

Historical Review

A HISTORY OF HAEMOPOIETIC CELL TRANSPLANTATION

Summary

Fifty years have gone by since the first experiments that were to lead to the wide application of haemopoietic cell transplantation. Many disciplines have been involved including radiation biology, immunology, molecular biology, drug development, blood component transfusion technology and numerous adult and paediatric clinical disciplines. At every turn, the solution of problems depended heavily on animal research ranging from mice to dogs to non-human primates. At present more than 20 000 human transplantations of haemopoietic cells from marrow, peripheral blood or cord blood are being performed annually. Initially these cellular transplantations were carried out only in terminally ill patients, but now in many instances transplantation is the preferred treatment and is carried out early in the course of the disease. Exciting research designed to continue improvement of the application to human patients includes the achievement of engraftment without lethal marrow ablative regimens, the use in autoimmune diseases, and the development of techniques for inducing tolerance for solid organ grafting. The development of effective anti-viral and anti-fungal drugs and the shift to out-patient care has resulted in dramatic reduction of the cost of transplantation as well as improved long-term survival. Pending the development of highly specific curative agents, it is likely that the use of haemopoietic cell transplantation will continue to increase during the early years of the third millennium.

Introduction

In the early part of the twentieth century, through the work of Alexis Carrel and others, it was quite well established that allografts of organs such as skin or kidney would function for a time but after 1 or 2 weeks the graft would be lost. In the 1940s Medawar and colleagues established clearly the immunological basis of allograft rejection. That allografts might not always be intolerable was suggested by Owen who found that 'freemartin' bovine dizygotic twins had a mixture of red blood cell types from each partner. It remained for Billingham, Brent and Medawar to show that donor-specific tolerance could be induced by injection of donor cells into newborn mice. The exciting early days of transplantation immunology have been described and referenced in detail by Woodruff (1960), written near the time of action, and Brent (1997), written with the clarity made possible by the passage of three decades.

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The beginnings of haemopoietic cell transplantation (HCT)

The story of marrow transplantation had an unlikely beginning in 1949 with the studies of Jacobson *et al* (1949), who found that shielding the spleen of a mouse during otherwise lethal irradiation permitted survival. Shortly thereafter, Lorenz *et al* (1951) reported that irradiated mice could be protected by an infusion of spleen or marrow cells. Initial experiments seemed to demonstrate that the 'irradiation protection' phenomenon was due to humoral factors. However, Barnes & Loutit (1954) reviewed their own and other experiments and concluded that 'the chemical hypothesis has not been proved by the complete exclusion of the cellular hypothesis'. Definitive data in favour of cellular reconstitution came from the observation of Main & Prehn (1955) that irradiated mice protected by an infusion of allogeneic marrow subsequently displayed tolerance of a donor skin graft. The dramatic photograph of a surviving skin graft from a white mouse on a recipient grey mouse offered proof of tolerance induced by marrow transplantation. Their observation was followed shortly by the report of Ford *et al* (1956) that lethally irradiated mice protected by a subsequent marrow infusion showed marrow cytogenetic characteristics of the marrow donor, and Nowell *et al* (1956) demonstrated the presence of rat cells in the marrow of irradiated mice protected against lethal irradiation by rat marrow. Subsequently, Trentin (1956) showed that the skin graft tolerance was specific for the donor strain.

Early studies of HCT in murine systems. Studies in murine systems established many of the factors responsible for success or failure of a marrow graft. The early studies are detailed in the book by van Bekkum & De Vries (1967). The most important observations were: (1) One of the prime questions to be answered for any consideration of marrow transplantation was how to get marrow cells to grow in the bone marrow. Early investigators had given cells intra-arterially, intra-peritoneally or by injection into the marrow cavities. Van Bekkum *et al* showed that marrow cells given intravenously were effective in repopulating the marrow spaces. (2) Allogeneic marrow cells successfully engrafted could mount an immune attack against the host resulting in a wasting syndrome known as 'secondary disease'. The disease was the result of an immune reaction of the engrafted lymphoid cells against the tissues of the host, now known as graft-versus-host disease (GVHD) (Billingham & Brent, 1959). (3) In allogeneic transplants the severity of the immune reaction of donor cells against the host was controlled by genetic factors (Uphoff, 1957). (4) Histocompatibility was governed by one major system and numerous minor systems (reviewed in Snell, 1992). (5) Methotrexate

