Irradiation of the Entire Body and Marrow Transplantation: Some Observations and Comments

By E. Donnall Thomas, Harry L. Lochte, Jr. and Joseph W. Ferreebee

Infusion of normal bone marrow will induce recovery in several animal species after exposures to irradiation that otherwise would prove lethal. The freshly infused cells "home" to the denuded marrow spaces and repopulate them. The question naturally arises whether marrow spaces and soft tissues infested with leukemic cells can be similarly cleaned out by diffuse ionizing radiation and repopulated with normal cells. With some strains of leukemia in some strains of mice, this has been accomplished.

Translation of the above experiments into terms that are clinically applicable is a matter of evident importance. For this purpose there is available little quantitative information regarding the effects of whole-body irradiation in man and only preliminary information concerning marrow transplantations after irradiation in our species. There are also dissimilarities between man and lower animals that make translation of the experimental data difficult. It is a purpose of this communication to present further clinical experience with whole-body irradiation and marrow transplantation in man and to discuss some of the physical and biologic problems observed.

Case Reports

Case 6. This 59-year-old man with chronic lymphatic leukemia received whole-body irradiation followed by intravenous infusion of marrow. The progressive appearance of circulating erythrocytes of the donor type and their subsequent disappearance represented a temporarily successful homograft. The details of the first 54 days in the hospital have been reported.
Whole-body irradiation was given this patient by placing him in a chair 250 cm. from the source, a General Electric Maximar Unit operating at 250 kv. and 5 ma., HVL 2.2 mm. Cu. The dose rate was 0.4 r./min. The irradiation field was uniform over the trunk but fell off appreciably over the head and lower extremities. The patient was turned about from time to time. The total dose recorded over an 8-day period was 450 r measured in air at mid-field on the side toward the source. Hence the tissue dose given was about 250 r.

The period after the 54th day was one of slow recovery. Cortisone was continued at 100 mg. per day. Five units of blood were administered between the 54th and 79th hospital day and none thereafter. The hemoglobin then rose slowly from 8 to 10 Gm. The white cell count ranged between 9,000 and 12,000 with the differential showing about 60% mature lymphocytes and 40% polymorphonuclear leukocytes. On the 51st day a deep abscess requiring incision and drainage developed in the left buttock. Culture showed a hemolytic staphylococcus, coagulase positive, sensitive to Chloromycetin. He was treated with Chloromycetin, and the wound healed slowly over the next six weeks. On the 106th day he was noted to have a paralysis of the left sixth nerve without any other finding on physical examination or skull films. The patient was discharged from the hospital on June 14, 1957 after 114 days in the hospital.

During the period from June 14 to August 14, 1957 he was at home, up and about and feeling quite well, except for an occasional pain behind the left eye and low backache. On July 29 the hemoglobin was 11 Gm., the white cell count 5,700 with the differential showing 38% polymorphonuclear leukocytes, 1% myelocytes, 58% mature lymphocytes, 1% monocytes and 2% eosinophiles.

The patient was admitted to the hospital on August 14, 1957 because of a sudden back pain. The hemoglobin was 8.3 Gm. and the white cell count was 6,200. A bone marrow study showed a cellular marrow. Megakaryocytes were normal. There was a moderate increase in the number of mature lymphocytes with an occasional lymphoblast. Erythroid and myeloid cells appeared normal. X-ray study showed osteoporosis with collapse of L-1. ACTH was given for a few days, and cortisone was gradually discontinued. Orthopedic measures resulted in improvement in the back pain.

From August 29 to September 9 the patient was at home but inactive because of back pain. On September 9 he was readmitted to the hospital because of a chill and fever. Blood cultures showed a hemolytic staphylococcus, coagulase positive. Despite intensive treatment with antibiotics and other measures, he went progressively downhill and died on October 7, 1957.

Postmortem examination showed a healing osteomyelitis of T-12 and L-1 with bilateral psoas abscesses. There was a bacterial endocarditis due to staphylococci. There was a sphenoid sinusitis due to Candida albicans with an associated osteomyelitis of the base of the skull and thrombosis of the left internal carotid artery and left cavernous sinus. There was an abscess of the lung due to Candida albicans. There was considerable involvement of the bone marrow, spleen, lymph nodes, liver and pancreas by chronic lymphatic leukemia. The bone marrow also showed abundant hematopoiesis with large numbers of megakaryocytes and maturing elements of both erythroid and myeloid series.

