel Prize in Physiology or Medicine, administered by the Nobel Foundation, is awarded once a year for outstanding discoveries in the fields of life sciences and medicine. It is one of five Nobel Prizes established in 1895 by Alfred Nobel himself. Nobel was personally interested in experimental physiology and wanted to establish a prize for progress through scientific discoveries in laboratories. The Nobel Prize is presented to the recipient(s) at an annual ceremony on 10 December, the anniversary of Nobel's death, along with a diploma and a certificate for the monetary award. The front side of the medal provides the same profile of Alfred Nobel as depicted on the medals for Physics, Chemistry, and Literature; its reverse side is unique to this medal (1, 2).

The idea of replacing diseased parts of body has been around for millennia. Envisioned were complex transplants such as the "successful" transplantation of an entire leg by the 3rd century sainted physicians Cosmos and Damien. As early as 600 b.c., the use of autogenous skin flaps to replace missing noses was conceived, and by the sixteenth century, Gaspare Tagliacozzi and other pioneering plastic surgeons were successful with such procedures. But not until the twentieth century was it ever mentioned that grafts might fail. Even the great eighteenth century experimentalist John Hunter, who transplanted human teeth and autotransplanted cocks' spurs into their combs, seemed unaware that homografts would fail (3). As true the 20th century has changed a lot in the transplantation field.

One among the others whose achievement was awarded with the Nobel Prize was Alexis Carrel (Figure 1).

He was born on 28 June 1873 near Lyon, France. Carrel's interest in transplantation was first manifested in 1902 in Lyon, when he transplanted a kidney from a dog's abdomen to its neck. The kidney produced urine immediately, and the animal died after a few days from an infection. In 1904, Carrel left



Figure 1 - Alexis Carrel in 1912.

France after failing in several examinations to qualify for a faculty position there. He moved to Chicago, where he partnered with the physiologist Charles Guthrie. They collaborated for barely 12 months, but during this time, they successfully transplanted the kidney, thyroid, ovary, heart, lung, and small bowel, averaging a publication on this work every 14 days (4). Carrel first published his work on organ transplantation in October 1905 (ie, the "Functions of a Transplanted Kidney"),

which was co-authored by Charles Guthrie. Carrel's success with organ grafts was not dependent on a new method of suturing but on his use of fine needles and suture material, his exceptional technical skill, and his obsession with strict asepsis. Carrel and Guthrie developed the so called Carrel's patch for kidney transplantation. This technique, still used today, removes a patch of aorta with the renal artery attached, in order to avoid the dangers of thrombosis posed by a small blood vessel anastomosis. Unfortunately relationship between Carrel and Guthrie cooled and in 1906 Carrel moved from Chicago to the Rockefeller Institute in Chicago. Next few years Carrel focused his research on surgical procedures on the heart. He was many decades ahead of his time, performing mitral valvulotomy, mitral valvuloplasty, and coronary artery grafting. He did the world's first coronary artery bypass graft, suturing

one end of a long segment of canine carotid artery to the aorta and the other to a coronary artery. Carrel was rewarded for his groundbreaking work by receiving the Nobel Prize in Physiology or Medicine in 1912, "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs" (4, 5). At the age of 39 years, he was also the youngest Nobel Laureate. When he reached age of 65 he was forced to retire so he came back to France. That was in 1939, After France capitulation, the Vichy government offered Carrel the opportunity to continue his work at his own institute, to be called the "Institute of Man." The institute opened in 1941. Because of his relationship with Nazi-supported Vichy, Carrel was widely regarded by his countrymen as a Nazi collaborator. After the liberation of France in 1944, he was relieved of all duties related to his institute and was placed under surveillance. An investigation began to evaluate the extent of his collaboration with the Nazis and the Vichy government, but no conclusions were reached. Unremitting attacks by the press left Carrel deeply depressed. He was a broken man when he died on November 5, 1944 (6). Already Carrel noticed that vascular grafts, he used did not survived too long, but nobody had idea why. This has changed thanks to the work of Sir Frank MacFarlane Burnet and Peter Brian Medawar. They shared the Nobel Prize in 1960 for discovery of acquired immunological tolerance.