(MTX) could prevent or ameliorate the graft-versus-host (GVH) reaction (Uphoff, 1958; Lochte *et al.*, 1962). (6) Cyclophosphamide (CY) alone could provide immunosuppression sufficient for allogeneic engraftment (Santos & Owens, 1969). (7) The importance of the thymus, T cells, B cells and other lymphoid subsets in transplantation biology began to be defined (Good *et al.*, 1962; Miller, 1963).

Early studies of HCT in canine models. The dog has long served as a random-bred animal model for studies of transplantation. Dogs are more readily available in families than non-human primates, and they are suitable for clinical procedures such as sampling of blood, transfusion support and transplantation of organs and tissues. The canine model has been particularly useful for the study of the principles and techniques of HCT that are applicable to humans (Ferrebee *et al.*, 1958). The most important observations included: (1) Dogs survived 2–4 times the lethal exposure to total body irradiation (TBI) if given an intravenous infusion of their own marrow cells set aside or cryopreserved before the TBI (Mannick *et al.*, 1960; Cavins *et al.*, 1962). (2) Dogs given supralethal irradiation and allogeneic marrow demonstrated the problems of failure of engraftment, graft rejection, engraftment with GVHD and, in some dogs, stable engraftment without GVHD, i.e. tolerance (Thomas *et al.*, 1962). (3) Dogs could be successfully engrafted without TBI using chemotherapy with CY or dimethyl busulphan (Storb *et al.*, 1969). Most of these dogs showed only donor cell engraftment but some were healthy mixed chimaeras. (4) Haemopoietic cells for engraftment could be obtained from the blood, as well as from the bone marrow (Cavins *et al.*, 1964). (5) Blood transfusions from the marrow donor or unrelated dogs could sensitize the intended recipient to transplantation antigens resulting in graft failure (Storb *et al.*, 1970b). (6) Marrow grafts between littermate pairs matched for dog leucocyte antigens (DLA) were often successful with the recipients becoming healthy chimaeras (Epstein *et al.*, 1968, 1969).

Early attempts to treat leukaemia by HCT. Barnes *et al.* (1956) reported the treatment of leukaemic mice by supralethal irradiation followed by infusion of normal mouse marrow. At almost the same time, attempts to treat human patients with TBI or chemotherapy and a marrow infusion were reported (Thomas *et al.*, 1957). In the human patients large quantities of marrow, screened to break up particles, could be infused intravenously without ill effect, but only one transient graft was observed. The only successful transplants utilized an identical twin donor (Thomas *et al.*, 1959). These observations in twins showed clearly that human patients could be protected from lethal irradiation by an intravenous injection of marrow cells.

In 1970 a review of approximately 200 allogeneic marrow graft attempts concluded that not one had been successful (Bortin, 1970). At that time the accumulated experiences were very discouraging, and some had suggested that attempts to transplant marrow in human beings were not justified. In retrospect, it appears that the unsuccessful allogeneic marrow transplantations were due in part to the lack of knowledge of human histocompatibility typing and in part to the use of irradiation exposures that were too low to

achieve the immunosuppression necessary for acceptance of a foreign graft. Mathé *et al.* (1965) achieved the first persistent allogeneic marrow graft in a patient with leukaemia, but the patient died of many problems that probably were due to the complications of chronic GVHD.

Development of the role of histocompatibility antigens in HCT. Antibodies induced by transfusions or pregnancy that reacted with antigens on human white blood cells were recognized by Miescher & Fauconnet (1954). Dausset (1958) and van Rood *et al.* (1958) used such antibodies to describe human leucocyte antigen (HLA) groups. Studies of skin graft survival in human volunteers had suggested that these leucocyte antigens were histocompatibility antigens, but the survival data were difficult to interpret and the technique carried the risk of transmission of disease and sensitization of the recipient (Dausset *et al.*, 1969). Proof of the importance of leucocyte groups in HCT in an outbred species came from studies of the DLA system (Epstein *et al.*, 1968; Storb *et al.*, 1968, 1970a, 1971). Dogs given supralethal irradiation and marrow from a DLA mismatched littermate died of graft rejection or GVHD. Most recipients of DLA-matched marrow, especially those given some post-grafting MTX to suppress the GVH reaction, became long-term healthy survivors (Fig 1). These observations set the stage for HCTs between matched human siblings.

