SUPRALETHAL WHOLE BODY IRRADIATION AND ISOLOGOUS MARROW TRANSPLANTATION IN MAN *†

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Infusions of normal marrow will prevent death from marrow failure in animals that have received lethal doses of total body irradiation, doses of the order of 1,000 roentgens (r.) (1). By analogy similar infusions might be expected to be useful in treating postradiative marrow failure in man. Two patients with leukemia requiring treatment by radiation have been given 850 r. and 1,140 r., respectively. Each patient had an identical twin to serve as donor of normal isologous marrow. In these twins it was possible to study the problems of lethal irradiation and marrow restoration free from the immunologic complications of homotransplantation. It was also possible to observe the effect of lethal irradiation upon leukemia in man.

METHODS

The methods of obtaining, preparing, storing and infusing bone marrow have been described previously (2, 3, 4). The two Co^{60} units used to administer whole body irradiation have also been described (5). All blood transfusions were of freshly obtained blood drawn into plastic bags containing 50 ml. of 1.5 per cent ethylenediamenetetraacetic acid (EDTA) and 0.7 per cent NaCl.[1] A platelet transfusion (one unit of platelets) represented the platelet concentrate from 500 ml. of blood obtained by differential centrifugation in plastic bags[1] (6). Platelet counts were performed with a phase microscope by the method of Brecher and Cronkite (7). Reticulocytes were counted by the method of Brecher (8). Hemoglobin was determined by the cyanmethemoglobin method (9).

CASE REPORTS

Case I: (D. C. Number 79389). This colored female aged two years and eleven months was admitted to the Mary Imogene Bassett Hospital for the first time on October 4, 1958. She was one of identical twins with a history of normal development. She was seen at the Harriet Lane Home of the Johns Hopkins Hospital, Baltimore, Maryland on June 11, 1958 because of swelling of the eyes and lips, diagnosed as angioneurotic edema, which responded to Benadryl®. She was admitted to the Harriet Lane Home on July 25, 1958 because of night sweats, vomiting, mild fatigue and a low-grade fever. At that time her white blood cell count was 45,000 per cu. mm., and the differential showed 57 per cent blast cells. The hematocrit was 20 per cent. A bone marrow study showed hypocellularity and numerous blast cells. A diagnosis of acute leukemia was made. Initially the patient was treated with 6-mercaptopurine, 2.5 mg. per day. On August 29, 1958 Prednisone® was started at 30 mg. per day and increased to 40 mg. per day on September 9. On September 26, 6-mercaptopurine was discontinued and Methotrexate® was started at 2.5 mg. per day. There was no sign of remission, and the patient's persistent anemia required transfusions of 250 ml. of whole blood on August 14, August 27 and September 14. Because of failure to secure a remission on chemotherapy and because the patient had an identical twin, it was decided to transfer her to the Mary Imogene Bassett Hospital for whole body irradiation and marrow transplantation.

Her physical examination on admission showed resemblance to Cushing syndrome. There were shotty cervical and inguinal nodes and one small left axillary node. The abdomen was protuberant, and the spleen extended 2 cm. below the left costal margin. The liver was not enlarged.

Laboratory data showed a normal urinalysis. The hemoglobin was 4.6 Gm. per cent. The white blood cell count was 3,600 per cu. mm. with 19 polymorphonuclear leukocytes, 2 band forms, 2 blast cells, 50 lymphocytes, 5 atypical lymphocytes, 1 young lymphocyte and 21 monocytes. There were 20 nucleated red cells per 100 white cells. The platelet count was 33,000 per cu. mm. and the reticulocyte count 2.7 per cent. A chest X-ray was normal.

The patient was continued on Prednisone®, 40 mg. daily. She had been receiving Methotrexate®, 7.5 mg. daily. This drug was discontinued on October 9. The patient was placed in strict isolation. She was observed for infection, and frequent cultures showed no significant organisms. Whole body irradiation was started on

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[1] Fenwal EDTA Blood-Pack, Ethicon, Somerville, N. J.