Figure 2 - Sir McFarlane Burnett in 1960

Sir Frank Macfarlane Burnet (Figure 2) was born at Traralgon, Victoria, Australia, on September 3rd, 1899, completed his medical course at the University of Melbourne, where he graduated M.D., in 1923. In 1944 he became Director of this Institute and Professor of Experimental Medicine in the University of Melbourne. It is impossible to give, in a brief space of

fundamental importance of Burnet's work (7). His work on the agglutinins of typhoid fever was followed

by the work on viruses for which he is nowadays justly famous. In 1935 he isolated a strain of influenza A virus in Australia, and subsequently did much work on serological variations and on Australian strains of the swine influenza (8). Burnet was a productive scientist, authoring about 30 books and countless publications that spanned six decades. His greatest work described concepts of immune tolerance and clonal selection. In 1941, published a monograph entitled *The Production of Antibodies*, which is now widely regarded as a classic publication in the field of immunology (9). In this work, he proposed notions of 'self' and 'non-self', which described how an individual's immune system was able to differentiate between the cells and protein that make up its own body from those of foreign micro-organisms or substances. In 1959 he authored another book, called *The Clonal Selection Theory of Acquired Immunity*, which described how the human body

developed and produced antigen-specific antibodies (10). His hypothesis that the body could learn to reject or accept particular antigens, a concept now known as 'immune tolerance', was more than a fanciful abstraction, as it exerted a powerful impact on the direction and momentum of medical

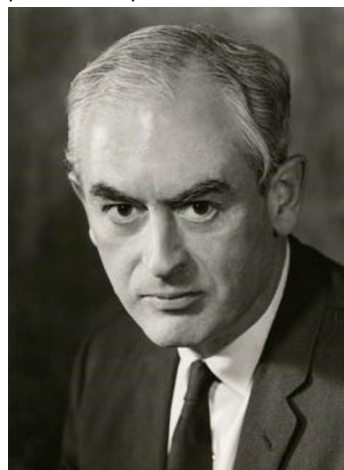


Figure 3 - Peter Brian Medawar in 1960

immunology. In part because of Burnet's work, patients worldwide have gained longer and better lives with transplanted hearts, livers, kidneys and other organs (11). He died from colorectal cancer in 31 August, 1985.

His partner in the Nobel Prize, Peter Brian Medawar was born on 28 February 1915, in Rio de Janeiro (Figure 3).

Medawar's earlier research, was done on tissue culture, the regeneration of peripheral nerves and changes of

shape of organisms that occur during this development. During the early stages of the Second World War he was asked to investigate why it is that skin taken from one human being will not form a permanent graft on the skin of another person. In 1947, Peter Medawar had been appointed Mason professor of zoology in Birmingham, where he continued his transplantation studies, with Rupert Billingham and Leslie Brent. He was elected to the Royal Society in 1949. Following his appointment as Jodrell professor of zoology and comparative anatomy at University College, London in 1951, he embarked, again with Billingham and Brent, on the critical work in inbred mice, to test whether experimentally induced chimerism would also result in tolerance to skin grafts from the donor strain (12,13). Medawar's key paper fully supported Burnet and Fenner's idea of adaptation of 'recognition of self' in the developing immune system (14). It was followed in 1956 by a monograph exploring the parameters of both tolerance and immunity to allogeneic transplants, and showing they were 'cell mediated' rather than humoral. This work affected the perception of those caring for patients in end-stage organ failure, e.g. kidney, since they raised the possibility of transplantation of allogeneic kidneys under a regime that protected them from immune attack, in the knowledge that actively acquired tolerance was a possible outcome. These results also contributed greatly to basic immunological knowledge, and allowed further development of the field of cellular immunology (15). His research career was prematurely interrupted in 1969, on account of a stroke. In 1986, he published his autobiography, a year before his death, the title of which highlights the contrast between his life with the physical limitations caused by the disease and his preserved lucidity (12). Died in London on 2 October, 1987.