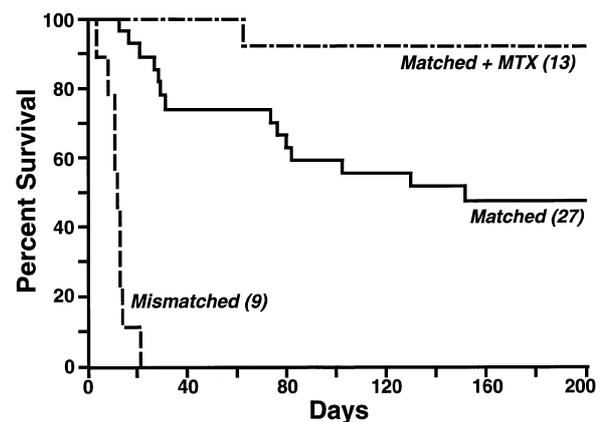


Fig 1. Survival of dogs given 1000 rad TBI and a marrow infusion from a littermate matched or mismatched for dog leucocyte antigens. Some recipients of matched marrow were given a short course of intermittent MTX after grafting to suppress the graft-versus-host reaction. (Adapted from Epstein *et al.* (1968) and Storb *et al.* (1971).)

The beginning of the modern era of human HCT

Early experience with HCT for immunodeficiency diseases. By the end of the 1960s effective platelet transfusion support, improved antibiotics and more effective anti-cancer agents had been developed. Most importantly, increasing knowledge of human histocompatibility antigen systems led to renewed attempts at allogeneic marrow grafting in human patients. Gatti *et al.* (1968) reported the first successful allogeneic marrow graft in a patient with severe combined immunological deficiency using a sibling donor presumed to be HLA identical with the patient. Subsequent typing, however,

showed that the patient and donor differed by one HLA antigen. Two similar successes were reported at almost the same time (Bach *et al.*, 1968; deKoning *et al.*, 1969). These patients did not require immunosuppressive therapy since they were immunoincompetent because of their disease. All three were reported to be alive and well 25 years later (Bortin *et al.*, 1994).

HCT for leukaemia. In 1969 the Seattle marrow transplant team began a series of marrow transplantations using HLA-matched sibling donors for patients in the end stages of acute leukaemia or aplastic anaemia. The first patient, in the blast phase of chronic myeloid leukaemia (CML), was thought to have a matched sibling as donor, but later refinements in HLA typing showed a one-antigen mismatch (Buckner *et al.*, 1970). A successful graft was achieved following 954 cGy of TBI. The patient recovered from acute GVHD only to die of a febrile illness. Autopsy results identified disseminated cytomegalovirus, an early example of many deaths due to opportunistic infections during the period of immunoincompetence following an allogeneic HCT.

In 1975 a review article summarized the state of knowledge of HCT at that time (Thomas *et al.*, 1975). The article described the results in 37 patients with aplastic anaemia and 73 with leukaemia, all transplanted after failure of conventional therapy. Notable was successful engraftment of some patients with aplastic anaemia and survival in remission of a few patients with leukaemia.

In the 1970s evaluation of the role of HCT in the treatment of leukaemia was difficult because almost all patients had been transplanted for advanced disease after failure of conventional therapy. For example, in 1977 the Seattle team reported 100 patients with advanced acute leukaemia who were prepared with CY and TBI and given marrow from an HLA-matched sibling (Thomas *et al.*, 1977a). At the time of the report, only 17 of the 100 were alive 1–3 years later. Of note, eight of these 17 are alive and well now more than 23 years after transplantation. Despite the high mortality described in most reports, the demonstration that some patients with advanced leukaemia could become long-term survivors in remission following supra-lethal chemo-irradiation and an infusion of marrow offered encouragement. The early demonstration of a plateau in a Kaplan-Meier plot of disease-free survival had indicated that some patients with advanced leukaemia might be cured (Thomas *et al.*, 1977b). Disease-free survival of more than 20 years duration now justifies the use of the word 'cure' in describing these patients.

