Application of Marrow Grafts in Human Disease

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THE INITIAL DISCOVERY of Jacobson *et al*[1] in 1949 that mice could be protected from an otherwise lethal dose of x-ray by lead shielding of the spleen led to the subsequent observation of others that a variety of lethally x-irradiated mammals could be saved from death by intravenously injecting syngeneic, allogeneic or in some cases xenogeneic marrow suspensions.[2] These initial observations provided the laboratory worker with the stimulus and much of the methodology for further fundamental investigations into the areas concerned with the differentiation and kinetics of hematopoietic stem cells, kinetics of antibody formation, thymus-marrow interactions, etc. The clinician was no less excited by these early observations because of the obvious implications of therapy for human disease. The majority of early attempts at marrow grafting in man failed,[3] however, because of lack of knowledge regarding tissue typing, immunosuppression and experience in the supportive care of patients with bone marrow aplasia. With new knowledge in these areas, there has been a resurgence of interest in the application of marrow grafts in human disease.[4] In the next few pages, I will try to outline some of the principles as well as the problems associated with marrow transplantation in man.

For purposes of clarity in later discussions, it is useful to view the interactions of the hematopoietic and lymphoid system in a somewhat oversimplified way.[5-7] In the marrow are pleuropotential stem cells (P cells) that may give rise to hematopoietic stem cells (H cells) or lymphcid stem cells (L cells). H cells leave the marrow via the blood to reside in the spleen and occasionally the liver. These cells, under the appropriate stimulus (primarily in the marrow), will differentiate into the more specialized granulocytes, erythrocytes and megakaryocytes.

The L cells may become bone marrow–derived lymphocytes, the so-called B lymphocyte, under the still undefined bursal equivalent in mammals. The B lymphocyte is highly specialized for eventual humoral

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antibody production requiring or not requiring the cooperation of a thymus-derived lymphocyte (depending upon the antigen). Some of these B cells migrate directly to the spleen, lymph node and peritoneal cavity. In the lymphatic tissues, the B lymphocyte, which is short-lived compared to the thymus-derived lymphocyte, occupies the outer cortex and medulla of lymph nodes as well as the periphery of spleen follicles and germinal centers.

The L cell may also migrate to the thymus or come under its hormonal influence to differentiate into a thymus-derived lymphocyte or T lymphocyte. The T lymphocyte will also migrate to the peripheral lymphatic tissues as well as return to the marrow. The T lymphocytes come to occupy the paracortical regions of the lymph nodes and periarteriolar areas of the spleen follicles and comprise a highly mobile population found in high concentration in the thoracic duct, lymph and peripheral blood. The T lymphocytes constitute the long-lived population and the cells of immunologic memory. Apart from its role in the cooperation with the B lymphocyte for certain types of humoral responses, it appears to be the cell involved in expressing cellular immunity.

The most logical application of marrow grafts would seem to be in those situations where there is failure of the P, H or L cells to perform their function either because of "experiments of nature" or because of external factors often created by man himself. One must recognize, however, the concept of at least two possibilities whenever a clinical situation appears wherein there appears to be a functional defect related to the marrow. Is the functional defect in question due to a failure of the microenvironment or is it due to an actual defect in the cell itself? Marrow transplantation is logical in the latter situation but not in the former.

Marrow transplantation has potential application in preparing individuals for organ grafting from the same donor and application in the treatment of certain forms of malignancy. The rationale for these approaches will be discussed below.

Failure of the Pleuropotential Cell (P Cell)

No proven examples exist of failure of the P cell in animal models or in human disease. Indeed, such conditions, if they do occur, are probably incompatible with life. There is a condition, however, where infants born with a form of lymphopenic thymic dysplasia have an additional defect, aleukocytosis. This condition has been termed reticular dysgenesia.[8,9] Because these children died in the first days of life, it has not been possible to obtain adequate information about their

hematopoietic and lymphoid systems. Morphologically, these children are extremely deficient. It has been suggested that this disorder involves a failure of the P cell to differentiate toward the H and L cell lines.[10] If the suggestion is true, we still have the question of whether or not we are dealing with a true cellular defect or a defect in the microenvironment. A marrow transplant in this situation might well clarify this issue.