The Nobel Prize in Physiology and Medicine from 1980 was awarded jointly to Baruj Benacceraf, Jean Dausset and George D. Snell for their discoveries concerning genetically determined structures on cell surface that regulates immunological reactions (16). Historically first discoveries were published by George D. Snell.

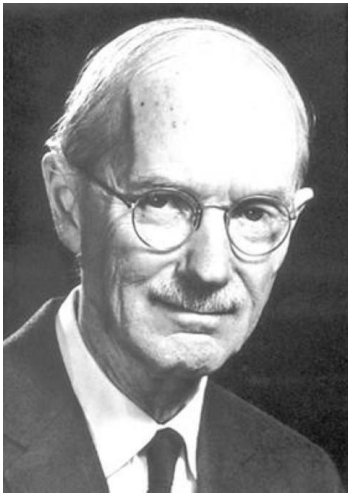


Figure 4 - George D. Snell in 1980

George David Snell (Figure 4) was born on 19th December 1903 in Bradford, Massachusetts, USA. In 1935, he joined the Jackson laboratory in Bar Harbor, Maine and remained there until his retirement as senior staff scientist emeritus in 1973. Jackson laboratory was considered an international hub for mouse genetics. He was already working in transplantation at the end of World War II. He realized that immunology would burgeon and that his work on the MHC

would help it to do so. G. Snell initiated work on immunological enhancement and reviewed developments in immunology on several occasions. He, along with immunologist Peter Gorer, conducted studies that resulted in the identification of the H-2 gene complex in mice, a term he introduced to determine whether a tissue graft would be accepted or rejected. G. Snell was a founder of the scientific journal titled 'Immunogenetics', and served as its first editor. He authored several books including 'Cell Surface Antigens: Studies in Mammals Other Than Man' (1973), 'Histocompatibility' (1976) and 'Search for a rational ethic' (1988) (17,18). He died on 6 June 1996 at Bar Harbor, Maine, at the age of 92.



Figure 5 - Jean Dausset in 1980.

The next of this "Big Three" was Jean Dausset (Figure 5) born on 19 October 1916 in Toulouse, France. During the II World War J. Dausset joined the Free French Forces in North Africa as an ambulance worker. In this occasion he got his first taste of hematology when he had to perform numerous blood transfusions on wounded soldiers. As the war was winding down in 1944, he returned to Paris where he worked in the Regional Blood Transfusion Center at the Saint-Antoine

Hospital. In 1948, Dausset went to work as an intern in the Children's Hospital in Boston. He worked there in a hematology lab for about four years. On his return from Boston, he became interested in the new immune-hematology techniques applied on red blood cells (Coombs test) and decided to transpose the methods to white blood cells in cases of leucopenia(19). In 1952 J. Dausset discovered that white blood cells were agglutinated by antibodies from patients who had received blood transfusions, and realized this was due to genetic differences between donor and recipient. He described the first leukocyte antigen, now called HLA-A2, in 1958. He realized that the human HLA system was similar to the H-2 gene system in mice, which had been identified by Snell shortly before, and thus that mice could be used as an experimental model for human immunogenetics. By grafting skin from volunteer donors to

volunteer recipients he worked out the complex relationship between tissue compatibility and graft survival, and found that the closer the tissue types, the better the chances of success. Professor Dausset was a member of the French National Academy of Sciences, professor at the College de France, a foreign member of the National Academy of Sciences, USA, an honorary member of the American Academy of Arts and Sciences, and a member of the founding Council and Vice President of the Human Genome Organization. Jean Dausset died the 6 of June 2009 in Palma de Mallorca, Spain, surrounded by his family (20).