HCT as an accepted treatment for malignant diseases. Success with patients with advanced disease provided an ethical basis for HCT earlier in the course of the disease. In the late 1970s, transplants for leukaemia in first remission or at the first sign of relapse quickly demonstrated a greatly improved overall survival (Thomas *et al.*, 1979a; Beutler *et al.*, 1979). Fig 2 shows the survival of the first 19 patients with acute myeloid leukaemia (AML) transplanted in first remission in Seattle. Eight of these patients are alive and well, now 19–21 years later. In the 1980s many similar observations rapidly led to the application of marrow grafting to patients with a variety of malignant diseases having in common a high

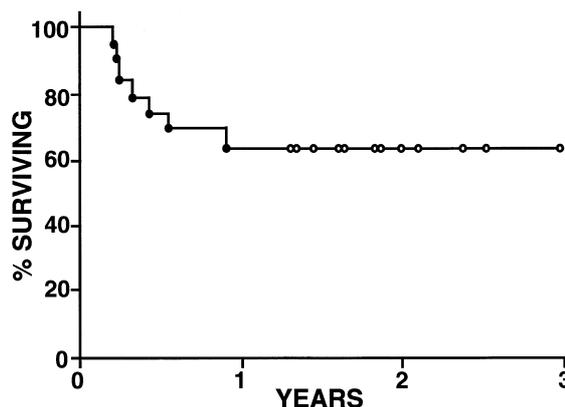


Fig 2. Nineteen patients with acute myeloid leukaemia achieved a remission with chemotherapy. They were then given high-dose CY and TBI and a marrow graft from an HLA-matched sibling followed by a short course of MTX. Their survival is shown as reported in 1979 (Thomas *et al.*, 1979a). (Reprinted with permission from *New England Journal of Medicine*.)

probability of failure of other forms of therapy. The clinical results accumulated over the past 20 years are given in the various disease-related chapters of the book *Hematopoietic Cell Transplantation* (Thomas *et al.*, 1999). CML has been of particular interest because of its unique cytogenetic marker, its fatal course in a median of 4–5 years, and the inability to cure the disease with chemotherapy. Initial attempts with syngeneic (Fefer *et al.*, 1973) or allogeneic (Clift *et al.*, 1982) HCTs suggested that long-term remissions were possible following preparation with high-dose chemo-radiotherapy. In 1986 good disease-free survival was reported in two large series of patients with CML who were treated by high-dose therapy followed by marrow transplantation from an HLA-identical sibling (Thomas *et al.*, 1986; Goldman *et al.*, 1986). Fig 3 shows the survival of those patients in the report from Seattle. Twenty-nine of the 67 patients transplanted in chronic phase are alive 13–19 years after transplantation. Of note, the longest surviving patient transplanted in blast crisis, who was 51 years old at the time of transplant, died 17 years later of an aortic aneurysm.

HCT for non-malignant disease. Marrow transplants for non-malignant diseases other than immunodeficiency disorders began with patients with aplastic anaemia (Thomas *et al.*, 1972; Storb *et al.*, 1974). Survival was approximately 40% for the early patients who were transplanted after failure of multiple transfusions and other therapies. Results improved dramatically when transplants were carried out earlier in the course of the disease, following preparation with CY and antithymocyte globulin and with the use of MTX and cyclosporine for control of GVHD (Storb *et al.*, 1994). Marrow transplant technology led to the first cures of thalassaemia major (Thomas *et al.*, 1982a; Lucarelli *et al.*, 1984) and of sickle cell disease (Johnson *et al.*, 1984).

