Eliane Gluckman

A brief history of HSCT

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1. How haematopoietic stem cell transplant was born: From the threat of atomic irradiation to animal models and to humans

After the atomic bomb explosion in Japan, ending WW2, many scientists began to explore ways of protecting humans from irradiation. The first experiments were performed in mice and later in dogs by E.D. Thomas (1). As early as 1956, the idea that bone marrow transplant might exert a therapeutic effect against malignancies was proposed by Barnes and Loutit who observed an anti-leukaemic effect of transplanted spleen cells in experimental murine models (2). They also observed that animals that had been given allogeneic rather syngeneic marrow cells died of "wasting disease", which would now be recognised as being graft-versus-host disease (GvHD). E.D. Thomas carried out the first transplants in dogs using high dose irradiation (3) and J. Van Bekkum established a transplant model in monkeys (4). In 1959, the first human bone marrow transplants gave a proof of concept that infusing bone marrow could provide haematological reconstitution in lethally irradiated patients with acute leukaemia (5). E.D. Thomas transplanted 2 patients with advanced acute lymphoblastic leukaemia with a syngeneic graft after high dose total body irradiation; the patients engrafted but died a few months later of relapse. G. Mathé gave allogeneic bone marrow for treatment of several patients who had suffered accidental irradiation exposure, most survived with autologous reconstitution (6). In 1965 Mathé was the first to describe long-term engraftment of a sibling bone marrow demonstrating chimerism, tolerance and an anti-leukaemic effect (7). Although the transplant itself was successful, the patient eventually died of varicella with chronic GvHD. In 1970, M. Bortin reported 203 transplants performed between 1958 and 1968 with only 3 patients alive at time of the report. The major causes of death were graft failure, GvHD and relapse. Following these disappointing results, few centres persisted and the number of transplants declined sharply. Major progress came from the discovery of the HLA system by J. Dausset (9) and J.J. Van Rood (10). Selection of HLA identical siblings as bone marrow donors diminished the risk of rejection and GvHD. Using animal models, R. Storb and E.D. Thomas developed the model of total body irradiation for conditioning (in dogs) and the use of methotrexate for GvH prevention (11), and in mice G. Santos showed that the use of cyclophosphamide could add immune suppression to the myelo-ablation of TBI (12). He was also the first to use busulfan instead of TBI (13).

2. From 1970 to the present time

Following this pioneer work major progress has been achieved and nowadays haematopoietic stem cell transplant has saved the life of many patients worldwide.
The major landmarks have been:

- **The use of cyclosporin for GvHD prevention:** cyclosporin is a cyclic oligopeptide immunosuppressant which is an inhibitor of T-cell activation. It is produced by a fungus and was discovered in the early 1970s. It was initially used in organ transplants, where the side effect of nephrotoxicity was noted, which was solved by adjusting the dose according to pharmacokinetic measurements (14, 15). Compared to methotrexate alone, the combination of cyclosporin and short methotrexate is still the gold standard for GvH prevention (16).

- **Better management of early complications:** This included isolation in laminar air flow rooms, gut decontamination and development of new broad-spectrum antibiotics. Toxicity was reduced by fractionation of TBI and better hydration was found to prevent cyclophosphamide-induced haemorrhagic cystitis.

- **Better treatment of infectious complications:** with new antiviral, antibacterial and antifungal drugs, including treatment of *Herpes simplex virus* infection with acyclovir and the introduction of ganciclovir for treatment of CMV infection. Fungal infections with *Candida sp* and *Aspergillus* which were the most common causes of death were actively treated and prevented by amphotericin B and new azoles (the first used was ketoconazole).

- **Development of bone marrow registries for treating patients without an HLA identical sibling donor.** The first unrelated bone marrow registry was established in London, in 1973, by Shirley Nolan whose son was diagnosed with Wiskott Aldrich syndrome. Following this first donor recruitment drive, the number of bone marrow and peripheral haematopoietic stem cell donors has increased all over the world with more than 18 million donors now registered, including 500,000 cord blood donors.

- **Improved methods of high resolution HLA typing.**

- **Use of new sources of haematopoietic stem cells:** G-CSF mobilised peripheral blood stem cells (17), cryopreserved umbilical cord blood (18), haploidentical related haematopoietic stem cells (19).

- **Autologous haematopoietic stem cell transplantation (20).**

- **New methods of GvHD prevention:** T-cell depletion, *in vivo* monoclonal anti T-cell antibodies.