The third awarded in 1980 was Baruj Benacerraf (Figure 6) who



Figure 6 - Baruj Benacerraf in 1980.

was born in Caracas, Venezuela, on Oct 29, 1920. In 1947, Baruj Benacerraf was a young medical doctor who had just been discharged from the US Army Medical Corps. Returning to the USA where he had studied, Benacerraf decided to make the switch from clinical medicine to research. Over the next decade or so, he continued his research into the mechanisms of the immune system, working in the USA and in France before settling at New

York University School of Medicine. The breakthrough came when Benacerraf noticed that a proportion of guinea pigs injected with particular antigens failed to mount an immune response. He realized that this was an important phenomenon and did further breeding experiments to show that the animals' responsiveness to these antigens was controlled by dominant autosomal genes that he termed immune response genes. Benacerraf was elected President of the American Association of Immunologists in 1973, President of the American Society for Experimental Biology and Medicine in 1974, and President of the International Union of Immunological Societies in 1980. That same year he was appointed President of the Sidney Farber Cancer Institute, an institution he led until 1992. After stepping down as president, he maintained an active presence at the Institute and continued working daily in his own lab into his 80s, he died of pneumonia on Aug 2, 2011, in Jamaica Plain, MA, USA, aged 90 years (21, 22).

The Nobel Prize in Physiology and Medicine was shared by Joseph E. Murray and E. Donnall Thomas for their achievement in organ and cell transplantation.

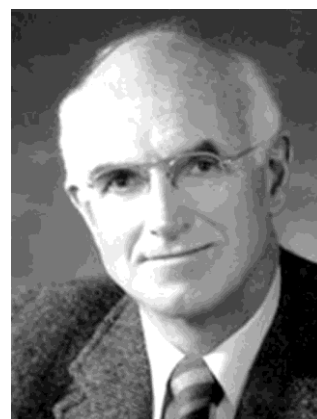


Figure 7 - Joseph E. Murray in 1990

Joseph Eduard Murray (Figure 7) was born on April 1, 1919 in Milford, Massachusetts. He was of Irish and Italian descent. After graduating with his medical degree Murray was inducted into the Medical Corps of the U.S. Army. He served in the plastic surgery unit which cared for thousands of soldiers wounded on the battlefields of World War II, working to reconstruct their disfigured hands and faces. His interest in transplantation grew out of working with burn

patients during his time in the army. After his military service,

Murray completed his general surgical residency and joined the surgical staff of the Peter Bent Brigham Hospital. On December 23, 1954, Murray performed the world's first successful renal transplant between the identical Herrick twins, an operation that lasted five and a half hours. He transplanted a healthy kidney donated by Ronald Herrick into his twin brother Richard, who was dying of chronic nephritis. Richard lived for eight more years, following the operation. In 1959, Murray went on to perform the world's first successful allograft and, in 1962, the world's first cadaveric renal transplant. In 2004, Murray and Ronald Herrick were honored at the U.S. Transplant Games, held at the Metrodome in Minneapolis, Minnesota. He suffered a stroke at his home on Thanksgiving and passed away on 26 November 2012, at the Peter Bent Brigham Hospital (later Brigham and Women's Hospital) in Boston at the age of 93. It was in this same institution that he performed the first successful kidney transplant (23-26).

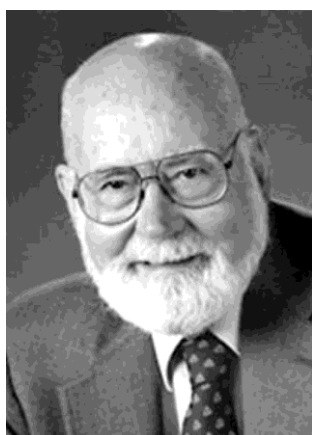


Figure 8 - E. Donnell Thomas in 1990

E. Donnell Thomas (Figure 8) known as "Don" to his friends, was born in a small town – Mart in central Texas, USA on 15 March 1920. He entered Harvard Medical School in 1943 and received his M. D. in 1946. Don Thomas completed one year internship in hematology after this he took a break in his studies to serve as a physician in US Army during the period 1948-50. After his stint with the US army, he worked as a postdoctoral fellow at the Massachusetts Institute of

