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Review

Half a century of Dutch transplant immunology

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ABSTRACT

The sixties have not only witnessed the start of the Dutch Society for Immunology (NvvI), but were also the flourishing beginning of the discipline of transplant immunology. The interest in immunology in the Netherlands had its start in the context of blood transfusions and not for instance in the field of infectious disease, as in many other countries. It began in the 1950-ties thanks to Joghem van Loghem at that time director of the Central Laboratory of Blood Transfusion in Amsterdam. The discoveries of these times have had major impact for transfusion medicine, hematopoietic stem cell transplantation and organ transplantation. In this review we will look back at some early highlights of Dutch transplant immunology and put them in the perspective of some recent developments.

1. The almost forgotten case history of the first patient whose life was saved by HLA

In 1958 a non-haemolytic febrile transfusion reaction had made clear to us that pregnancy could induce what later turned out to be antibodies against HLA [1]. At that time access to a computer which was able to perform a cluster analysis required to unravel the complexity of the HLA system turned out to be next to impossible. However, one was located in the ministry of Inner Affairs which was used to calculate and print our salary counterfoils. The analysis resulted in the identification of what later would be called HLA-Bw4 and -Bw6 in 1962 and the thesis of Jon van Rood, entitled: "Leucocyte Grouping; A Method and Its Application" [2]. After a sabbatical in New York, he returned to the University Hospital in Leiden, which was in the fortunate position to have one of the first hospital Blood Banks in the Netherlands, and where he did most of the clinical haematology rounds together with Freddie Loeliger, the coagulation expert. There they were confronted with a woman who was bleeding literally from all orifices, due to severe aplastic anaemia after antibiotic treatment with chloramphenicol. Because the Blood Bank had developed technologies to provide platelet transfusions, this patient received the first platelet transfusions prepared from donor blood by George Eernisse in 1964. The patient stopped bleeding and random platelet transfusions were given until the patient, who had been pregnant, formed after a few weeks' leukocyte antibodies. Platelet recovery after the platelet transfusions dropped to zero and she started bleeding again. As it was known that the 9 "HLA" antigens that were recognised at that time in Leiden were genetically determined it was investigated whether some of the eight brothers and sisters of the patient might turn out to have a negative leucocyte agglutination cross match with her serum. This turned out to be the case and every week one of these sibling donors came to Leiden to donate platelets, which all had an excellent recovery (Fig. 1). A splenectomy was done a few months later and the patient recovered, and continued to visit the outpatient clinic [3].

2. Bone marrow transplantation and why the Dutch registry is called Europdonor

Another major development during these early days was therapeutic bone marrow transplantation. This was largely possible because the University Leiden had managed to obtain a contract with the Dutch government to establish an Institute for Radio Pathology and Radiation Protection (IRPRP) in order to be prepared to treat victims of a nuclear accident. For that purpose, an Isolation Pavilion was built to treat such patients. Dick van Bekkum of the Radio Biological Institute in Rijswijk provided data on a successful stem cell transplant protocol after Total Body Irradiation and gut decontamination in inbred mice, which they liked to upgrade for patients. On our request he started to work with Rhesus monkeys to confirm his findings in a larger outbred animal model and recruited

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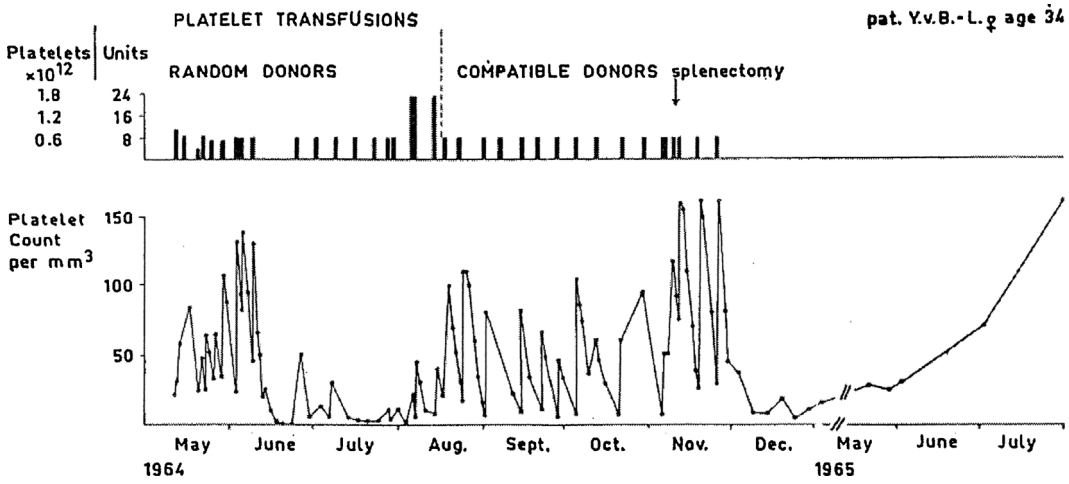

Fig. 1. The case history of the first patient whose life was saved by HLA knowledge.