Comment: This patient received considerable whole-body irradiation followed by transplantation of normal marrow and a temporary "take" of the marrow graft. The temporarily active marrow graft may have been helpful in carrying him through the critical post-irradiation period. The partial remission observed in his leukemic process was of a type often seen after smaller doses of whole-body irradiation. His course illustrates the susceptibility to infection of patients who have leukemia and receive whole-body irradiation. From the autopsy study it is apparent that multiple staphylococcal lesions were present some six months before death, at the time of the buttock abscess and the left sixth nerve palsy. It is recognized that patients with leukemia frequently have chronic infections, particularly after prolonged treatment with cortisone. Whole-body irradiation increases this tendency. Control of infection in such patients is a major problem.
Case 7. This 29-year-old man entered the hospital on June 29, 1957. For six weeks he had noted fatigue and occasional fever. On admission to the hospital his temperature was 101 F. There was no splenomegaly or lymphadenopathy, but the liver was enlarged 8 cm. below the right costal margin. Laboratory data showed a hemoglobin of 9.2 Gm.

The white cell count was 36,500, and the platelet count 35,000. The bilirubin was 1.05 mg.%. A bone marrow aspiration showed the predominant cell to be a myeloblast.

The patient was started on 6-mercaptopurine, cortisone and antibiotics. He developed increasing signs of hemolytic anemia with the hemoglobin falling to values around 6 Gm. and the bilirubin rising to 10.9 mg.% on the 14th day and to 17.0 mg.% on the 20th day. This was associated with a rapidly increasing transfusion requirement. The white cell count fell to 6,100 on the 11th day and to 1,500 on the 13th day.

On the 14th day the patient developed nausea and vomiting considered to be a toxic reaction to 6-mercaptopurine, and this drug was discontinued. On the 17th day a bone marrow aspiration showed a somewhat hypocellular marrow, only a rare megakaryocyte and essentially no red cell precursors. Most of the marrow cells were myeloblasts. From the 15th through the 19th day the patient’s temperature ranged from 99 F. to 104 F.

He developed bilateral rales, and a chest film on the 20th day showed changes consistent with a patchy bronchopneumonia.

Because of the apparent failure of both cortisone and 6-mercaptopurine to bring about a remission, it was decided to attempt whole-body irradiation and bone marrow transplantation. Irradiation was started on the 20th day and continued with short interruptions for 26 hours. Irradiation was given by quadrants as follows: upper anterior half of the body, upper posterior half of the body, lower anterior half of the body and lower posterior half of the body. Each of these areas received a total dose of 400 r measured in air (G.E. Maximar Unit, 250 kv., 10 ma., HVL 2.2 mm. Cu., TSD 225 cm., dose rate 1 r/min.). The estimated average tissue dose was 600 r.

At the end of the period of irradiation the patient was given 3.9 x 10^6 nucleated marrow cells. The patient’s type was AB, D negative; the donor’s type, A, D positive. The marrow cells were obtained by means of a sterile post mortem on a 73-year-old woman who died of a cerebrovascular accident. The marrow was passed through stainless steel screens, centrifuged to remove fat, and frozen to −80 C. in TC-199 with 5% human serum albumin and 15% glycerol. The elapsed time from death until the beginning of the freezing process was 3 hours and 45 minutes. The marrow had been kept frozen for 25 days, thawed, and the glycerol concentration reduced, before intravenous administration, as previously described.