Failure of the Immune System (L Cell)

Thymectomy in the newborn mouse has profound effects on the development of the immune system. In this situation, the absence of the appropriate microenvironment (thymus) precludes the continued development of T lymphocytes. Neither thymus extracts nor thymus cell suspensions can completely restore neonatally thymectomized animals to normal immunologic reactivity. If such mice are grafted with intact thymus tissue, however, they enjoy a normal life span, normally developed lymphoid tissues, and normal immune mechanisms. In such situations, most of the lymphoid cells multiplying in the spleen and thymus implant are of host (not donor) origin.[11] This latter observation and the requirements of an intact thymus structure lend support to the notion that it is the epithelial structures of the thymus that provide the necessary microenviornment for the development of the T lymphocyte.

The neonatally thymectomized mouse may represent a model for the clinical entity, congenital absence of the thymus and parathyroid glands with aortic arch anomaly, as described by DiGeorge.[12] Children with this apparently nonheritable syndrome fail to show any evidence of cellular immunity. They fail to show skin reactivity to a variety of bacterial, fungal and viral antigens. Delayed hypersensitivity to skin sensitizers cannot be induced in them. Furthermore, their lymphocytes fail to respond to PHA in culture and allogeneic skin grafts are not rejected.[12]

Thymic rather than marrow transplants would seem to be quite logical in this condition. In two instances where this has been attempted, delayed hypersensitivity and lymphocyte transformability were rapidly restored.[13,14] In both instances, theoretic and practical problems were encountered. Nevertheless, these initial attempts were encouraging. Donor-type lymphocytes were not found in the blood of these patients after thymic transplantation, which, of course, was to be expected from the experimental work of Miller.[11] It is interesting to speculate whether or not sufficient numbers of T lymphocytes might be transplanted with marrow in the human to repair, at least temporarily, the immunologic defect in DiGeorge syndrome. A marrow transplant

would not seem to hold any advantage over a thymic implant except that of ease of procurement. On the other hand, the risk of graft-versus-host disease (GVH) would seem to be greater with a marrow transplant as opposed to a thymic implant.[15]

There are certain immune-deficiency syndromes with no demonstrable ability to make antibody or express cell-mediated immune reactions, with varying degrees of lymphopenia and different modes of inheritance.[16] It has been suggested that some of these diseases arise from a primary inability of in the P cell to differentiate into the L cell or in a primary defect in the L cell itself.[10] Indeed, a therapeutic effect has been seen with marrow grafts from histocompatible siblings.[17–20] One of the reported cases was the sex-linked form of lymphopenic hypogammaglobulinemia [19] and two were the autosomal form (Swiss-type).[18,20]

There are a number of other immunologic deficiency diseases that may be related to failure of a differentiative pathway of the L cell because of a cellular or microenvironment defect. Unfortunately, however, the description, classification and understanding of these diseases are still far from complete.[21] Nevertheless, marrow transplantation has been attempted in two of these disease syndromes.

The Wiskott-Aldrich syndrome (sex-linked recessive) is characterized by recurrent pyogenic infections, eczema and thrombocytopenia.[22,23] There is lymphopenia, lack of delayed hypersensitivity as assayed by skin tests and defective lymphocyte blastogenesis *in vitro* in response to PHA and to specific antigens.[24] These patients also have a defective humoral antibody response to carbohydrate but not to protein antigen.[25] The lack of antibodies to carbohydrate antigens is thought to be due to a failure to process the antigen, presumably by macrophages.[25]

Bach *et al* [26] transplanted marrow to a patient with the Wiskott-Aldrich syndrome. The donor was a HL-A matched sibling and the patient was prepared with immunosuppressive, employing the alkylating agent cyclophosphamide (CY) as outlined by Santos *et al.*[27] The patient experienced a dramatic clinical improvement and remained well for at least 24 months thereafter. Platelet levels, however, did not increase markedly and marrow karyotypes were recipient cell in type. Karyotype analysis of the blood revealed a relatively stable population of donor-type lymphocytes (about 20%).[28] A number of questions are raised by this case. By what mechanism was this patient improved? Was it due in part to transfer factor [29] that has been reported at least partially to repair this condition [30] or was it due to the few donor lymphocytes that enjoyed a long-term engraftment?.

Mucocutaneous candidiasis is a chronic infection by *Candida albicans*

involving the skin, nails, scalp and vaginal and buccal mucous membranes.[31] Many patients with this disease fail to exhibit cutaneous cellular hypersensitivity to the causative organism although they are capable of specific immunoglobulin production.[32,33] Lymphocytes from these patients are usually capable of blast transformation in response to PHA and in some cases to *Candida* antigen[34,35] even though these patients are unable to produce macrophage migration-inhibition factor (MIF, a mediator associated with delayed hypersensitivity after antigeneic challenge) or exhibit delayed hypersensitivity when skin-tested.