Hans Balner to develop MHC typing in these animals. Their stem cell transplant results were impressive and in 1968 Han de Koning and colleagues performed one of the three first successful stem cell transplants in children suffering from congenital immune deficiency. The other two were performed by Bob Good and colleagues in Minneapolis, USA. All three patients survived more than 25 years and the Dutch patient is still alive 45 years later [4].

In the Isolation Pavilion a bone marrow transplant program was started and a first unrelated donor provided bone marrow for a patient with aplastic anaemia and a first successful haploidentical transplant to a patient with Severe Combined Immune Deficiency [5–7]. The platelet support of patients with leukaemia and transplantation turned out to be a heavy burden. Regular platelet transfusions, containing many leukocytes, appeared strong inducers of HLA antibodies developing in over 60% of patients and not all of them possessed compatible family members. During the annual meeting of the 'Deutsche Transfusion's Geselschaft' in 1970 van Rood presented the Leiden results with HLA compatible platelet transfusions and pointed out that international cooperation was essential to support thrombocytopenic patients in need of HLA matched platelet transfusions. The proposal was to start an organisation named Europdonor and for which the 20 HLA laboratories in Europe were each offered sufficient anti-HLA reagents (at that time regarded as research tools and not (yet) commercially available) to type 1000 blood transfusions donors [8]. At that time, circa 20,000 HLA typed donors in Europe were assumed sufficient to help the majority of patients in need of HLA matched platelets or unrelated bone marrow! In this plan, the Eurotransplant computer facilities should collect, print and distribute these HLA typings. However the proposal did not catch on and Europdonor became a functioning reality only in the Netherlands [9]. By 1988, 20,000 donors had been HLA-typed and had provided thousands of life-saving platelet transfusions. Meanwhile, by leukocyte-depletion of blood products, HLA immunization reduced and preventive platelet transfusions before a bleeding occurred became possible [10]. In 1988 the IRPRP organisation stopped, but Europdonor could continue functioning as a Foundation thanks to governmental funds. In 1994 Anneke Brand and Fred Falkenburg established the Dutch cord blood bank.

3. The start of renal transplantation and Eurotransplant

In 1954 it had become clear that organ transplantation between monozygotic twins was feasible, which asked for the next step. Major discoveries at the level of immunosuppressive therapy and the understanding of histocompatibility led in 1966 in Leiden to the first allogeneic renal transplantation from a mother to her son with end stage renal failure. It could be shown that matching for HLA made a difference in prognosis, and during the third Histocompatibility workshop in Torino in 1967 van Rood proposed to start Eurotransplant [11]. The probability to find a donor and recipient with a matching tissue type would strongly increase when there would be a large database with the HLA typing of patients on the waiting list. Initially 12 transplant centres in three countries participated, but this rapidly expanded and nowadays over 70 centres from 8 countries, including the Netherlands, Belgium, Luxemburg, Germany, Austria, Slovenia, Croatia and Hungary, are actively participating. Since its foundation, more than 140,000 donor organs have been allocated by Eurotransplant.

In these early days of experimental medicine, a lot was learned from erythrocyte and platelet transfusions in patients, but also from several volunteers who received experimental skin grafts. The protocol worked as follows: volunteer recipients received first an intradermal injection of cells from a donor who was mismatched for one HLA antigen with the volunteer (e.g.HLA-B7) and then experimental skin grafts from two other volunteers: one who was HLA-B7 positive and the other HLA-B7 negative. One of these volunteer was a married woman (mrs P.) who received a skin graft which we expected to survive 10–12 days, but after 24 days the graft was still doing fine. Only then it became clear she had been pregnant, which was hypothesised to be an explanation for the unexpected long survival: at that time called graft enhancement i.e. prolonged survival caused by antibodies directed against the donor. Especially the group of Rob Koene in Nijmegen performed at that time excellent research on the basic aspects of enhancement in mouse models [12]. Mrs P volunteered to cooperate to find out, rejected the skin graft a day later and it could be shown that she had anti Class II HLA antibodies. This enabled the development of a serological test for HLA Class II typing, which made the selection of unrelated organ and stem cell donors much easier [13,14].

4. From major to minor antigens

The concept of MHC restriction, as shown in the 70′ by Zinkernagel and Doherty in murine models of viral infection, could also be demonstrated in a patient (Mrs R.) suffering from aplastic anaemia and treated by ATG and a haplo-identical stem cell transplant from her brother. The donor's stem cells caused a temporary chimerism but then disappeared and the patient recovered. Using the Cell Mediated Lympholysis test (CML) it was found that the blood of