As indicated, the patient was desperately ill before he received whole-body irradiation. There was no particular increase in his lassitude or nausea during and immediately after the irradiation. On the day after the irradiation he felt much improved, and for the subsequent four days he felt better than at anytime during his hospital stay. His hemolytic anemia disappeared entirely. During the eight days immediately preceding irradiation he had received nine transfusions in order to keep his hemoglobin at a level of 6 Gm. In the four days following irradiation, he received only two transfusions and each was associated with the expected increase in hematocrit. The white blood cell count fell to 122 on the fourth day postirradiation and to 48 on the sixth day. On that day the platelet count was 24,000, reticulocyte count 0. On the fourth through the sixth day postirradiation the patient had increasing fever, reaching a maximum of 104 F. During this period he had increasing signs of rales and bronchial breathing. On the fifth day a blood culture was negative. After the infusion of marrow his peripheral blood was examined for D positive cells by the previously described direct Ashby technic. On the sixth day definite clumps of cells were seen with the D antiserum. For some days the patient had an increasing tachycardia. On the sixth day the lungs were filled with rales, the pulse went up to 140, the blood pressure fell and he died that evening.

Postmortem examination showed multiple coalescing areas of hemorrhages in the lungs. The spleen showed widely scattered lymphoid follicles devoid of active germinal centers.
but containing normal mature lymphocytes. No definite leukemic infiltration was seen. The lymph nodes showed decreased numbers of mature lymphocytes and no germinal centers. The macrophages contained hemosiderin and large numbers of phagocytized red blood cells. Moderate numbers of plasma cells and rare polymorphonuclear leukocytes were present. One lymph node adjacent to the thyroid contained occasional large cells with conspicuous nucleoli. These cells were not definitely identified, but probably represented residual leukemic cells. The bone marrow showed markedly decreased cellularity. There were many macrophages containing phagocytized red blood cells. An estimated 20% of the normal number of megakaryocytes were seen, as were a moderate number of plasma cells. There were scattered small foci of erythropoiesis. Neither myelopoiesis nor definite leukemic infiltration were noted. The mucosa of the lower esophagus was ulcerated and replaced by a pseudomembrane containing bacterial colonies. The remainder of the gastrointestinal tract was normal. In all tissues the number of polymorphonuclear leukocytes was greater than would be suggested by the peripheral blood count.

Comment: This patient illustrates the danger of initiating whole-body irradiation in the face of an established infection, bronchopneumonia. It appears doubtful that a patient can be carried through the critical postirradiation period under such circumstances. The amount of hemorrhage found in the lungs at autopsy was surprising. It may have been due to bleeding into areas of infection, or it may represent bleeding due to lack of platelets, probably both. It occurred without gross external bleeding.

Worthy of note are the following: (1) there was no radiation sickness after 600 r total-body irradiation administered at low dosage rate (26 hours). In fact, the patient felt much better for a few days after irradiation. (2) Irradiation was followed by an immediate cessation of the severe hemolytic process. (3) There was immunologic and histologic evidence to suggest beginning function of the marrow graft. (4) During a critical postirradiation period of low platelet count, extensive bleeding occurred in the lungs and was a contributing cause of death.

Case 8. This 25-year-old man entered the hospital on September 9, 1957. A diagnosis of acute leukemia had been made 16 months before. Several courses of steroids and 6-mercaptopurine resulted in remissions permitting him to carry on normal activity. In August 1957 his disease returned and did not respond to maximum doses of cortisone and 6-mercaptopurine. He entered the hospital to receive whole-body irradiation and bone marrow.

On admission his temperature was 103 F. There was clotted blood in the nose. There was one small lymph node in the right axilla. The liver was enlarged 4 cm. below the right costal margin and the spleen tip was palpable. The hemoglobin was 11.4 Gm. per 100 ml. The white cell count was 19,200, the platelet count 9,000. A bone marrow aspiration showed predominantly blast cells.

He was irradiated by quadrants as described in Case 7. On the second hospital day he received 25 r to each quadrant; on the third day, 25 r; on the fourth day, 250 r; and on the fifth day, 100 r, making a total dose of 400 r measured in air (G.E. Maximar Unit, 250 kv. 15 ma., HVL 2.2 mm. Cu., TSD 225 cm., dose rate 1.5 r min.). The estimated average tissue dose was 600 r.

One hour after the last irradiation the patient was given bone marrow intravenously. The patient was type O, D+,E+. The bone marrow came from a sterile postmortem on a 74-year-old woman, type O, D+,E-. It was prepared, kept frozen in glycerol for five days and given as previously described.13 7.8 x 10⁶ nucleated marrow cells were given without reaction.