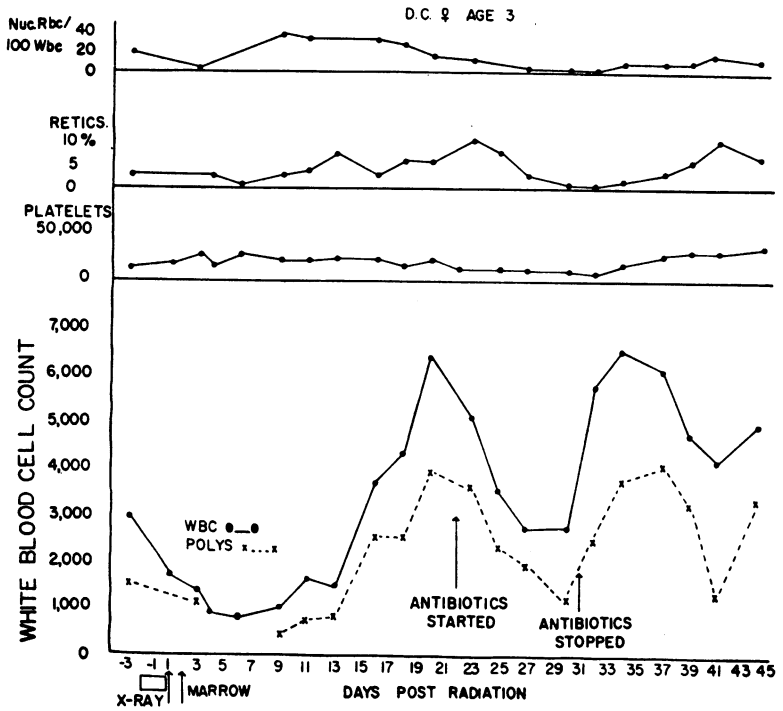

FIG. 1. HEMATOLOGIC EVENTS IN CASE 1

First irradiation. The small rectangle labeled "X-ray" indicates the administration of a tissue dose of 200 r. The arrows on the abscissa indicate marrow infusions.

October 10. Irradiation was administered with a General Electric Maximar Unit operating at 250 KV. and 5 ma., HVL 2.2 mm. Cu. On October 10 she received an air dose of 75 r. to the front of the body and also to the back of the body. The total irradiation time was 225 minutes. This procedure was repeated on October 11. The total calculated mean midline tissue dose was 200 r.

The marrow donor was considered to be an identical twin on the basis of appearance, a documented single placenta and identical blood type. On October 7 the marrow donor was taken to the operating room, and under general anesthesia 25 marrow aspirations were performed on the sternum, tibiae and anterior and posterior iliac crests. This marrow was transferred immediately to Hanks' solution containing 0.1 mg. of Connaught heparin [2] per ml. and passed through stainless steel screens. A total of 0.92×10^9 nucleated marrow cells was obtained. A differential count on this marrow showed it to be normal. The marrow was frozen in 15 per cent glycerol and stored at $-80°$ C. (4). On October 12 this marrow preparation was thawed, deglycerolized and administered to the irradiated recipient. On October 13 the marrow donor was again subjected to 20 marrow aspirations under general anesthesia from the above listed sites. A total of 0.35×10^9 nucleated marrow cells was obtained, screened and administered immediately to the recipient. There was no reaction to the administration of either of these marrow preparations.

The hematologic events postradiation are shown in Figure 1. The patient did not vomit or exhibit diarrhea as the result of the irradiation. She did quite well clinically. On the fourth day following irradiation she was given one unit of platelets. On the ninth day she was discovered to have a hemolytic staphylococcus aureus, coagulase negative in her throat culture. This organism was sensitive to chloramphenicol and erythromycin. On the twenty-second postirradiation day her temperature went up to 103.4 F°. There was no clinical evidence of infection. However, she was started on Chloramphenicol®, 800 mg. daily, erythromycin, 800 mg. daily, and Mycostatin®, 300,000 units daily. Over the next four days the patient's temperature varied from normal to 103°. Thereafter she became afebrile except for diurnal variations with maximum readings of 100.2°. On the thirty-first postirradiation day antibiotics were stopped. The changes in the white blood cell count during the period of antibiotic administration are illustrated in Figure 1. On the twenty-fifth postirradiation day the patient was given 300 ml. of fresh whole blood. A bone marrow study on that day showed a cellular marrow. Several normal megakaryocytes were seen. The myeloid-erythroid ratio was 5 to 1. There was an increased number of mature lymphocytes but no abnormal cells. This was in-

