

Transplantation Bulletin

THE RESTORATION OF MARROW FUNCTION AFTER LETHAL IRRADIATION IN MAN: A REVIEW

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In several mammalian species, after lethal irradiation, marrow function can be restored in a week or two by intravenous infusion of normal cells (1-5). By selecting minor differences in host and donor, it can be shown that the repopulation of marrow is by cells of donor origin (6-8). This repopulation may be permanent or temporary, depending to some extent upon the amount of irradiation that precedes it and the residual ability of the host's own cells to regenerate and push out the invaders.

Following radiation exposure, the patient must weather a period of marrow aplasia. The longer the marrow remains aplastic, the greater will be the opportunity for invasion by bacteria, viruses and yeasts, and the greater will be the likelihood of death from infection or from platelet insufficiency and capillary hemorrhages. Hence, isolation from parasites, control of infection, platelet transfusions and early restoration of marrow function are important in lowering mortality rates. Marrow function in man has been restored, after exposures to 600-1000 roentgens, by intravenous infusion of cells of normal marrow. The cells may be taken from the patient himself prior to radiation, or they may come from an identical twin if one is available, or they may be taken from an unrelated donor of suitable blood type. Also, with good supportive care, the less

heavily irradiated patient (200-400 roentgens) has been kept alive long enough for residual elements of his own marrow to multiply and restore function autogenously (9-11).

Newton (12), Kurnick (13), and McGovern (14), their colleagues, and no doubt others, have used infusions of autologous marrow to hasten restoration of marrow function in individuals receiving consequential amounts of radiation. A sample of the patient's own normal marrow has been removed prior to treatment and set aside frozen in glycerol. Some weeks later, when therapy has been completed, this seed sample has been thawed and re-infused. Return of function has appeared to be more rapid in these patients than in control subjects not receiving infusions. Atkinson and colleagues (15) and Thomas and associates (16), have observed a benign clinical course and a rapid restoration of normal function in irradiated leukemic twins given infusions of normal marrow taken from their normal identical partners. In Thomas's 2 patients, following 850 and 1140 roentgens respectively, marrow function returned in 2 weeks and illness during this brief period of aplasia was not severe.

In a series of individuals accidentally exposed to 400-1000 roentgens of whole-body irradiation, Mathé *et al* have shown a prompt reappearance of marrow function, including erythrocytes of donor type, following infusions of marrow taken from volunteers (10). It is probably significant that the infusions of homologous marrow that worked so well were administered late, a month after the radiation exposure. Following an initial burst of graft activity, autogenous function returned and cell production of donor type gradually subsided. Mathé and associates have also established normal marrow function, partially of donor type, in 2 young patients with acute leukemia treated with 850 rad of total-body irradiation from Co⁶⁰ (17, 18). As in the accident cases, early function in the graft was followed by a return of function in residual elements of the host's own marrow. Erythrocyte populations were at levels 10-30% donor and 70-90% host at the end of 2 months. Thomas and associates have (19) recently had

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success in restoring marrow function in an irradiated leukemic infant after 900 roentgens of whole body irradiation, but without evidence of successful engraftment of either the fetal or adult hematopoietic tissue that was infused.

In each instance where success has been attained the engraftment seems correlatable with the late administration of the foreign marrow infusion, administration not on the first day immediately following radiation, but administration 1, 2, or even 3 weeks later, at a time when the progressive deterioration of the host's defenses may have permitted more efficient growth of the foreign cells.

A secondary syndrome occurred in Mathé's leukemic subjects 50 days after irradiation and 40 days after marrow infusion (20). The episodes were characterized by fever, cough, vomiting, diarrhea, insufficiency of digestion and weight loss. A hyperglobulinemia developed in one of these patients. This patient had received marrow from 2 donors. Hypogammaglobulinemia was observed in the other patient. This patient received marrow from only one donor. The clinical syndrome, i.e. the secondary disease, disappeared in both patients when the number of erythrocytes of donor type decreased markedly, that is when the grafts ceased to function. A biopsy of a lymph node during the secondary syndrome in the hypogammaglobulinemic patient, 90 days after irradiation, showed a lymphoid atrophy similar to that observed in irradiated dogs restored with homologous marrow (31). A lymph node biopsy in the other patient, 120 days after irradiation and at a time when the secondary syndrome had terminated, showed small follicles of regeneration in the peripheral cortical areas.

In time of occurrence and in general appearance the illnesses were similar to what is seen in other species after successful transplantation of foreign marrow (21, 22), but not after transplantation of autologous or isologous or fetal marrow (23, 24). In animals, the chief histologic finding is secondary atrophy of lymphoid areas. Spleen and lymph nodes that have been repopulated by graft cells become the later sites of an immunologic disturbance, in effect a reaction of the graft against host tissues. During the disturbance there is digestive upset, weight loss, fever, and at times infection. Many animals die; some recover (25, 26). In the patients described, recovery followed symptomatic dietary management and antibiotics.

Apropos of treatment of patients with leuke-

mia, it is of interest that symptoms of radiation toxicity—nausea, vomiting, and collapse—have been mild or absent at doses of 800–1000 roentgens when the radiation has been administered by high energy photons at rates of 20–40 roentgens per hour for 20–30 hours.

Attention might also be directed to the fact that radiation followed by marrow transplantation has not led to prolonged remission of leukemia when the marrow transplantation has been autologous or isologous. McGovern's patient and Thomas' identical twins with leukemia have had recurrences in 2–4 months. In mice, a stronger anti-leukemic effect is obtained with radiation and homologous marrow than is obtained with radiation and isologous marrow (27–30). It will be important, therefore, to see whether foreign marrow reaction (secondary disease) is helpful in eradicating leukemia in man. Certainly radiation alone at the 1000 roentgens level does not appear to do so.

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