Buckley *et al*[36] reported immunologic reconstitution in a patient with chronic mucocutaneous candidiasis by means of a bone marrow transplant without preceeding immunosuppresive therapy. Delayed hypersensitivity to *Candida* and two other antigens was detected 6 months after the transplant and a good therapeutic result was said to have been obtained. There was no evidence in this case, however, for the take or persistance of the infused marrow cells. It would be tempting to ascribe the patient's improvement to transfer factor carried by the infused marrow cells since transfer factor has improved children with this disease.[37] This cannot be the entire explanation, however, since Buckley *et al*[38] were able to induce delayed hypersensitivity to a contact allergen after the transplant. Transfer factor can only transfer the delayed hypersensitivity of the donor and not the ability to be sensitized.[29]

Failure of the Hematopoietic System (H Cells)

Failure of the microenvironment may result from the lack of important local stromal factors as well as a more general deficiency of hormones, natural poietins or nutritional requirements. In the broadest sense, failure of the microenvironment would also include situations where noxious factors are operative, such as infectious agents, chemical agents, physical agents or immunologic factors operative in certain autoimmune conditions. Many of the causes of microenvironment failure have been known for some time and are trivial and easily correctable, while the cause of others have been more occult but nevertheless have been found after intensive and often brilliant investigation.

The concept of the stromal microenvironment determining hematopoietic differentiation has gained considerable support from studies of mice with mutations at the *W* and *Sl* loci.[39] Mice of genotype Sl/Sl^d or W/W^v are markedly anemic, have no pigment-producing cells in their skin and are sterile. The basis for these defects are different for each of the mutations. The W/W^v mice have defective hematopoietic stem cells[40] as well as defective pigment-producing cells.[41] In Sl/Sl^d mice

there is a defect in the microenvironment that prevents hematopoiesis [42] and pigment production. In both conditions, the L cell and its microenvironment appear to be intact.[43]

The Sl/Sl^d mouse, as noted above, provides a relatively clear example of a situation in which the microenvironment for hematopoiesis is genetically defective while the H cell itself appears normal. Recently, it has been reported that such mice may be restored to normal by grafts of spleen stroma which are able to provide the proper microenvironment for normal hematopoiesis.[44] This latter observation is of great interest and offers therapeutic possibilities for the as yet to be discovered human counterpart of the Sl/Sl^d model.

The W/W^v mouse provides perhaps the best model of marrow failure due to an H cell defect.[39,40] Indeed, the defective hematopoiesis in these mice have been repaired by allogeneic marrow transplants after whole-body x-irradiation.[45]

Ionizing radiation as well as a variety of cytotoxic agents are capable of producing lethal effects by destroying or at least severely injuring the H cell. The transplantation of syngeneic marrow has effectively reversed these lethal effects in many instances.[2] In other situations, allogeneic marrow has also been able to reverse these effects occurring after x-ray [2] and the alkylating agents aminochlorambucil [46] and CY.[27,47,48] Although marrow infusions have successfully reversed potentially lethal doses of ionizing radiation in reactor accidents [49,50] or in therapeutic misadventure with cytotoxic agents,[46] the greatest incidence of potentially fatal aplasia is seen under conditions where aplasia is induced intentionally for the purposes of marrow grafting.

As was noted in preceeding discussion, a variety of chemical and physical agents may be causally related to aplasia. About 50% of all cases of aplasia have no known cause.[51] *A priori* in most of these situations, one does not know with any degree of certainty whether the persisting defect is in the microenvironment or in the H cell itself. Some insight into this question has been provided, however, by clinical studies wherein various forms of aplasia have been corrected by marrow infusions.

At least 10 patients with aplasia have received syngeneic (*ie*, identical twins) marrow transplants. Three died before the effect of the infusion could be evaluated and two were not benefited by the procedure. Five patients recovered completely and the time of recovery after infusion indicated successful marrow transplantation. Of the successful cases, 3 were idiopathic, 1 was after chloramphenicol and 1 after anticonvulsant drugs were administered.[52]

Amiel *et al* [53] reported successful partial but persistent allogeneic marrow takes that dramatically improved the clinical status of the patients in 1 case of idiopathic aplasia, 1 case after chloramphenicol and in 1 case after hepatitis. No evidence of a take was demonstrated in 4 other cases of idiopathic aplasia. Immunosuppression was provided by pretreatment with an antilymphocyte globulin fraction.