[2] Connaught Medical Research Laboratories, Toronto, Canada.

terpreted as normal marrow without evidence of leukemia.

The patient continued to feel well and her activities were increased. Between the sixteenth and the twenty-eighth postirradiation day, Prednisone® was decreased to a level of 10 mg. daily. The patient was discharged from the hospital on November 25, the forty-fifth day after irradiation.

The patient did well for approximately three weeks and then began to run a low-grade fever. She was seen at the Harriet Lane Home on December 29, at which time there was no clinical evidence of infection. She had had no bleeding. The hemoglobin was 6 Gm. per cent, the white blood cell count 6,300 per cu. mm. and the platelet count 58,000 per cu. mm. Blood smears showed 15 per cent monocytes and 4 per cent blast cells, interpreted as monoblasts. In the meantime, the twin Co^{60} irradiation unit had been placed in operation at the Mary Imogene Bassett Hospital. Accordingly, it was decided to re-irradiate the patient at a higher dose level. She was admitted to the Mary Imogene Bassett Hospital on January 17, 1959. Prednisone® had been discontinued on December 29 and the previously observed Cushing syndrome features were no longer present. There were petechiae on the buccal mucosa. The spleen was not palpable.

Initial laboratory data showed a normal urinalysis. Peripheral blood counts are given in Figure 2A. A bone marrow study before radiation showed a cellular marrow with occasional megakaryocytes. Approximately 50 per cent of the marrow cells were blasts of stem cell type.

Whole body irradiation with the Co^{60} sources was started on January 22 and completed on January 23. The irradiation time was 22 hours and 20 minutes, and the total elapsed time was 26 hours and 21 minutes. The total dose administered was 1,140 r. in air measured at the midline of the patient. (Calculated midline tissue dose, 1,003 r.).

Marrow was obtained from the normal twin as previously described. On January 24, the first day after irradiation, a total of 1.36×10^9 nucleated marrow cells was administered. On January 28, the fifth postirradiation day, marrow was again obtained from the twin and a total of 0.95×10^9 cells was administered to the patient. Because of failure of the platelet count to recover, a third series of marrow aspirations was performed on February 26, the thirty-fourth day following irradiation. This material was not screened but was administered immediately to the recipient. Approximately 0.1×10^9 nucleated marrow cells was administered directly into the posterior iliac crest, and an additional 0.8×10^9 nucleated cells was given intravenously. There was no evidence of reaction to the marrow infusions.

The postradiation hematologic data are shown in Figure 2A, and the clinical course of events is shown in Figure 2B. The patient was given oral neomycin for a period of four days before irradiation was begun. On the first day after irradiation she was started on gamma

