Jon Van Rood: Pioneer at the Crossroad of Human Leukocyte Antigens and Transplantation
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Jon Van Rood (born in 1926) has made major contributions to the fields of transfusion medicine as well as organ and stem cell transplantation. His group was the first to start unraveling the complexity of the human leukocyte antigen (HLA) system through collaborative studies that used panels of sera and leukocyte samples. Furthermore, using HLA typing, he introduced the first HLA-matched platelet transfusions and developed routine leukocyte depletion as a means to prevent HLA alloimmunization. Van Rood has also been active in the fields of kidney transplantation (Eurotransplant) and stem cell transplantation (Eurodonor). He combined scientific laboratory research with application to clinical medicine. He retired from his university position in 1991 but remains active in the field.

Johannes Joseph (Jon) Van Rood (Fig 1) was born in The Hague, The Netherlands, in 1926. After experiencing the German occupation as a teenager, he studied medicine at the Leiden University. There he was influenced by Piet Gaillard, professor of histology, who may well have performed the first successful human allograft ever. Gaillard transplanted cultured parathyroid gland tissue into a patient from whom the parathyroid gland had been accidentally removed. After graduating in 1950, Van Rood spent a brief clinical clerkship with Prof Robert Loeb at the Presbyterian Hospital in New York. Subsequently, he further developed his clinical skills during a locum tenens as a family practitioner in a village near Leiden. He then returned to the Leiden University to train in internal medicine. The then newly appointed chairman of the department of medicine, Prof Jaap Mulder, had just started a blood transfusion service at the university hospital. Routinely, medical leadership (and accountability) was provided by the most junior medicine resident, and it also became Van Rood’s turn. The actual work in the blood bank was however provided by 2 technologists. One of them, Aad van Leeuwen, became his closest scientific coworker for 40 years and shared in many of his successes. A copy of Mollison’s Blood Transfusion in Clinical Medicine was lying on the work counter in the single room of the blood bank. Van Rood’s interest in transfusion medicine started while he was browsing through it. He enjoyed his assignment in the blood bank and got actively involved with its organization. At the time, the blood bank in Leiden collected only 4200 U/y; however, the introduction of thoracic surgery at the hospital dramatically increased the need for blood transfusions. Initially, attempts to increase the donations were hampered by popular suspicion that the blood would be used mainly for the Korean War. Nonetheless, the blood bank grew steadily.

During these early days, nonhemolytic transfusion reactions, which initially were attributed to possible pyrogens introduced during the resterilization of blood bottles and needles, were a significant clinical problem. Dausset (born in 1916) and Nenna from Paris reported in 1952 that the serum of polytransfused patients contained strong leukocyte agglutinins, which they suspected to be autoantibodies. Simultaneously, van Loghem et al from Amsterdam showed that nonhemolytic transfusion reactions were caused by leukocyte antibodies and that blood transfusions depleted of leukocytes did not usually induce such transfusion reactions. Patient R in Leiden had aplastic anemia and needed monthly blood transfusions. After each transfusion, he developed a transfusion reaction characterized by fever, hypotension, nausea, and severe shaking chills. Antiallergy drugs and...
cortisone did not help diminish the clinical symptoms. Strong leukocyte agglutinins against a panel of healthy donors were discovered in his serum. Van Rood depleted the leukocytes from a red cell unit, and, after its transfusion, no reaction occurred! This novel treatment was complicated by the absence of technology for leukocyte depletion. However, he solved this problem by “borrowing” liver biopsy needles and a suction pump.

In 1958, Mrs H, a multiparous woman who had never before been transfused, received a red cell transfusion because of postpartum bleeding. She developed a severe nonhemolytic transfusion reaction. Leukocyte antibodies (agglutinins) were found in her serum and in that of several (4 of 30) other postpartum women. This clinical observation led Van Rood to conclude that pregnancy was capable of inducing leukocyte antibodies. It also led to his first major publication. Subsequent studies showed that these antibodies reacted with the leukocytes of the husband and some (or all) of the children. This polymorphic reaction pattern led to family studies. Rose Payne (1909-1999) simultaneously conducted similar studies at Stanford University. In 1958, Daussert reported on an antibody, anti-Mac (now anti–human leukocyte antigen [HLA]-A2), in 3 sera, with the agglutinins having been induced by blood transfusion and reacting with the leukocytes of approximately half of the donors studied. Unfortunately, the patients who produced the anti-Mac sera lost the agglutinin activity soon thereafter, which precluded collaborative studies.