On the first and second hospital days the patient ran temperatures between 101 F. and 103 F. Associated with the period of irradiation, the fever disappeared, the patient felt much better and had no evident radiation sickness. From the first through the fifth postirradiation day the patient had diarrhea with watery or semifomed stools numbering four to eight per day. Thereafter, the diarrhea subsided and did not recur. These stools were guaiac 2+ to 4+, and on the fifth day a single grossly bloody stool was passed. He continued to develop petechiae and had several nosebleeds. Because of these he was
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given a total of seven transfusions of fresh whole blood using plastic bags and silicone needles from the fifth to the 10th postirradiation day. From the second day the patient exhibited a tachycardia ranging from 120 to 150, and from the fifth day he exhibited a swinging temperature with daily peaks of 103 F. to 105 F., uninfluenced by vigorous antibiotic therapy with various combinations of penicillin, streptomycin and Chloromycetin. On the 11th day he became hypotensive and expired on the 12th day postirradiation.

The white blood cell count was 12,700 before irradiation, 350 on the first day following irradiation and in the range of 10 to 100 after the fifth day. The platelet count was 20,000 on the fourth day. The uric acid reached a maximum of 23.6 mg. % on the first day, and it decreased to 7.9 mg. % on the seventh day. A blood culture on the seventh day showed hemolytic staphylococcus aureus, E. coli and pseudomonas aeruginosa. On the seventh day a blood culture showed clostridium perfringens, hemolytic staphylococcus aureus and pseudomonas aeruginosa.

Postmortem examination showed the lungs to contain numerous areas of recent hemorrhage from 1 to 6 cm. in diameter. Microscopically these areas of hemorrhage were of varying age with varying amounts of resolution by phagocytic cells and organization by fibroblasts. In a minority of the hemorrhagic areas, the alveoli contained colonies of cocci surrounded by macrophages filled with organisms. Polymorphonuclear leukocytes were not present. Postmortem culture of the lungs grew a hemolytic staphylococcus, coagulase positive, and of the blood, pseudomonas aeruginosa. The spleen weighed 720 Gm. Microscopically there were focal collections of normal lymphocytes and plasma cells but no true lymphoid follicles. The sinuses were engorged with blood, and the lining reticuloendothelial cells were filled with phagocytized red blood cells and hemosiderin. There were no foci of leukemic infiltration. The changes in the lymph nodes were similar to those in the spleen. The bone marrow showed markedly decreased cellularity. Occasional plasma cells and rare polymorphonuclear leukocytes were seen. The majority of the cells present were mature lymphocytes. Megakaryocytes and erythropoietic elements were not identified. Leukemic cells could not be found. The esophagus showed some ulcerations covered with fibrin containing numerous colonies of cocci. The remainder of the gastrointestinal tract was normal. There were foci of lymphocytes in both ileum and colon. The liver weighed 3250 Gm. Microscopically it appeared normal, and there was no adequate explanation of the enlargement. In the subdural space over both cerebral hemispheres there were fresh blood clots approximately 3 mm. in thickness and covering an area measuring 10 x 5 cm.

Comment: This patient showed no evidence of successful transplantation of marrow. His resistance to bacterial invasion was grossly inadequate. A variety of organisms invaded the blood stream. Several fresh blood transfusions, given to provide red cells, platelets, gamma globulin and properdin, had no measurable benefit. Again, radiation sickness did not occur, and the patient felt improved until infection supervened.

Case 9. This three-year-old girl was admitted to the hospital on September 15, 1957. In October 1956 she became anemic, and a diagnosis of acute lymphocytic leukemia was made. She was treated with Meticorten and 6-mercaptopurine. She had a good remission and was maintained on Meticorten, 5 mg. daily. In April 1957 she again became anemic. The Meticorten was increased to 30 mg. daily, she was again given 6-mercaptopurine and a second remission was achieved. She was then maintained on 6-mercaptopurine, 1.75 mg./Kg. and Meticorten, 12.5 mg. per day. On August 16, 1957, she was seen because of the appearance of low-grade fever and was found to have 4% blast cells and 66% lymphocytes in the peripheral blood, with a total white count of 5,550. On September 11 she was found to have a white blood cell count of 58,300, a hemoglobin of 10.8 Gm. and a platelet count of 34,000. 95% of the cells in the peripheral blood were in the lymphatic series. Because of relapse resistant to conventional therapy she was referred to the hospital to receive whole-body irradiation and marrow transplantation.