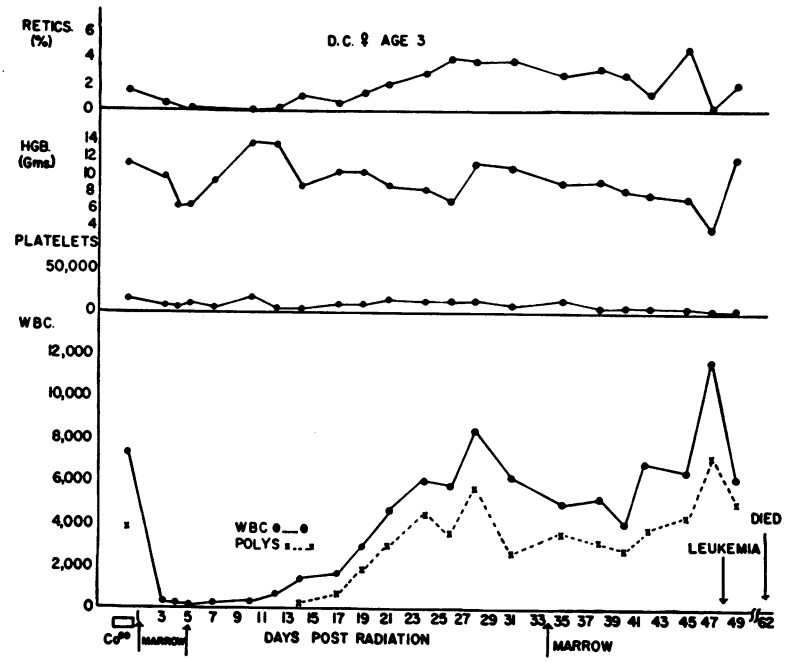

FIG. 2A. HEMATOLOGIC EVENTS IN CASE 1

Second irradiation. The small rectangle labeled "Co^{60}" indicates the administration of a midline air dose of 1,140 r. The arrows on the abscissa indicate marrow infusions.

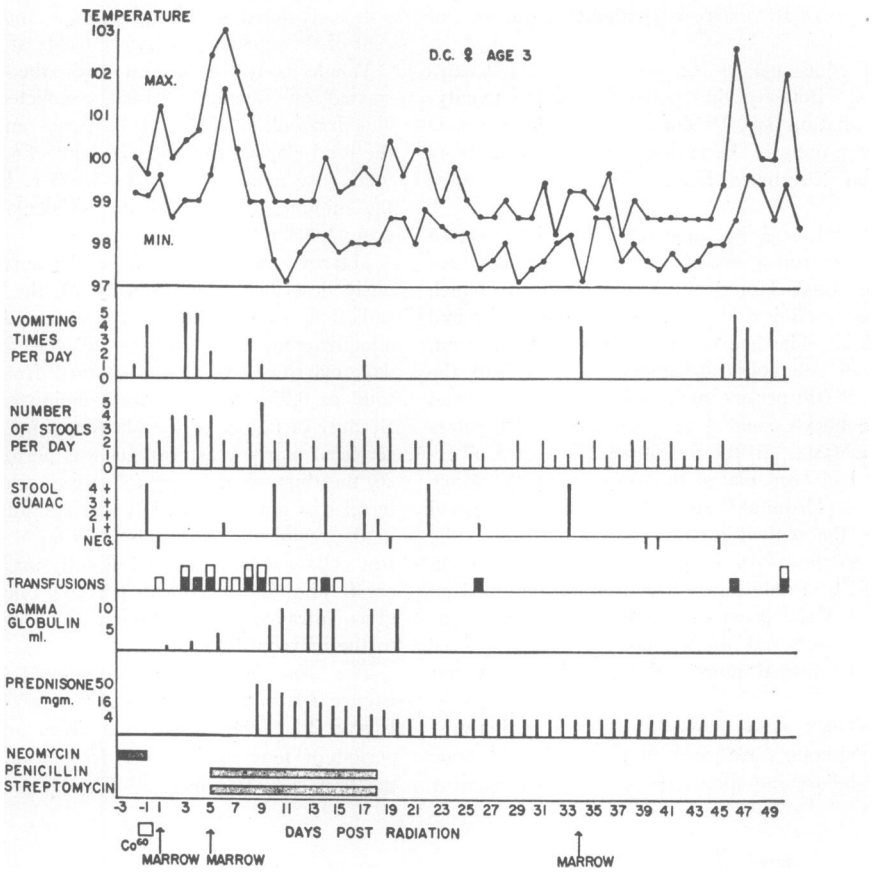

FIG. 2B. CLINICAL EVENTS IN CASE 1

Second irradiation.

□ Platelet transfusions.

■ Fresh whole blood transfusions.

globulin, 1 ml. intravenously with slowly increasing doses up to approximately 10 ml. every other day ending on the nineteenth postirradiation day. On the fifth postirradiation day her temperature went up to 102.4°, and she was started on penicillin and streptomycin. She was afebrile by the ninth postirradiation day.