The preparative regimen. In the 1950s it was recognized that patients with leukaemia would require preparation for engraftment with regimens that were both immunosuppressive and antileukaemic. Irradiation was a logical choice since

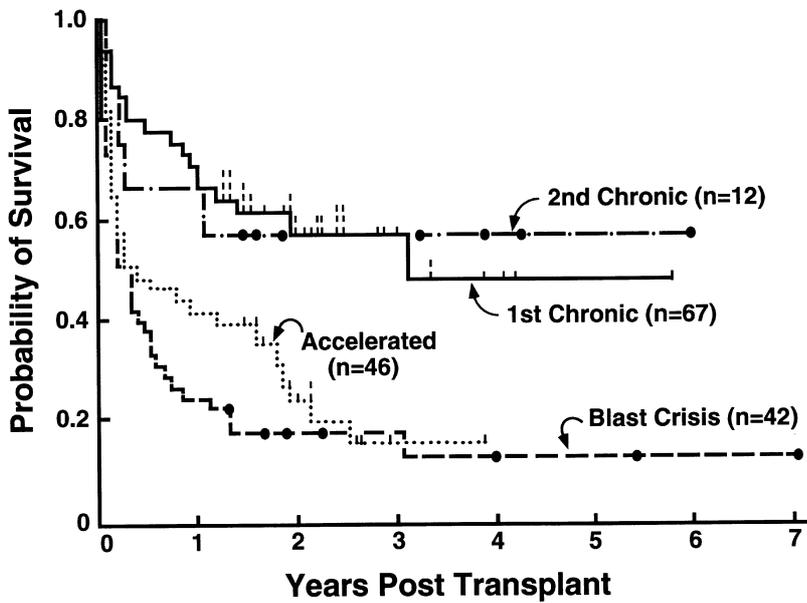


Fig 3. Survival for patients with CML after marrow transplantation from HLA-matched siblings according to phase of the disease (Thomas *et al*, 1986). (Reprinted with permission from *Annals of Internal Medicine*.)

leukaemic cells were known to be highly sensitive to irradiation, and irradiation had been widely used in animal studies of marrow transplantation. Since high-voltage machines were not available, opposing ^{60}Co sources were used in an attempt to get uniform TBI in large animals and human patients (Ferrebee & Thomas, 1958). Because the patients were desperately ill with advanced leukaemia, TBI was given in a single exposure in an effort to establish a graft quickly. When the Seattle team began sibling marrow transplants based on histocompatibility typing, 1000 rad TBI was administered at 7 rad/min. The few patients who successfully engrafted showed early recurrence of leukaemia as had been observed with the identical twin transplants. These results indicated that irradiation alone would not be sufficient to eradicate all leukaemic cells as Barnes *et al* (1956) had anticipated.

Santos & Owens (1965) reported that CY was a potent immunosuppressive agent in the rat model. Since CY was known to be an effective antileukaemic drug, the Seattle team gave CY, 60 mg/kg, on each of two days before TBI. This regimen produced the first long-term disease-free allogeneic recipients (Thomas *et al*, 1975). As patients were transplanted in the earlier stages of leukaemia and supportive care improved, immediate transplantation was not necessary, fractionation of the TBI became feasible, and a randomized study showed the superiority of fractionation (Thomas *et al*, 1982b; Deeg *et al*, 1986).

Santos *et al* (1983) devised an effective preparative regimen consisting of high-dose busulphan (BU) and CY. Their regimen was of particular importance because it avoided exposure to irradiation and made HCT possible in institutions without facilities for total body irradiation. A randomized comparison of the BU/CY regimen with the CY/TBI regimen in patients with CML showed no difference in disease-free survival and that both were effective (Clift *et al*, 1994).

A randomized comparison of the same two regimens in patients with AML in first remission showed the CY/TBI regimen to be superior (Blaise *et al*, 1992). A regimen of TBI with etoposide and CY has shown promise in patients with high-risk leukaemia (Long *et al*, 1997) or with CML (Snyder *et al*, 1994). Many transplant teams are using irradiation and chemotherapeutic agents in various combinations for preparative regimens (Shank, 1999; Bensinger & Buckner, 1999), but randomized studies of most of these preparative regimens have not been reported.

The source of haemopoietic stem cells (HSCs) for HCT. Most early studies of HCT used marrow as the source of stem cells. Later, CD34^+ cells separated from the marrow were shown to be effective (Berenson *et al*, 1991). The use of HSCs from other sources has occasioned the shift in terminology from bone marrow transplantation (BMT) to haemopoietic cell transplantation (HCT).