Technology. In 1953, he worked as an instructor at Harvard Medical School. Don Thomas developed his interest in bone marrow and leukemia during medical school. Inspired by the successes of Sydney Farber with antifolate therapy for acute lymphoblastic leukemia, he initially studied marrow-stimulating factors under John Loofborrow, then later in his own laboratory. In 1955, he was recruited to be chief of the Mary Imogene Bassett Hospital in Cooperstown, and it was there that he began his BMT studies in dogs and his first clinical attempts to perform BMT in patients. By 1957, the first six patients had died within 100 days, the sole survivor a patient with leukemia who received a marrow infusion from his twin sibling. That patient survived the transplant, but unfortunately later died from a relapse of his malignancy. Many patients had been cured of leukemia using this technique by the late 1970s. Since then Don Thomas and his colleagues improved their success rate significantly. In addition to leukemia and other cancers of the blood, bone marrow transplants are used to treat certain inherited blood disorders and to aid people whose bone marrow has been destroyed by accidental exposure to radiation. He was a member of 15 medical societies, including the 'National Academy of Sciences', 'Medical and Scientific Advisory Committee' and 'National Cancer Institute'. He was President of 'American Society of Hematology' and served on the editorial boards of eight medical journals. He received honorary 'Doctorate of Medicine' from 'University of Cagliari', Sardinia in 1981, 'University of Verona' in 1991 and 'University of Parma', in 1992. He was also awarded the honorary degrees from 'University of Barcelona' in 1994 and 'University of Warsaw' in 1996. E. Donnell Thomas died at the age of 92 on 20th October 2012 in Seattle (23, 27-29).

Transplantation would not developed without discovering of the immunosuppressive drugs. The first step for sure was

steroid treatment, but synthesis of azathioprine was the real breakthrough. This was noticed by the Nobel Prize Committee and in 1998 among three awarded were Gertrude B. Elion and George H. Hitchings who discovered this drug.



Figure 9 - Gertrude B. Elion in 1998.

Gertrude Belle Elion (Figure 9) was born in New York City on January 23, 1918. Her mother arrived in the United States from Poland at the age of fourteen. Elion decided to dedicate her life to medicine after the deaths of her grandfather from stomach cancer. She received her degree in 1941 and found work and valuable experience as a chemist at a food company, and at Johnson and Johnson. Later that year, Elion was offered another position working with nucleic acids alongside Hitchings at

Burroughs Wellcome Company. Hitchings assigned Elion to investigate purines, which are building blocks of DNA. They soon discovered, from observing the role of purines in nucleic acid metabolism, that bacterial cells require certain purines to make DNA. Along the way, Elion published 225 papers on her findings. By 1950, Hitchings and Elion successfully synthesized two compounds—diaminopurine and thioguanine. For the first time, a treatment that could interfere with the formation of leukemia cells and induce remission. Elion discovered 6-mercaptopurine (thioguanine), which she created by replacing one sulphur atom with an oxygen atom. Treatment using thioguanine is responsible for curing 80 percent of children with leukemia. This compound is also used to treat acute myelocytic leukemia (AML) in adults. In addition to 6-MP, Elion went on to discover a series of drugs that attack the life cycle of nucleic acid, including allopurinol—which inhibits uric acid synthesis, making it a viable treatment for gout—and azathioprine (Imuran), an effective immunosuppressive drug. Her discovery of azathioprine was extremely important to transplantation, because it made possible for people to receive organ transplants without their body rejecting them. On the heels of Hitchings' retirement in 1967, Elion became head of the Department of Experimental Therapy. Her next success was synthesis of the acycloguanosine, also known as acyclovir. Elion retired in 1983, eight years after Hitchings. Though she was unable to complete her Ph.D., George Washington University and Brown University awarded Elion honorary doctorates. In

1991, she became the first woman to be inducted into the National Inventors Hall of Fame, and was presented with the National Medal of Science by President George H.W. Bush. She died on 22 February 1999, in Chapel Hill, North Carolina (30-36).