In contrast, agglutinins induced by pregnancy remained detectable decades after the last delivery. This enabled Van Rood’s group to collect 60 sera that were tested against a panel of 100 leukocyte samples. The results were analyzed with an early computer that had recently been installed at the Dutch Department of the Interior for personnel administration. These studies led to the identification of several clusters of sera, each cluster recognizing presumably a single antigen. The clusters showed significant associations with each other. Two allelic clusters recognizing 4a and 4b (now HLA-Bw4 and HLA-Bw6, respectively) were further analyzed and confirmed by family studies. This methodology formed the basic approach to the unraveling of the complexity of HLAs by Van Rood’s group and soon by all workers in the field. This work led to Van Rood’s PhD in 1962: “Leukocyte Grouping, A Method and Its Application.”

As is usual for physician-scientists in The Netherlands, after completing his PhD work, Van Rood spent a sabbatical year in the United States. He worked at the Public Health Research Institute in New York with Frank Adler and Marvin Fishman on factors influencing the production of antibodies. Even more important were his interactions with many established and young immunologists in New York and with physicians who were interested in kidney transplantation and bone marrow transplantation (BMT).

In 1964, Bernard Amos organized the first international workshop on histocompatibility in Durham, North Carolina, and Van Rood’s group presented data on several other antigens, which now also belong to the HLA-B locus. The composite data of this first workshop were chaotic. Therefore, the next year, Van Rood organized the second workshop in Leiden. It became clear from these investigations with sera and from studies with experimental skin transplants that these
leukocyte antigens were indeed transplantation antigens representing the major histocompatibility complex in man. This system was officially named HLA in 1975. The unusually long survival of an experimental skin graft in a multiparous woman led Van Rood and, in particular, Aad van Leeuwen to conclude in 1972 that HLA-D antigens, which so far had been only demonstrable with typing cells (in mixed lymphocyte cultures), could also be detected by serological means (HLA-DR). This major accomplishment made tissue typing for clinical transplantation simpler as well as much less time consuming and led the way to its widespread adoption.

To bring the results of the laboratory data to clinical transplantation, Van Rood’s group started typing donors and recipients of kidney transplant survivors in 1966 in several transplant centers in Europe and the United States. Forty transplants had been performed at these centers, and the 18 survivors and their donors exhibited an unusual leukocyte-antigen compatibility. When Van Rood presented the data in 1967, he also suggested the start of an exchange program of cadaveric donor kidneys in Europe on the basis of leukocyte typing. This was the start of the Eurotransplant consortium. The office was, and still is, located in Leiden. Actually, the group started to facilitate clinical transplants even before the organization had been formally established. The first harvested kidney was transported via a helicopter from Louvain to Leiden with the help of the Belgian army. Eurotransplant now has 75 participating centers in 6 countries (Austria, Belgium, Germany, Luxemburg, The Netherlands, and Slovenia), and it facilitated 3000 kidney transplants in 2005. The waiting list of Eurotransplant currently contains 15,000 patients.

The group at the Radiobiological Institute in Rijswijk, approximately 20 miles from Leiden, had been very active in experimental BMT. Under the leadership of Dirk van Bekkum and Otto Vos, they explored many aspects of transplants in mice and later in monkeys. They studied the preparative regimen and the stem cell dose, and they made major contributions to the pathology and immunobiology of graft-vs-host disease. The combination of excellent preclinical models and optimal donor choice through HLA typing led to 3 successful pediatric BMTs in late 1968, 1 of which was performed in Leiden. This initiated the era of BMT as a standard therapy for many disorders. The further development of hemato-oncology and BMT in Leiden was stimulated by Van Rood and Bruno Speck (1934-1998). They made the first (unsuccessful) attempt to treat a patient with severe aplastic anemia with BMT from a phenotypically matched unrelated donor. Speck also introduced antilymphocyte globulin as treatment for aplastic anemia but returned in 1973 to Switzerland to start a prominent BMT center in Basel.