During the immediate postirradiation period the patient suffered repeated epistaxes. Because of this she received frequent infusions of fresh platelets or fresh whole blood. Because of bleeding Prednisone® was started on the eighth day following irradiation. After initial doses of 50 mg. she was maintained on 16 mg. daily and slowly tapered to 4 mg. daily by the nineteenth day. Thereafter she was maintained at this level. By the eleventh day the major bleeding had subsided. The patient was eating well. She then did well clinically, except for febrile reaction to blood transfusions on the forty-sixth and forty-ninth postirradiation days.

On the thirty-second postirradiation day a marrow aspiration was performed and numerous particles were obtained. The myeloid-erythroid ratio was 5 to 1 with a normal maturation sequence in both series. There was no evidence of leukemia. A careful search of a number of marrow particles failed to demonstrate any megakaryocytes.

On the forty-eighth postirradiation day a marrow aspiration showed 22 per cent blast cells and a diagnosis of recurrent leukemia was made. The patient was discharged from the hospital on March 17, the fifty-third day after irradiation.

On March 21 she fell at home and developed a hematoma of the forehead. She was admitted to the Harriet Lane Home on March 22 in coma. The white blood cell count was 61,700 per cu. mm., and the differential count showed 35 per cent blast cells. She died on March 26, the one hundred sixty-sixth day following the first irradiation, and the sixty-second day following the second irradiation. A postmortem examination was not performed. It should be noted that the remission after 1,140 r. was 48 days whereas it was 66 days after the original 200 r.

Case II: (D. W. Number 80151). This white female aged four years and nine months was admitted to the Mary Imogene Bassett Hospital on December 10, 1958.

She was one of identical twins with a normal history of growth and development. In November of 1957 she complained of aches and pains. Progressive lethargy and increased irritability followed. In April of 1958 she was admitted to the Eglin Air Force Base Hospital. The hemoglobin was 6.5 Gm. per cent, and the white blood cell count was 5,200 per cu. mm. A surgical bone marrow biopsy was performed, and the diagnosis of acute leukemia was made and confirmed by the Armed Forces Institute of Pathology. She was treated with prednisolone, 20 mg. a day, and a complete remission was obtained in five weeks. She was maintained on 15 mg. prednisolone daily. In October of 1958 she again had increasing lethargy and irritability. On several occasions she had generalized convusions, at one time requiring a tracheotomy for control of oropharyngeal secretions. The spinal fluid was normal. At this time her hemoglobin was 6 Gm. per cent, and bone marrow studies showed the predominant cell to be a lymphoblast. She was treated with transfusions and Aminopterin®, 0.5 mg. per day, but the drug had to be discontinued after 10 days because of ulcerative stomatitis. On November 19, 1958 she was started on Dilantin® for control of convulsions and Methotrexate®, 2.5 mg. daily. Prednisolone was discontinued after a single dose of 40 units of corticotropin intramuscularly. After three weeks she showed no evidence of remission in her leukemia. For this reason she was transferred to the Mary Imogene Bassett Hospital for whole body irradiation and marrow transplantation.

Physical examination on admission showed scattered ecchymoses. There were a few small firm lymph nodes in the neck. The spleen was enlarged 2 cm. below the left costal margin. There was a well healed tracheotomy scar.

The hemoglobin was 15.3 Gm. per cent. The white blood cell count was 8,300 per cu. mm. with 57 polymorphonuclear leukocytes, 26 lymphocytes, 9 monocytes, 1 eosinophile, 2 band forms, 1 atypical lympocyte, 3 young lymphocytes and 1 blast cell. The platelet count was 139,000 per cu. mm. Stool was guaiac negative. On December 13 a bone marrow aspiration showed 40 to 50 per cent blast cells.