The results reported above are encouraging and clearly demonstrate that in some cases of aplasia, the microenvironment is able to support the proliferation and differentiation of H cells. The reported failures with allogeneic cells [3] do not rule out the possibility that a stem cell defect was operative since immunosuppression may not have been adequate in these patients, many of whom may have been presensitized to major or minor transplantation antigens of their donor because of preceding blood transfusions.

Fanconi's syndrome or congenital pancytopenia is a condition wherein there are varying degrees of pancytopenia as well as other congenital malformations. The etiology of the disorder is unknown but is generally believed to be hereditary, perhaps due to a recessive gene, or the result of reciprocal chromosomal translocation in one of the parents and a duplication deficiency in the affected offspring. Cytogenetic studies have revealed a variety of structural abberations and a specific type of polyploidy.[54] Although it is possible that this disease is due to an H cell defect, it is also possible that it may represent a failure of the complete hematopoietic environment. Marrow transplantation in this disease would undoubtedly yield interesting clues as to its true etiology.

Apart from disorders of the H cell itself, there may be cellular defects in the erythrocyte, granulocyte or megakaryocyte cell lines. In many instances, cellular defects are suspected as it is in the clinical hemaglobinopathies, congenital spherocytosis or in the flextail mutation in mice where the mutation affects differentiation of erythropoietic cells but has no effect on the production of granulocytes.[55] In a number of instances, however, the available evidence does not allow one to discriminate between cellular defects independent of the microenvironment or defects of the micoenvironment that may be private to a given line of differentiated hematopoietic cells. A condition has been described, for instance, of an anemic individual whose plasma contained no transferrin.[56] This person might have been classed as having a type of idiopathic anemia possibly related to a cellular defect in the erythrocyte series if levels of transferrin not been determined. It is interesting to speculate that a marrow graft nevertheless may have repaired the anemia since cells derived from marrow infusions are capable of producing transferrin.[57]

In principle, it would seem logical to attempt marrow transplantation in the more severe forms of the hemoglobinopathies such as sickle cell anemia and certain types of the thalassemias. Except for a few unsuccessful attempts recently, [4] transplantation for these disorders has not been used in the past. Although these diseases may be servere, the prognosis is much better than that of aplastic anemia, acute leukemia and some of the immunologic deficiency diseases. Success with marrow transplantation in these latter areas undoubtedly will lead to an increase in therapeutic trials in sickle cell anemia and thalassemia.

Marrow Transplantation as a Prelude to Organ Grafting

The successful transplantation of allogeneic or even xenogeneic marrow allows the permanent survival of other tissue grafts from the same donor [58] or in the case of inbred animals from the same inbred strain.[2] Rats [47] and mice [48] given allogeneic marrow or lymphohematopoietic cells after CY treatment will accept both host- and donor-type skin while rejecting third-party skin. Such animals will also accept host-type kidney grafts.[59] Indeed, mice given rat bone marrow after lethal irradiation will accept subcutaneously placed grafts of rat pulmonary tissue.[60] At the present time, however, this offers only a hope for the future use in the clinic because of the as yet unresolved hazards associated with marrow transplants in man.

Use of Marrow Grafts in Malignancy

There are at least three reasons why one might wish to employ marrow transplantation in malignancy: (1) to provide the means of administering doses of anticancer agents in what would ordinarily be lethal doses were it not for the protection afforded by transplanted marrow; (2) to provide specific immunotherapy by the transplantation of syngeneic marrow and (3) to provide a therapeutic effect by means of a mild or controlled GVH utilizing allogeneic marrow.

For purposes of discussion, it is useful to consider that tumor cells may offer normal as well as tumor-specific transplantation antigens as two potential targets for reactive lymphoid cells or cytotoxic antibody. Lymphoid-derived and leukemic tumor cells are relatively rich in normal transplantation antigens while nonlymphoid-derived tumors such as fibrosarcoma and adenocarcinoma tumors may be relatively poor in such antigens. On the other hand, the strength of tumor-specific transplantation antigens will vary from tumor to tumor.