George H. Hitchings (Figure 10) was born on April 18, 1905, in Hoquiam, Washington, USA. The illness and untimely death of his father had a profound impact on the young boy and he decided to become a doctor on growing up. He received his bachelor's



Figure 10 - George H. Hitchings in 1998

degree in 1927 and stayed on at the University of Washington

to earn a master's degree in 1928. Hitchings then attended Harvard University, where he received his PhD in biochemistry in 1933. His work at Harvard centered on analytical methods used in physiological studies of purines, which are a class of compounds composed of a two-ringed structure containing carbon and nitrogen. For the next decade Hitchings held a variety of temporary appointments. In 1942, however, he joined the Wellcome Research Laboratories—then located in Tuckahoe, New York—as a biochemist. This research facility was operated by the British pharmaceutical firm Burroughs Wellcome and Company, which is now part of GlaxoSmithKline. Two years later Hitchings hired Gertrude Elion as a laboratory assistant, thereby beginning a lifelong collaboration on drug development. By 1950 used line of research had paid off. Hitchings and Elion synthesized two antimetabolites, diaminopurine and thioguanine as described above. This latter discovery led to a new drug, azathioprine, and a new application, organ transplants. Azathioprine suppressed the immune system, which would otherwise reject newly transplanted organs. In the 1960s Hitchings and Elion determined that infectious diseases could be fought if drugs could be targeted to attack bacterial and viral DNA. This work resulted in pyramethamine, which was used to treat malaria, and trimethoprim, which was used to treat meningitis, septicemia, and bacterial infections of the urinary and respiratory tracts. In 1967, Hitchings became Vice President in Charge of Research of Burroughs Wellcome. He also served as Adjunct Professor of Pharmacology and of Experimental Medicine from 1970 to 1985 at Duke University. In 1976 he became Scientist Emeritus at Burroughs Wellcome Co. He founded what is now the Greater Triangle Community Foundation in 1983, and served as its director for life. In the last years Hitchings suffered from Alzheimer's disease and died on February 27, 1998 in Chapel Hill, North Carolina, USA (35-37). The last described Noble Prize winner was Ralph N. Steinman (Figure 11). He was born into an Ashkenazi Jewish family on 14 January 1943, in Montreal, Canada. Steinman received a Bachelor of Science degree from McGill University and received his M.D. (magna cum laude) in 1968 from Harvard Medical School. He completed his internship and residency at Massachusetts General Hospital. After completing his medical training, he was drawn to biomedical research. He joined The Rockefeller University in 1970 as a postdoctoral fellow in the

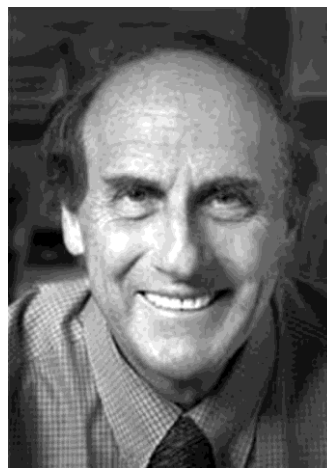


Figure 11 - Ralph M. Steinman in 2011.

