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EDITORIAL

Bone Marrow Transplantation—A Present-Day Challenge

The demonstration that mice given lethal doses of irradiation could be "saved" by the introduction of splenic[1] or bone marrow[2] material was at first ascribed to humoral factors. Later, workers in Loutit's laboratory,[3] among others, raised doubts about this and suggested that the marrow of the irradiated animal was actually destroyed and repopulated by the injected hematopoietic material.

Congdon and Lorenz[4] demonstrated that *rat* bone marrow could be used successfully in *mice* to prevent radiation death. Was it possible that heterotransplantation, hitherto thought impossible, was actually taking place or was this due to a humoral mechanism? That successful transplantation and repopulation could actually take place was recently demonstrated by ingenious techniques developed in British and American laboratories. Ford et al.[5] used a "chromosome-marker"; the American workers Nowell, Cole et al.[6] used the alkaline phosphatase technique. An atypical "marked" chromosome was found in some mice, which were then used as donor animals. Irradiated mice were injected with marrow from the donor animals. The irradiated mice not only survived the lethal radiation but presented normal-appearing bone marrow—*containing the "marker" chromosomes*. This indicated that the transplanted marrow had "taken" and had repopulated the irradiated marrow.

The American demonstration was even more striking. Working with the knowledge that the mature granulocytes of rats are strongly positive for alkaline phosphatase, and the same cells of mice completely negative, Nowell et al. injected bone marrow from normal rats intravenously into lethally irradiated mice. Not only was there evidence of repopulation of mouse bone marrow by the alkaline phosphatase positive rat cells, but after 2–4 weeks, virtually the entire population of the bone marrow granulocytes was made up of alkaline phosphatase positive cells. Normal nonirradiated mice injected with rat bone marrow showed no evidence of such repopulation, indicating that x-irradiation destroyed the normal immune defense against homo- and hetero-transplanted material.

Lorenz,[7] and more recently Loutit's group went a step further.[8] *Leukemic* mice were given lethal doses of x-ray, enough to destroy both the leukemic tissue and the normal marrow present. When these mice were given intravenous injections of bone marrow material from normal mice, most of the mice not only survived the lethal irradiation but showed no evidence of leukemia. The following cautious and suitably cogent observation was made: "If the experiences of several laboratories could be pooled, some general laws might be evolved which should help in planning an extrapolation from mouse to man for the treatment of those types of leukaemia which are so rapidly fatal as to warrant the use of desperate measures."

These observations, and other similar ones (cf. Lindsley, Odell, and Tausche[9]) indicate that (1) lethal irradiation can be survived providing normal marrow is injected; (2) marrow injected intravenously seeks out normal marrow sites, apparently escaping the pulmonary barrier; (3) irradiation strips the immunologic defenses to such a degree that not only homotransplants (from the same animal species), but even heterotransplants can be effective. From the standpoint of clinical practice, these facts might be applicable, as has been suggested, for the treatment of human acute leukemia, certainly a condition warranting "desperate measures." That this thought has captured the imagination is borne out by the recent award from the Leukemia Research Foundation to Dr. Loutit's group for his investigations in this field.

Also of interest in this regard are the experiments of Russell et al.[10] of Bar Harbor, who studied genetically determined microcytic, hypochromic anemia in mice (resembling thalassemia?). Moderate radiation (200 r) in these anemic mice, when followed by the intravenous injection of normal mouse marrow resulted in repopulation by normal marrow, at least as indicated by the production of normal red cells by the previously anemic animals.

In aplastic anemia, severe hereditary anemias, and even in leukemia, one would surely hesitate to give a patient a lethal dose of irradiation for the purpose of "knocking out" immune defenses prior to the injection of normal marrow. Conceivably this might not be successful, even if techniques were developed to give the marrow in sufficiently large amounts. It is certain therefore that less drastic alternative methods for reducing immune body development are desirable, and one or two have already been broached. Thus Howes (1951)[11] was able to transplant human cancer to some animals by previous treatment with cortisone, which is known to reduce antibody production. More recently Herbut and Kraemer,[12] dissatisfied with both the x-irradiation and the cortisone techniques, and having in mind the importance of *properdin* in immunologic mechanisms, decided to use Zymosan. This is a complex carbohydrate derived from yeast which has been shown to combine with properdin both in vitro and in vivo, rendering the properdin inactive. By injecting Zymosan intravenously, the Philadelphia investigators were able to transplant successfully a human carcinoma of the colon into Wistar rats. Presumably the Zymosan reduced or neutralized the effect of the properdin, thus resulting in cessation of immunologic activity and thus in successful "takes" of heterotransplants.

The transplantation of human bone marrow must be considered as a distinct therapeutic necessity, particularly in this period of "civilization," which features the all-importance of the atom. The bone marrow (and the blood) are the most vulnerable of all body tissues to ionizing radiation, and if bone marrow could be transfused as readily as blood, this would certainly be a great boon. The Biology Division of the Oak Ridge National Laboratory, in collaboration with groups of investigators throughout the country, is devoting a good part of its unequalled facilities for studying the various problems involved in bone marrow transplantation. Setting the matter of ionizing radiation aside, this potentially great therapeutic method could be profoundly useful in such phases of hematologic practice as the treatment of hypoplastic anemia, and acute leukemia; the terminal phases of chronic leukemia, lymphosarcoma and Hodgkin's disease, and

disseminated carcinoma; and even in the treatment of such severe genetically determined anemias as thalassemia major (Cooley's anemia) and sickle cell anemia. It is hoped that a combined and prodigious effort will make human bone marrow transplantation a feasible method in the not too distant future.

William Dameshek

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