- **Use of donor lymphocyte infusions to treat relapse (21).**

- **New methods of reduced intensity conditioning to decrease early transplant related mortality (22).**

### 3. International cooperation

International collaboration through a number of non-profit organisations has been a key factor for the development of haematopoietic stem cell transplantation.
Thanks to the dedication and far-sighted view of a few pioneers, it was realised that it was essential to work together in order to facilitate the development of haematopoietic stem cell transplant, help new centres and laboratory facilities to be established, provide guidelines, develop accreditation through JACIE and promote the development of new research protocols.

EBMT (European Group for Blood and Marrow Transplantation) was born in 1974 when the number of bone marrow transplants was very small and results quite disappointing. The first meeting was held in Saint Moritz at the initiative of J.J. Van Rood and B. Speck. Three teams were present, the Leiden group with J. Vossen and J.J. van Rood, the Basel group with B. Speck and the Paris group with E. Gluckman. This was a very small meeting with not more than 10 participants; the idea was to meet in a nice place where we could both work and exercise our skills in skiing. Both qualifications were and remained for a long time a prerequisite to be member of the group. Over many years the group met in different ski locations including Saint Moritz in Switzerland and Courchevel in France and slowly the meeting attracted more and more haematologists from all over Europe interested in bone marrow transplantation.

CIBMTR (Center for International Blood and Marrow Transplant Research) was founded in 1972 by M. Bortin in Milwaukee. In 1972, just four years after the first successful haematopoietic stem cell transplantation (HSCT), pioneers in the field realised the significance of what they were undertaking. Several of the pioneers in this evolving science also understood the importance of collaborating in order to better understand the data being generated at individual centres. Dr. Mortimer M. Bortin and several colleagues established the IBMTR at the Medical College of Wisconsin to do just that. Physicians in the field agreed to voluntarily contribute their patient data to this outcomes registry. At the time, there were only about 12 transplant centres and fewer than 50 patients per year worldwide receiving a transplant. M. Horowitz the current director has developed the database and this worldwide database now includes data on 350,000 autologous, related and unrelated donor transplant recipients. CIBMTR is also performing both observational and prospective research.

NMDP (National Marrow Donor Program) was founded in 1986 and the first NMDP-facilitated transplant took place in December 1987. Today the registry is called Be the Match Registry and has grown to 9 million donors and nearly 145,000 umbilical cord blood units.

WMDA (World Marrow Donor Association). On March 10th 1988 an ad hoc committee was formed to discuss international collaboration for identification of matched unrelated donors, initially started as the Cooperative Marrow Donor Programme. The founders of this group were: Prof. J.J. van Rood, Prof. J. Goldman and Prof. E.D. Thomas. Prof. J. Goldman proposed a change in the name of the organisation from
Cooperative Marrow Donor Programme to World Marrow Donor Association (WMDA). The WMDA is a voluntary organisation of representatives of bone marrow donor registries, cord blood banks, other organisations and individuals, with an interest in haematopoietic stem cell transplantation. It provides a forum for mutual discussion of all issues regarding the clinical use of haematopoietic stem cells from unrelated donors across international boundaries. These discussions, which take place in working groups, make it possible to formulate guidelines on logistics, quality control, accreditation, ethics, finances and registry accreditation. It works in close association with BMDW (Bone Marrow Donors Worldwide). BMDW is continuing the effort to collect the HLA phenotypes and other relevant data of volunteer stem cell donors and cord blood units. The current number of donors is 17,596,872 and cord blood units 482,451.

Eurocord is a registry of cord blood transplants which works in close collaboration with cord blood banks (members of Netcord) to analyse results of cord blood transplant and provide quality standards and accreditation to the unrelated cord blood banks. It has collected more than 7,000 cord blood transplant from 483 centres, 50 countries and 54 cord blood banks.

4. Main EBMT Landmarks
The main EBMT Landmarks have been:
- The evaluation of progress in allogeneic and autologous bone marrow transplantation.
- The establishment of a European bone marrow transplant registry with the publication of current indications for transplant, categorised as validated, experimental or not recommended.
- Publication of a yearly survey of haematopoietic stem cell transplantation in Europe.
- The definition of JACIE standards for establishment and accreditation of a bone marrow transplant unit.
- The organisation of an annual meeting, a ESH-EBMT training course and a ESH-EBMT handbook.
- The organisation of working parties with elected chairs.
- The creation of the EBMT nurses group.

5. Conclusion
Since the first transplant to the present time, enormous progress has been made and many patients survive a lethal disease thanks to the efforts of a few pioneers and also to the immense dedication of all the participants in this drive to cure more
patients. This has been made possible by the early recognition that we had to work together through close and frank collaboration, and by realizing that a bone marrow transplant unit is a result of a team effort including physicians from different specialties, scientists, nurses, laboratory technicians, radiotherapists, blood banks, and data managers.

References