Laboratory of Cellular Physiology and Immunology. He spent his entire career at Rockefeller, where he was appointed assistant professor in 1972, associate professor in 1976, and professor in 1988. He was named Henry G. Kunkel Professor in 1995 and director of the Christopher Browne Center for Immunology and Immune Diseases in 1998. In 1973, Steinman and Cohn discovered dendritic cells, a previously unknown class of immune cells that constantly formed and

retracted their processes. This discovery changed the field of immunology. For the next four decades, until his death in 2011, Steinman's laboratory was at the forefront of dendritic cell research. He and his colleagues established that dendritic cells are critical sentinels of the immune system that control both its innate and adaptive responses – from silencing to actively resisting its challenges. He also showed that dendritic cells are the 2 main initiators of T cell-mediated immune responses. In 2010, he initiated at The Rockefeller University Hospital a phase I clinical trial with the first dendritic cell- targeted vaccine against HIV. Diagnosed with pancreatic adenocarcinoma in March 2007, Steinman believed that dendritic cells had the potential to fight his aggressive tumor. Ralph N. Steinman died on 30 September 2011, three days before his Nobel Prize was announced. Unaware of his death at the time of its announcement, the Nobel Committee made an unprecedented decision that his award would stand (38-40).

Across the XX century many scientist focused on the field of transplantation. Achievement of few of them was awarded with the Nobel Prize. I hope that the XXI century will be more fruitful for transplantation and the Nobel Prize Winners involved in this part of science.

REFERENCES

- Breithaupt H (2001) The Nobel Prizes in the new century: An interview with Ralf Pettersson, Director of the Stockholm Branch of the Ludwig Institute for Cancer Research, the Karolinska Institute, and former chairman of the Nobel Prize Committee for Physiology/Medicine. *EMBO Reports*. Nature Publishing Group. 2: 83–5.
- Feldman B (2001) The Nobel prize: a history of genius, controversy, and prestige. Arcade Publishing. ISBN 1-55970-592-2.
- Baker CF, Markmann JF (2013) Historical Overview of Transplantation. *Cold Spring Harb Perspect Med*. 3: a014977.
- Malinin TI (1979) Surgery and life, the extraordinary career of Alexis Carrel, pp. 22–29. Harcourt Brace Jovanovich, New York.
- Sade RM (2005) Transplantation at 100 Years: Alexis Carrel, Pioneer Surgeon. *Ann Thorac Surg* 80:2415–8.
- Cusimano R, Cusimano M, Cusimano S (1984) The genius of Alexis Carrel. *Can Med Assoc J*. 1984 Nov 1;131(9):1142-50.
- Fenner F (1995) Frank Macfarlane Burnet. *Australian Academy of Science Biographical Memoirs of Deceased Fellows. 1899-1985*. (Accessed November 15 2017). Available at: www.asap.unimelb.edu.au/bsparcs/aasmemoirs/burnet.htm
- Burnet FM (1956) *Enzyme, Antigen and Virus: a Study of Macromolecular Pattern in Action* Cambridge University Press, Cambridge.
- Burnet FM, Freeman M, Jackson AV, Lush D (1941) *The Production of Antibodies: a Review and Theoretical Discussion*. Monograph of the Walter and Eliza Hall Institute of Research in Pathology and Medicine, No. 1, Macmillan, Melbourne, Australia.