On admission to the hospital the patient was placed in strict isolation. She was continued on Dilantin® and phenobarbital, but Methotrexate® was discontinued. No steroids were given. On December 14 she was started on oral neomycin, 2 Gm. daily and Compazine®, 5 mg. daily. Whole body irradiation from the twin Co^{60} units was carried out on December 15 and 16. The duration of irradiation was 24 hours and 20 minutes. The elapsed time was 27 hours and 22 minutes. The total dose measured in air at the midline of the patient was 850 r. (calculated midline tissue dose, 748 r.). The patient had been vomiting one to three times daily and having considerable nausea before irradiation was started. This did not change during the period of irradiation but ended on the second postirradiation day. She had no significant diarrhea.

The patient's twin sister was assumed to be an identical twin on the basis of appearance and identical blood type. On December 17, the first day after irradiation, the normal twin was taken to the operating room where, under general anesthesia, a total of 20 marrow aspirations were performed on the tibiae and anterior and posterior

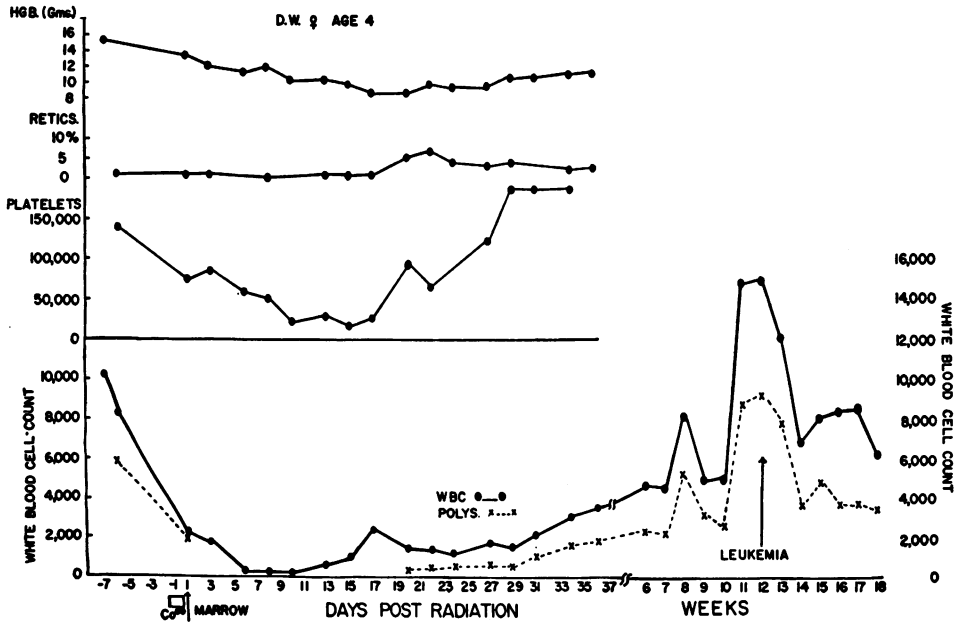

FIG. 3A. HEMATOLOGIC EVENTS IN CASE 2

The small rectangle labeled "Co^{60}" indicates the administration of a midline air dose of 850 r. The arrow on the abscissa indicates marrow infusion.