Physical examination on admission showed some small lymph nodes in the neck; the spleen was down 3 cm. and the liver down 5 cm. The hemoglobin was 12.6 Gm., white blood cell count 31,400, 5% polymorphonuclear leukocytes, 9% monocytes, 92% cells
of the lymphoid series, approximately 25 to 35% being blast cells. There were 5 nucleated red cells per 100 white cells.

On the second hospital day the patient was given 25 r of whole-body irradiation to the front of the body and to the back of the body. On the third hospital day she was given 125 r front and back. On the fourth hospital day, she was given 200 r, front and back, making a total of 350 r measured in air at body surface, (G.E. Maximar Unit, 250 kv., 15 ma., HVL 2.2 mm. Cu., TSD 225 cm., dose rate 1.5 r mm.). The estimated average tissue dose was 525 r.

On the morning of the first day postirradiation she received bone marrow intravenously. The patient's blood type was O, C+, D+. In order to use genetically related marrow, the father (blood type O, C-D+) was chosen as the donor. The father was taken to the operating room and under anesthesia a total of 12 bone marrow aspirations were performed on the sternum and each anterior and posterior iliac crest. The bone marrow was taken into heparin, passed through stainless steel screens to break up the marrow particles and immediately given to the patient. A total of 2.58 billion nucleated marrow cells were given.

The patient felt well in the immediate postirradiation period. On the last day of irradiation she vomited one time, but continued to take food by mouth. The stools were normal throughout the period in the hospital, except for the fourth, fifth and sixth days postirradiation when she had three semi-solid stools each day showing gross contamination with blood. On the last day of irradiation the patient's temperature went up to 102 F., and she was started on penicillin and streptomycin. She was maintained on isolation with attendants and visitors wearing masks and gowns after the period of whole-body irradiation. From the first through the seventh day the temperature remained at levels of 101 F. to 104 F. On the sixth day a blood culture grew hemolytic staphylococcus aureus, coagulase positive, resistant to penicillin and streptomycin but sensitive to Chloromycetin. She was started on Chloromycetin on that day, and on the eighth day her temperature came down and was normal on the ninth and tenth days. Her temperature then went back up to a range of 101 F. to 103 F. After the first postirradiation day she ran a persistent tachycardia in the range of 140 to 150. On the fourth day spontaneous epistaxis occurred. She was given 500 ml. of fresh whole blood using plastic and siliconized equipment. On the seventh day she received another 300 ml. of fresh whole blood. On the 12th day a blood culture again grew out hemolytic staphylococcus aureus, coagulase positive, resistant to penicillin and streptomycin but sensitive to Chloromycetin and Cathomyacin. From the 11th through the 16th day the patient presented the picture of overwhelming septicemia with progressive deterioration. In the last two days of life, penicillin and streptomycin were discontinued, and she received Chloromycetin and Cathomyacin. She died on the 16th hospital day postirradiation.

After irradiation the white blood cell count decreased rapidly, reaching levels of 16 on the third day and staying in the range of 20 to 40 through the ninth day. On the tenth day, the white blood cell count was 106 and thereafter rose slowly to a level of 394 on the day of death, with all cells being lymphocytes. The hemoglobin remained at levels of about 10 Gm.

The autopsy on this child was limited to the examination of a portion of one rib. The cellularity of the marrow was markedly decreased. There were numerous foci of hemorrhage and phagocytic cells were filled with hemosiderin and red blood cells. The only other cells seen were rare plasma cells and lymphocytes. Megakaryocytes were absent.

Comment: Despite the use of genetically related marrow without any period of preservation there was no evidence of a successful marrow graft. The absence of significant radiation sickness should be noted. By the sixth day postirradiation septicemia due to staphylococcus aureus had appeared, and thereafter the patient ran a septic course to death. It is doubtful whether a successful marrow graft making its appearance after the sixth day would have resulted in benefit to this patient. Again, sepsis was the dominant clinical factor.