The infusion of syngeneic marrow after x-irradiation or chemotherapy in animals has generally been disappointing particularly in

situations where tumor-specific antigens are weak or in doubt.[2] A similar failure of this approach to show a marked effect in the clinic has been reported by Thomas *et al*,[50] who reported on 3 patients with acute leukemia who were given 800–1000 rads whole-body x-irradiation and then marrow from an identical twin. These patients recovered from the irradiation but leukemia recurred 48–84 days later. A fourth patient was given 1596 rads and syngeneic marrow and showed hematopoietic recovery but died early after the transplant of hepatic failure, presumably due to viral hepatitis.

In situations where strong tumor-specific transplantation antigens were present or suspected in rodents, lethal x-irradiation or chemotherapy followed by syngeneic marrow and lymphoid cells has occasionally had remarkable therapeutic results,[2] but has often been without therapeutic benefit.[61–63] In experiments where an antigenic tumor was treated with a nonimmunosuppressive agent (dimethyl myleran), a marked therapeutic effect was seen.[61] The success of therapy apparently depended upon the synergism between the antitumor action of the drug and the immunologic resistance of the host to tumor-specific transplantation antigens.

Another approach has been to employ syngeneic lymphohematopoietic cells sensitized to putative tumor antigens. This form of immunotherapy has been reported to be successful even against established clinically detectable primary tumors induced by Moloney sarcoma virus.[63] In addition, an additive therapeutic effect of CY treatment given prior to sensitized syngeneic cells has been reported.[63]

Identical twin human donors have not been immunized with putative tumor antigens for obvious ethical reasons. Thomas *et al*,[50] however, have employed a unique approach. They treated 3 patients with leukemia and one with lymphosarcoma with whole-body x-irradiation followed by syngeneic marrow transplants and subsequent buffy coat cells from the donors. The patients were then given weekly subcutaneous injections of previously stored but irradiated tumor cells in an attempt to immunize donor cells. Two patients relapsed with leukemia, one 33 days and the other 8 months later. Another died of intersitital pneumonitis, without leukemia. The patient with lymphosarcoma was in complete remission 105 days post-transplant at the time of the report. The effectiveness of this novel approach can only be judged after further trials.

Lethal doses of whole-body x-irradiation [2] or high but nonlethal doses of CY [62] followed by allogeneic bone marrow and lymphoid cells have been shown in many cases to give a marked antitumor effect and have

even resulted in the total eradication of leukemic or lymphoid-derived tumors in animal systems. A few animals were able to survive free of tumor [2] but the majority died of GVH. Effective treatment of GVH disease increased the number of tumor-free survivors.[62,64]

In at least two reports, it was noted that severe GVH was without effect on a fibrosarcoma and adenocarcinoma in the mouse.[63,65] It has been suggested that the difference in results with lymphomas and leukemias on the one hand and these nonlymphomatous solid tumors on the other is a reflection of the relative richness of transplantation antigens on the surface of lymphoid and leukemic tumor cells (increased sensitivity to GVH) as opposed to other tumors.[65] In one case of a viral-induced fibrosarcoma in mice, the use of allogeneic cells presensitized to tumor antigens was effective in eliminating tumor cells when administered after CY.[63]

In general, transplanting allogeneic non–HL-A identical marrow in human leukemia after lethal doses of x-ray or CY has either failed to show takes or has resulted in death from GVH.[2,3,66] The one exception is a case of acute lymphocytic leukemia reported by Mathe *et al.*[58] The patient survived free of leukemia for 20 months after a lethal dose of x-ray and marrow infusion, but he died of a generalized herpes infection.

The major transplantation antigens in man are controlled by genes at one chromosmal locus designated HL-A.[67] Genetic analysis of family typing data permits the recognition of allogeneic siblings who are identical for both parental alleles. For purposes of discussion, these donor-recipient pairs will be called HL-A identical sibling matches. Recently, a number of marrow transplants have been attempted in patients with acute leukemia or lymphoma after lethal whole-body irradiation or CY treatment, using HL-A identical sibling matches. The rationale and experimental data related to the use of CY for marrow transplantation in man has been developed previously.[27]

Santos *et al* [68] performed marrow grafts in 5 patients with acute myelocytic leukemia and in 1 with acute monocytic leukemia, using HL-A matched siblings. Patients were prepared with four daily doses of CY (50–60 mg/kg per dose) and all but 1 patient recieved additional CY after the grafting. One patient, who may have been presensitized to donor antigens, did not show evidence of engraftment but did enjoy a remission of his disease before relapse 3 months later. Prompt marrow engraftment was seen in the other 4 patients who had donors of the opposite sex. During the first 30 days after transplant, both host- and donor-type cells were seen on karyotype analysis. Subsequently, however, only donor-type cells were seen. Two patients died of bacterial

sepsis, one at 32 days and the other at 47 days after transplant. One patient died of GVH with terminal generalized viral infection 75 days after transplant and 1 patient died of acute staphylococcal pneumonitis 215 days after transplant. None of the 4 patients with marrow engraftment showed evidence of leukemia at autopsy.