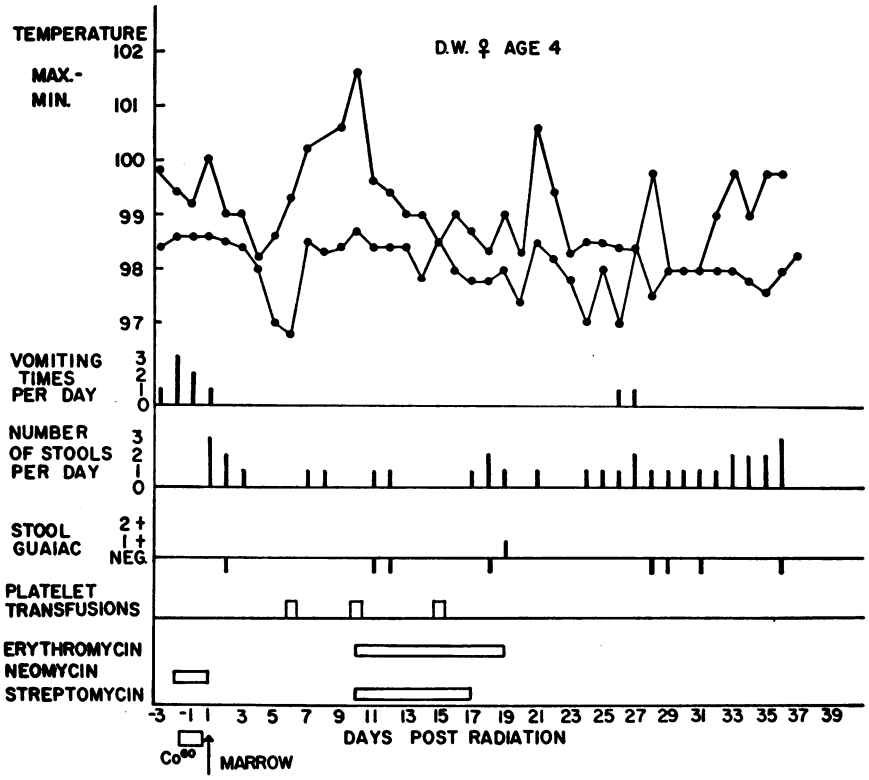

FIG. 3B. CLINICAL EVENTS IN CASE 2

iliac crests. This marrow was transferred immediately to Hanks' solution containing 0.1 mg. of Connaught heparin[2] per ml. It was passed through stainless steel screens and administered immediately to the patient. The total number of nucleated marrow cells after correction for nucleated cells in the peripheral blood was 3.9×10^8. There was no reaction to the administration of the marrow. Examination of smears of this marrow showed a normal differential.

The hematologic events are shown in Figure 3A. Returning marrow function was evident by the thirteenth day. A bone marrow aspiration was performed on the thirtieth day after irradiation. The cellularity was normal. Normal megakaryocytes were present. The myeloid-erythroid ratio was 2 to 1. The maturation sequence of both myeloid and erythroid cells was normal, and no abnormal cells could be found. Plasma cells could not be identified. The impression was normal marrow except for the absence of plasma cells.

The clinical events are shown in Figure 3B. The patient's appetite improved. She was up and about and active around her room. A throat culture on the seventh day after irradiation showed a staphylococcus aureus sensitive to erythromycin. On the ninth day she had fever. On the tenth day she was started on streptomycin and erythromycin. Fever disappeared and these drugs were discontinued on the eighteenth postirradiation day. On the twenty-first postirradiation day she developed mild nausea and fever. Her mother, who was in constant attendance, had at this time a moderate gastroenteritis. Patient and mother promptly recovered without therapy. The patient continued to be normal and was discharged from the hospital on January 22, 1959, the thirty-seventh postirradiation day.

She was then well until 12 weeks after irradiation when she developed bone pain. A marrow aspiration disclosed recurrent leukemia. Prednisone® was administered with a subsequent partial remission, 18 weeks after irradiation at the time of writing.

DISCUSSION

The twins described in this report were assumed to be identical on the basis of appearance and identity of blood types. Their histocompatabilities were not verified by skin transplantation. Transplantation of skin from the sick twin to the well twin was not advisable because of the possibility of transplanting leukemia if the twins were identical. A skin transplant from the well twin to the sick twin would have been difficult to interpret because of the variable effect of leukemia and steroid therapy on survival of skin transplants (10). Finally, there was little time to be lost since both leukemic patients were rapidly becoming worse.