To support the hematology and BMT services of the Leiden University Hospital, George Eernisse, who had also performed fundamental work on erythrocyte survival time studies using DF, started using leukocyte typing to select platelet donors for transfusion into patients with platelet refractoriness. In 1964, they were able to stop life-threatening bleeding in a patient with severe aplastic anemia who had developed extensive leukocyte antibodies. They leukocyte typed the patient’s large extended family and successfully transfused matched platelets. This patient is probably the first patient in the world whose life was saved thanks to HLA typing. She recently attended the 50th anniversary of the Leiden Blood Bank! Europondonor was founded in 1970 to provide platelet transfusion support from matched donors to patients who already had developed HLA antibodies and had become refractory to random platelets. From the beginning, a small number of these donors also provided bone marrow. Ultimately, the Europondonor file contained the HLA types of 20,000 platelet and stem cell donors. In 1988, Europondonor was incorporated, and its main emphasis became the recruitment of volunteer bone marrow donors.

On the other side of the HLA antibodies equation, Eernisse and Brand showed that alloimmunization can be prevented by depleting the leukocytes from platelet and red cell transfusions. Leukocyte-poor platelets were obtained by an additional centrifugation step. Leukocyte-poor red cells were obtained with a cotton-wool filtration system introduced by Van Loghem’s group in Amsterdam. Indeed, by 1975, leukocyte depletion of all platelet and red cell products had become the standard of care for every patient with hematologic disorders at the Leiden University Hospital. This approach rapidly spread to several countries in Europe.

Van Rood continued his work in tissue typing and clinical transplantation. Under his guidance,
more than 70 PhD theses on the role of HLA in organ and stem cell transplantations, disease associations, and immune response were prepared. Among his trainees were Frans Claas (immunogenetics of transplantation), Els Goulmy (minor histocompatibility antigens), Guido Persijn (Eurotransplant), Malice Lagaay (pretransplant blood transfusion), Zhang Lie (tolerance and noninherited maternal antigens), Rene de Vries (HLA association with disease), and Marius Giphart (molecular biology of HLA). More recently, Van Rood and Claas\textsuperscript{16} and Van Rood et al\textsuperscript{17} tackled the topic of noninherited maternal HLAs in the immune response. Van Rood has authored and coauthored more than 450 articles.

Van Rood’s enormous energy was instrumental in cofounding the Dutch Society for Immunology in 1964 and the European Group for Blood and Marrow Transplantation in 1974. He also was the driving force behind and founding president of the European Federation for Immunogenetics in 1985, which is the European equivalent of the American Society of Human Immunogenetics. In 1988, Van Rood gave the European Federation for Immunogenetics’ first Ceppellini Lecture, named in honor of Ruggero Ceppellini, one of the pioneers of HLA typing who had died that year. Ceppellini was known for his phrase “nature has certainly not maintained a polymorphism such as that of HLA, only to frustrate transplant surgeons.”

In 1991, Van Rood retired from his position as chairman of the Leiden University Department of Immunohematology and Blood Transfusion. He remains active in Eurotransplant and Eurodonor and pursues active (and verbally forceful!) participation in many meetings and conferences on the role of histocompatibility in the clinical transplantation of organs and stem cells.

For his extensive contributions to the cutting edge of tissue typing and its role in clinical transplantation, Van Rood received many honorary doctorates and awards. Among the most prominent were the Wolf Prize (Israel) in 1978, the Dr AH Heineken prize of the Royal Netherlands Academy of Arts and Sciences in 1990, and the Medawar Award of the Transplantation Society in 1996. He became a member of the Royal Netherlands Academy of Arts and Sciences in 1978 and a foreign associate of the US National Academy of Sciences in 1993.

Among Van Rood’s extracurricular activities, sailing has been foremost. He has spent as much time as possible aboard his boat. Actually, to combine business with pleasure, he organized a very popular annual immunology course aboard the 2-masted clipper de Dageraad, where participants discussed scientific topics while helping sail. Van Rood never could be buttonholed into either the laboratory aspects of HLA typing or the clinical role of laboratory tests. In a unique way, he has combined high-quality scientific laboratory research with practical applications to health care. As such, he really is a true pioneer in the field of human transplantation.

REFERENCES

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