Case 10. This 18-year-old girl was admitted to the hospital on January 28, 1958. In February 1957 she developed symptoms of anemia, and a diagnosis of acute leukemia was
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made at that time. Treatment with prednisolone and 6-mercaptopurine produced a remission. Two months before admission she began to relapse despite this therapy. Shortly before admission the hemoglobin was 5.8 Gm. and white blood cell count 8,000, with the differential showing 90% blast cells. She was referred to the hospital to receive whole-body irradiation and marrow transplantation.

Physical examination showed a temperature of 100.2 F. There was obvious pallor. There were a few palpable lymph nodes in the left posterior cervical chain, but no other lymphadenopathy. The liver and spleen were not palpable. The platelet count was 170,000 and reticulocyte count 0.1%. Uric acid was 4.9 mg.%

When the patient was admitted to the hospital she was conducted directly to a single room where she was put on strict reverse precautions. All individuals entering the room scrubbed before entering and wore caps, masks, gowns and foot coverings. Frequent cultures were obtained of the patient’s nose, throat and stool, of various areas in the room, and of the nose and throat of individuals caring for her.

A bone marrow aspiration performed on the second hospital day showed a cellular marrow. About 95% of the marrow cells were abnormal in type. These cells were mononuclear with frequently indented nuclei. Many of the cells contained 1 or 2 small nucleoli, the cytoplasm was very scant and no granules were seen. A few mature lymphocytes were found. Only occasional normal bone marrow elements could be recognized.

On the fourth hospital day whole-body irradiation was started. She was given 75 r measured in air to each of four quadrants as described in Case 7 (G.E. Maxiunn Unit, 250 kv., 10 ma., HVL 2.2 mm. Cu., TSD 225 cm., dose rate 1 r/min.). This dose was repeated on the fifth and sixth hospital day. The total estimated average tissue dose was 325 r. On the postirradiation day she was given bone marrow intravenously. The bone marrow was procured from the patient’s sister by a total of 17 aspirations on the sternum, anterior and posterior iliac crests. The total number of nucleated bone marrow cells after correction for admixture with peripheral blood was 3.0 billion. Both donor and recipient were type O. Both were identical as follows: C+, e+, D-, E-, e+, M-, N+, Kell+. The only difference found was that the patient was Duffy A− and the sister was Duffy A+. During the period of irradiation the patient was given 4 Gm. of Neomycin daily in an effort to sterilize the gastrointestinal tract and prevent invasion of the blood stream from intestinal organisms. She was given Achromycin, penicillin and Chloromycetin as dictated by the frequent cultures. She was maintained on cortisone, 100 mg. daily. During the period of irradiation she was continuously nauseated and vomited on several occasions. She had two to five stools daily, but all these symptoms disappeared after the first postirradiation day. She received frequent transfusions of fresh whole blood using platelet-preserving equipment. This was designed to provide her with platelets to prevent bleeding and also to provide gamma globulin and properdin in an effort to provide a better defense against bacterial invasion. From the first day through the 23rd day postirradiation she received a total of 15 transfusions. These transfusions were frequently preceded by phlebotomy in order to keep her mildly anemic and thus provide a stimulus to bone marrow function.

During the period after irradiation through the 22nd postirradiation day, the patient ran a low-grade fever with occasional temperatures of 103 F. On the 21st day postirradiation the patient became critically ill with a temperature of 105 F. At that time she was found to have a staphylococcal organism sensitive only to Furadantin. Accordingly, Chloromycetin was stopped, and she was given intravenous Furadantin. The following day she was considerably improved, and at that point the formed elements of the blood began to return. The course of the white blood cell count and platelet count is shown in figure 1. Associated with the return of white cells and platelets, there was a return of reticulocytes indicating renewed formation of all three formed elements of the blood.