10. Burnet FM (1959) *The Clonal Selection Theory of Acquired Immunity*. Cambridge University Press, London.
11. Tan SY, Ponstein N (2017) Frank Macfarlane Burnet (1899–1984): Australia's gift to immunology. *Singapore Med J*. 58: 508–509.
12. Medawar PB (1984) *Memoir of a Thinking Radish: An Autobiography*. Oxford: Oxford University Press.
13. Simpson E (2004) Reminiscences of Sir Peter Medawar: in hope of antigen-specific transplantation tolerance. *Am J Transplant*. 4:1937-40.
14. Billingham RE, Brent L, Medawar PBM (1953). Actively acquired tolerance of foreign cells. *Nature (London)*. 172: 603–606.
15. Billingham RE, Brent L, Medawar PBM (1956). Quantitative studies on tissue transplantation immunity. III. Actively acquired tolerance. *Phils Trans R Soc Lond B* 239: 357–414.
16. Marx JL (1980) 1980 Nobel Prize in Physiology or Medicine. 7:621-3.
17. Snell GD, Dausset J, Nathenson S (1976) *Histocompatibility*. New York: Academic Press.
18. Mitchinson JL (2003) George David Snell. *Biogr Mem Natl Acad Sci*. 83:252-68
19. Mandel JL, Lathrop M, Cann HM. (2009) Jean B Dausset, 19 October 1916-6 June 2009. *Eur J Hum Genet*. 2009 Nov; 17(11) : 1365-6.
20. Degos L (2009) Jean Dausset a scientific pioneer: intuition and creativity for the patients (1916–2009) *Haematologica* 94: 1331–1332.
21. Pincock S. (2011) Baruj Benacerraf. *Lancet*. 2011 Sep 17;378(9796):1066.
22. Germain RN, Burakoff SJ. (2011) A remembrance of Baruj Benacerraf (AAI '57) 1920-2011. *J Immunol*. 2011 Dec 1;187(11):5465-9.
23. Groth CG, Brent LB, Calne RY et al (2000) Historic landmarks in clinical transplantation: conclusions from the consensus conference at the University of California, Los Angeles. *World J Surg*. 2000 Jul;24(7):834-43.
24. Adenwalla HS, Bhattacharya S (2012) Dr. Joseph E. Murray. *Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India* 45: 596–597.
25. Murray JE, Merrill JP, Harrison JH (1958) Kidney Transplantation Between Seven Pairs of Identical Twins. *Annals of Surgery* 148: 343–357.
26. Morris P (2013) Joseph E. Murray(1919–2012). *Nature*, 493:164.
27. Thomas ED (1985) Overview of Marrow Transplantation. *Western Journal of Medicine* 143:834– 837.
28. van den Brink M.R.M., Hansen J.A. (2013) A tribute to E. Donnall Thomas. *J Clin Invest*. 123: 3-4. doi:10.1172/JCI67590.
29. Galr R., Goldman L. (2013) E Donnall Thomas (1920–2012) *Bone Marrow Transplantation* 48:1.
30. Marelene R-C., Rayner G. (1998). *Women in biochemistry. Women in chemistry: Their changing roles from alchemical times to the mid-twentieth century* (pp. 152-156). Danvers, MA: American Chemical Society and Chemical Heritage Foundation.
31. McGrayne SB (2002) Damn the Torpedoes. *Full Speed Ahead! Science* 296: 851-852.
32. National Academy of Sciences (2000) *Biographical Memoirs V.78. Gertrude B. Elion*. Washington, DC: The National Academies Press.
33. Avery ME (2008) Gertrude Belle Elion. 23 January 1918 — 21 February 1999. *Biographical Memoirs of Fellows of the Royal Society* 54: 161–168.
34. Koenig R (2006) *The Legacy of Great Science: The Work of Nobel Laureate Gertrude Elion Lives On*. *The Oncologist* 11: 961-965 doi: 10.1634/theoncologist.11- 9-961.
35. Raju TN (2000) The Nobel chronicles. 1988: James Whyte Black, (b 1924), Gertrude Elion (1918–99), and George H Hitchings (1905–98) *Lancet* 355:1022.
36. Goodwin L (1989) George Hitchings and Gertrude Elion- Nobel Prize winners. *Parasitology Today* 5: 33.
37. Hitchings GH (1969) *Chemotherapy and Comparative Biochemistry: G. H. A. Clowes Memorial Lecture*. *Cancer Res* 29: 1895-1903.
38. Steinman RM, Cohn ZA (1973) Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J. Exp. Med*. 137: 1142–62.
39. Greenberg PD (2011) Ralph M. Steinman: A man, a microscope, a cell, and so much more. *Proceedings of the National Academy of Sciences of the United States of America* 108: 20871–20872.
40. Rowley DA, Fitch FW (2012) The road to the discovery of dendritic cells, a tribute to Ralph Steinman. *Cellular Immunology* 273: 95-98.