Peripheral blood stem cells. Transplantation with peripheral blood stem cells (PBSCs) rather than marrow began with the demonstration of these cells in the blood of mice (Goodman & Hodgson, 1962), dogs (Cavins *et al*, 1962; Fliedner *et al*, 1976) and non-human primates (Storb *et al*, 1977). Collection of these cells became practical with the development of centrifuge technology for collection of peripheral blood white cells in quantity. Peripheral blood cells were used for transplantation for patients whose marrow could not be collected because of disease or previous irradiation therapy (Kessinger *et al*, 1988). It was found that the number of PBSCs in circulation could be increased by chemotherapy and by the administration of haemopoietic growth factors (To & Juttner, 1987; Gianni *et al*, 1989; Juttner *et al*, 1990). Stem cells can be separated and purified based on their expression of CD34 (Korbling *et al*, 1994). The donor need not go to the operating room, as for a marrow transplant, since the cells can be collected by vein. Although the greatest use of PBSCs has been for autologous grafting, they can also

be used for allogeneic grafting but with an increased risk of chronic GVHD (Schmitz *et al*, 1995; Storek *et al*, 1997). The use of PBSCs has been particularly important because they result in rapid engraftment and because the number of stem cells that can be collected is greater than from the marrow.

Cord blood stem cells. The demonstration of the presence of HSCs in cord blood suggested the use of these cells for HCT (Broxmeyer *et al*, 1989). The first successful HCT using cord blood stem cells (CBSCs) was reported by Gluckman *et al* (1989). Cord blood is an attractive source of stem cells since it is a by-product of pregnancy. Banks of cryopreserved and HLA typed CBSCs have now been established in many institutions (Rubinstein *et al*, 1995; Gluckman *et al*, 1997). The utility of CBSCs is being evaluated, particularly the suggestion that these cells may be immunologically immature and less likely to cause GVHD.

Graft-versus-host disease. Billingham & Brent (1959) defined the immunological basis of the graft-versus-host reaction in murine studies. Extensive studies in murine systems have defined the role of T cells and of histocompatibility systems in the graft-versus-host reaction (reviewed in Korngold & Sprent, 1987).

The magnitude of the problem in human patients was not appreciated until consistent engraftment of donor marrow was achieved in the early 1970s. Even with an HLA-matched sibling donor, GVHD occurred in one-half of the patients. Prevention or treatment with MTX and/or glucocorticoids was only partially effective (Thomas *et al*, 1979b). Powles *et al* (1978) first described the use of cyclosporin A to treat GVHD in man. Studies in the canine model indicated that the addition of cyclosporine to a short course of MTX resulted in improved prevention of GVHD (Deeg *et al*, 1982). The effectiveness of the combined drug regimen was subsequently demonstrated in randomized studies in human patients (Storb *et al*, 1986, 1988). The regimen of a short course of MTX combined with 6 months of cyclosporine after an allogeneic HCT became the 'gold standard' for comparison of new regimens to prevent GVHD.

Reisner *et al* (1981) and Prentice *et al* (1984) described the amelioration of GVHD in human patients by the removal of T cells from the marrow inoculum. It is now recognized that removal of T cells from the graft can prevent GVHD, but at the cost of graft failure, delayed immunological recovery and loss of the graft-versus-leukaemia (GVL) reaction (Martin & Kernan, 1990). Marrow or PBSCs depleted of T cells continues to be attractive for HCT for non-malignant diseases, where the GVL reaction is unnecessary, and for malignant diseases, where the GVL effect can be restored by donor leucocyte infusions.

Advances in immunology are providing new approaches to prevention of GVHD without necessarily impairing immunological recovery or inhibiting the GVL reaction (reviewed in Blazar *et al*, 1997).