Graw *et al*[69] performed marrow grafts with HL-A matched siblings in 7 patients with acute lymphocytic leukemia. A CY schedule designed after that described by Santos *et al*[27] was used in five instances but the dose was lower (45 mg/kg for each of 4 successive days) and whole-body x-ray was used in 2 patients. One patient failed to show a take (there was a major blood group mismatch) but prompt evidence of engraftment occurred in the other 6. One of the patients treated with x-ray failed to show a graft and the other died of GVH. Patients treated with CY never demonstrated complete chimerism[70] (*ie*, host-type lymphohematopoietic cells were present in all analyses) and acute leukemia recurred in all but 1 who died of GVH. Where testable by karyotype analysis, the recurrent leukemia was shown to be of host origin.[70] The recurrence of leukemia in these cases may possibly be related to the failure of these workers to obtain "complete" chimerism. It is most likely that the doses of CY were too low in these cases as contrasted to the higher doses employed by Santos *et al*.[68] Experiments in a rodent model reported elsewhere add credence to this suggestion.[47]

Thomas *et al*[71] treated 6 patients with acute leukemia and one with Hodgkin's disease with 1000 rads of whole-body x-irradiation, then with marrow from HL-A matched siblings and subsequently administered methotrexate to control GVH. The patient with Hodgkin's disease died of GVH but free of tumor at autopsy 37 days after transplant. Three patients died without evidence of a take. Two patients showed prompt marrow engraftment but relapsed with leukemia. One patient has a complete graft and is free of leukemia 200 days post-transplant.[72] In one of the cases of leukemia recurrence in a female, the leukemic cells were shown to possess the male karyotype of the donor.[73] The latter observation obviously suggests that an oncogenic virus was involved. Recent observations such as those of Brockman *et al*[74] show that the streptovaricins inhibit RNA-dependent DNA polymerase present in an oncogenic RNA virus and offer the hope for the future that such compounds might be administered after transplantation to prevent the transformation of donor cells by possible oncogenic viruses.

GVH Disease

GVH has been encountered in several situations in which individuals

have been unable to defend themselves against grafts of immunologically competent allogeneic cells either because of immunoincompetence produced by disease states [16] or because of immunosuppressive treatment.[2] The clinical and pathologic aspects of this disease in animals and man have been extensively reviewed elsewhere.[2] In animals, CY,[2,75] methotrexate [2,76] and antilymphocyte sera [2,77] have been successful in controlling the severity of GHV. In addition, fractionation of marrow has also been shown to be effective.[78]

In man, there have not been enough clinical trials to indicate which of the above methods might be employed to successfully control severe GVH. The results of administering CY and methotrexate after transplantation of HL-A matched sibling transplants, however, has been encouraging. Of 16 such marrow transplants performed by the groups at Johns Hopkins University[68] the University of Washington [71] and the National Cancer Institute,[69] where there was evidence of engraftment, mild (transient skin rash) or no GVH was seen in 6 patients. Moderately severe GVH with definite skin involvement and occasional abnormalities in liver function was seen in 5. Severe GVH that led to death occurred in 5. It is of interest that 3 of the 5 patients with severe GVH either did not receive after the transplant CY or methotrexate (as is the present practice of the 3 groups) or were given unirradiated lymphocytes contaminating platelet donations (a situation known to increase the severity of GHV).

Conclusions

The rationale for and some of the results of marrow transplantation in human disease have been outlined. There have been a few notable successes but the majority of clinical attempts have failed. Nevertheless, the information gained in the practical and theoretic spheres suggests optimism for the future of this procedure. Continued animal and clinical research centered on the control of GVH, prevention of oncogenic viral transformation and the supportive care of individuals during periods of aplasia hopefully will justify the present optimism.

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