In identical twins there is no immunologic marker to distinguish donor and recipient. Hence, a successful marrow transplant must be identified

by indirect proof—in this case, comparison with the course of events expected in the absence of a successful transplant. In treating leukemics with whole body irradiation and homologous marrow transplants, we have observed one patient whose own marrow resumed function after 325 r., but only after a lapse of 21 days (3). We have irradiated several patients with doses above 400 r. Subsequent homologous marrow transplants were unsuccessful, and regeneration of the patient's own marrow did not occur within 30 days. A group of normal individuals accidentally exposed to large sublethal doses of radiation have shown returning marrow function only after five weeks (11). A patient given 200 r. followed after a week by 250 r. in preparation for a kidney transplant also required four weeks for a return of marrow function (12). From these observations one may conclude that the return of marrow function in less than two weeks in the patients described here, who received 850 and 1,140 r., is indicative of a successful transplant of isologous marrow.

In mice, isologous marrow transplants are achieved without difficulty (1). We have observed almost no sickness and a return of marrow function in 7 to 10 days in dogs receiving autologous marrow and up to 1,500 r. of whole body irradiation (13). The benign clinical course of the patients described here indicates that isologous, and, by analogy, autologous transplants are as easy to achieve in man as in other animal species. A dose of two or three billion cells appears adequate.

The eventual return of leukemia in both our patients was disappointing but not unexpected. Burchenal, Hemphill, Holmberg and Wiegand (14) observed that transplanted leukemia in mice could not be sterilized by 1,000 r. given at a rate of 86 r. per minute. Several investigators have failed to cure leukemia in the mouse with doses of radiation on the order of 900 r. followed by transplantation of isologous marrow (15, 16). Atkinson, Mahoney, Schwartz and Hesch (17) have observed a remission of two months in a leukemic patient after 200 r. followed by isologous marrow. McGovern, Russell, Atkins and Webster (18) have observed a remission of three months in a leukemic patient who received 600 r. followed by an infusion of autologous marrow that had been stored during a previous remission. It appears then that neither sublethal nor supralethal (up to 1,140 r.) whole body irradiation will cure leukemia, barring the possibility of an unusually sensitive leukemia, but will produce a significant remission in patients who have relapsed despite conventional chemotherapy. The best result that we have had is a remission of six months after 325 r. without a marrow transplant (3).

Evidently something more than radiation is needed to eradicate leukemia. Two possible approaches are suggested. First, one may transplant homologous marrow after lethal irradiation and depend on the homologous marrow to provide an immunologic environment unsuitable for survival of the leukemia (19). This approach has apparently eradicated leukemia in some mice (15, 16). However, these mice subsequently have a high incidence of death from delayed foreign marrow disease due to a reaction of the graft against the host. Whether delayed foreign marrow disease will be either serious or useful in man, and whether it can be controlled by the clinical supportive measures available are questions currently being studied.

A method of circumventing foreign marrow reaction has been suggested (20) using fetal hematopoietic tissue of sufficient immaturity to be nonreactive against the host. So far grafts of fetal marrow have not been successful in man (21). Even if successful, it is possible that they may be tolerant of the leukemia as well as of the host and thus be of no benefit in eradicating leukemic cells.

The second approach to the problem of eradicating leukemia lies in the observation that with chemotherapy and X-ray the cure rate of transplantable leukemia in the mouse is an inverse function of the number of cells present—the smaller the number of leukemic cells, the greater the possibility of cure (22, 23, 24). This suggests that the patient in remission, with a relatively small mass of leukemic cells, is an advantageous subject for radiation. It further suggests that chemotherapeutic agents may be more effective if administered during an immediate postradiation period when the number of leukemic cells is relatively small.

SUMMARY

Leukemia has been studied in two sets of identical twins. One leukemic twin was irradiated

with 850 r. and the other with 1,140 r. from Co^{60} sources. Each was then given bone marrow from the respective normal twin. Successful transplantation of this isologous marrow was determined by the return of marrow function, evident after less than two weeks, and by a benign clinical course following radiation. Leukemia recurred after remissions of seven weeks in one case and 12 weeks in the other.

From these two patients our conclusions are as follows: *1*) Transplants of isologous marrow are readily achieved in man. *2*) One thousand r. of whole body radiation does not produce troublesome acute radiation sickness in man when given at a rate of 20 to 40 r. per hour. *3*) Whole body irradiation at the 1,000 r. level produces a remission but not a cure of leukemia when followed by isologous marrow.

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