During the postirradiation period the patient developed a herpes simplex lesion on her nose. This became infected with a hemolytic staphylococcus albus. This lesion progressed to an angry ulcerated area with edema and swelling of the face and obstruction of the nose. With the return of formed elements to the blood, this lesion began to recede and by the 36th postirradiation day had cleared completely.
She was afebrile from the 23rd through the 26th postirradiation day. On the 27th postirradiation day the temperature went up to 102.86 F. She was then afebrile until the 33rd postirradiation day when the temperature went up to 104 F. Because of the possibility of a drug fever, both penicillin and Furadantin were discontinued. On the 36th postirradiation day the temperature again went up to 103 F. It then slowly declined through the 39th postirradiation day. During the latter part of this period she was on no antibiotic and was maintained on cortisone, 37.5 mg. daily. She felt well and was active in her room. A bone marrow study done on the 36th postirradiation day showed normal cellularity. Microscopic examination showed a normal number of megakaryocytes. The myeloid-erythroid ratio was approximately 2:1. Maturation sequence in both myeloid and erythroid cell series was normal. Occasional plasma cells were seen. She was discharged from the hospital on the 41st postirradiation day.

When seen on the 55th postirradiation day the patient appeared well. She had noticed some loss of hair, but regrowth of new hair was evident. A temperature record showed no reading over 100 F. She was eating well. Hematologic data are shown in figure 1.

**Comment:** This patient entered the hospital with acute leukemia in relapse despite conventional therapy. Over a period of three days she received a tissue dose of whole-body irradiation of approximately 300 r. She was then given 3.0 billion nucleated marrow cells from a closely related donor, her sister.\(^1\) Irradiation was followed by a disappearance from the peripheral blood of all nucleated cells, both normal and malignant. During this period the patient was protected from death due to infection by isolation, multiple antibiotics and fresh transfusions. After 21 days normal cellular elements returned to the peripheral blood and after 36 days a bone marrow aspiration demonstrated normal marow.

The patient's blood type differed from that of her marrow donor only in the Duffy antigen. Without adequate identification of the marrow-donor's red cell in the circulation of the

![Fig. 1.—Summary of hematologic observations, Case 10.](image-url)
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It is not possible to state that marrow transplantation has been successful. It seems more likely that the whole-body irradiation induced a remission in the leukemia and that subsequently regrowth of the patient's own marrow occurred. The multiple transfusions employed in this case may also be of importance in bringing about a remission.

This patient demonstrates that it is possible to control the problem of infection for a three-week period in the absence of circulating leukocytes. Further, regardless of mechanism, she demonstrates that whole-body irradiation may be of value to the individual with leukemia in relapse despite conventional therapy.

Case 11. This four-year-old female child was admitted to the hospital on March 7, 1958. She had had acute leukemia for 16 months with remissions achieved by aminopterin, cortisone, 6-mercaptopurine, and A-methopterin. Relapse despite these medications began one month before her transfer to this hospital for whole-body irradiation and marrow transplantation.

Physical examination showed pallor, scattered petechiae and enlargement of both liver and spleen to four centimeters below the costal margins.

Laboratory data showed the white blood cell count to be 59,000 with the predominant cell being a lymphoblast. Hemoglobin was 9.3 Gm., platelet count was 4,000. Nose and throat cultures showed resistant strains of E. coli and hemolytic staphylococci albus.

On the third hospital day she was given 100 r measured in air to the entire body anteriorly and another 100 r to the entire body posteriorly. Irradiation was given with a C.E. Maximar Unit (250 kv., HVL 2.2 mm. Cu., 15 ma., FSD 225 cm., dose rate 1.5 r/min.). This dose of irradiation was repeated on the fourth and fifth hospital day. The total estimated average tissue dose was 450 r.

On the morning after the last day of irradiation she was given bone marrow from her mother. The patient and the mother were both type A and differed only in that the patient was M- and the mother M+. The mother was taken to the operating room, and under general anesthesia a total of twenty bone marrow aspirations were done from the sternum, anterior and posterior iliac crests and two spinous processes. The marrow was added to Hanks' solution containing heparin, passed through a series of screens, and administered intravenously to the patient over a 10-minute period. The total elapsed time from the beginning of marrow aspirations until the end of administration to the patient was 1 hour and 15 minutes. The total number of nucleated marrow cells given was 1.89 billion after correction for admixture with peripheral nucleated cells. There was no evidence of any kind of reaction to the administration of the marrow.