The GVL reaction. In the original article on treatment of murine leukaemia by X-rays and homologous marrow transplantation, Barnes *et al* (1956) recognized that lethal X-rays might not kill all leukaemic cells and stated 'but, if homologous bone marrow from a different strain of mouse were given, the colonizing cells might retain the capacity of

the donor to destroy by the reaction of immunity these residual leukaemic cells – and perhaps also the host'. Studies in a murine system indicated the existence of a GVL effect which might be separated from the GVH reaction (Bortin *et al*, 1979). Odom *et al* (1978) reported a patient who entered remission of relapsed leukaemia during a GVH reaction. The apparent existence of a GVL effect was reported by Weiden *et al* (1979) who described a statistically significant reduced incidence of recurrent leukaemia in 79 recipients of allogeneic marrow with GVHD as compared to 117 without GVHD.

In a few patients who had relapsed after a marrow transplantation, remissions were achieved when immunosuppressive drugs were discontinued (Higano *et al*, 1990; Collins *et al*, 1992). In the late 1980s investigators began to explore cautiously the possible anti-leukaemic effect of donor lymphocyte infusions for patients who relapsed after transplantation (reviewed in Slavin *et al*, 1996). Kolb *et al* (1990) first reported the achievement of long-term remissions and possible cure of relapsed CML by donor lymphocyte infusion together with interferon alpha. Cullis *et al* (1992) proved that donor lymphocyte infusion alone could induce long-lasting remission. Numerous reports have confirmed the anti-leukaemic effect of donor lymphocyte infusions, but with risks to the host of marrow suppression and GVHD as Barnes *et al* (1956) had anticipated (reviewed in Kolb, 1999). Donor lymphocyte infusions, or infusions of subsets of lymphocytes or of cloned lymphocytes, represent an important new approach to the immunology of HCT that is being actively studied in many centres.

HCT using unrelated donors. In the 1970s almost all HCTs used HLA-matched family members as donors. Since only about 30% of patients in need have a suitable family member donor, most could not be transplanted. A few transplants were performed using unrelated donors when matched donors were found fortuitously (Speck *et al*, 1973; Horowitz *et al*, 1975; The Westminster Hospitals Bone-Marrow Transplant Team, 1977; Hansen *et al*, 1980), but the heterogeneity of the HLA haplotypes underlined the need for large panels of volunteers to facilitate the finding of a suitable donor. The establishment of the Anthony Nolan Foundation in England and the Laura Graves Foundation in the United States led to the establishment of such programmes in many countries. Large panels of unrelated donors, world-wide now numbering more than four million, have made possible a rapid increase in unrelated donor transplants including shipment of donor cells from one country to another (Howe & Radde-Stepaniak, 1999). The results of marrow grafts using matched unrelated donors have improved during the past 5 years. For example, in one study of patients with CML who were transplanted within a year of diagnosis the 5-year disease-free survival was 74% (Hansen *et al*, 1998). Serological typing techniques for HLA are now being replaced by molecular techniques that permit a precise characterization of the genes of the MHC. These techniques disclose an even greater heterogeneity of the MHC which makes it much more difficult to find a completely matched donor. It is therefore imperative to identify the kind and degree of mismatching that will be clinically acceptable.

Autologous HCTs. Numerous studies in inbred syngeneic mice demonstrated the effectiveness of marrow stem cells in protecting the animals against otherwise lethal irradiation (see above). Similarly, in the canine model, marrow could be collected and set aside or cryopreserved. Following otherwise lethal exposure to TBI, intravenous infusion of the stored marrow led to survival of most animals (Mannick *et al.*, 1960).

Autologous marrow grafts for human patients were used in the 1950s (Kurnick *et al.*, 1958; McGovern *et al.*, 1959). These grafts seemed to protect against marrow toxicity. The clinical benefit was uncertain, probably because of ineffective eradication of the disease in the patients. However, a recent report describes a patient with malignant lymphoma who received high-dose nitrogen mustard and an autologous marrow transplantation in 1959 followed by a remission of 21 years duration (Haurani, 1997).

Since the end of the 1970s (Gorin *et al.*, 1978) there has been a dramatic increase in the use of autologous HCTs following high-dose chemotherapy and/or irradiation therapy of both haematological malignancies and solid tumours (Horowitz, 1999). Unfortunately, many autologous HCTs have been carried out in an uncontrolled manner, and often in controlled studies many patients assigned to autologous transplantation did not actually get the assigned treatment (Cassileth *et al.*, 1998). Carefully planned and executed studies will be necessary to define the ultimate role of autologous HCTs.

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