On the fourth postirradiation day a 22 cm. fetus became available as the result of a therapeutic abortion. The fetal liver and spleen were removed sterilely and immediately placed on ice. The tissues were minced with a razor blade and then passed through successive stainless steel screens with the final screen opening being 86 microns. The cells were washed, centrifuged and resuspended in 5% human albumin and tissue culture medium 199. The final mixture was passed through a screen with a 43 micron aperture. The cells were given intravenously to the patient over a 45-minute period with no evidence of a reaction of any kind. 26.5 x 10^6 spleen cells and 1.4 x 10^6 liver cells were given. The nucleated liver cells were made up of approximately 1/4 liver cells and 3/4 hematopoietic cells.

The patient was given 2 Gm. of Neomycin by mouth daily on each irradiation day in an effort to prevent bloodstream invasion by intestinal organisms. On the last day of irradiation and throughout the remainder of the hospital stay the patient received a fresh transfusion either every day or every other day. The transfusions were either of whole blood or platelet-containing plasma as dictated by hemoglobin requirements. All transfused blood was M- so that production of M+ cells by the transplanted marrow could be detected. The patient was maintained on steroids and various combinations of penicillin, erythromycin, and Chloromycetin.

The white blood cell count was 1,678 on the second day of irradiation and 183 on the last day of irradiation. On the first postirradiation day it was 28. Thereafter, the white
blood cell count ranged between values of 50 and 89, and platelets ranged between 1 and 14 thousand. The uric acid was 20.0 mg.% on the second day of irradiation and 6.5 mg.% on the first postirradiation day.

During the first two days in the hospital the patient's temperature ranged between 99 F. and 100 F. On the first day of irradiation she was nauseated. That evening she vomited once or twice and her temperature went up to 106 F. During the second day of irradiation her temperature declined to around 100 F. She was anorexic, but did not vomit. On the third irradiation day her temperature ranged between 100 F. and 101 F., and she had four stools. From the first through the sixth postirradiation day she had three to seven stools daily. Thereafter, she had no more diarrhea. The patient was quite comfortable from the second through the ninth postirradiation day despite increasing fever during this period. After the sixth postirradiation day her temperature ranged between 101 F. and 104 F. She had occasional epistaxes. On the eighth postirradiation day the left eardrum became cloudy and the canal was red. There was some tenderness over the mastoid. On the eleventh postirradiation day gross hematuria was observed. On the twelfth postirradiation day she developed rales and bronchial breathing in both lung bases, more marked on the left. She continued to grow progressively worse over the next 24 hours with signs of pneumonia, and she expired on the thirteenth postirradiation day.

Postmortem examination showed a left mastoiditis due to E. coli. The lungs showed a hemorrhagic pneumonia due to E. coli, with numerous organisms apparent in the sections. Areas of pulmonary edema were noted. No polymorphonuclear leukocytes were seen in the sections. The bone marrow was very hypocellular. Plasma cells were the predominant element. Occasional isolated nucleated red cells were seen. There were no islands of erythropoiesis and no leukemic infiltrates. The lymph nodes showed decreased cellularity with perivascular collections of mature lymphocytes but no lymph follicles. The spleen was also hypocellular with no lymph follicles. Both lymph nodes and spleen showed scattered plasma cells and phagocytes with ingested red cells. In the small intestine there were scattered 1 to 2 cm. intramucosal hemorrhages but no ulcerations. No lymphoid tissue was present. There was a blood clot in the right renal pelvis. No tissue showed recognizable leukemic infiltrates.

Comment: This patient with acute leukemia in relapse despite conventional therapy received a tissue dose of 450 r whole-body irradiation. On the first postirradiation day she received marrow obtained from her mother, and on the fourth postirradiation day she was given erythropoietic cells obtained from the liver and spleen of a 4½ month foetus. She proceeded to die of infection due to resistant organisms known to be present in her nose and throat before irradiation was given. Death occurred before significant return of marrow function might be expected. Postmortem examination showed no evidence of hematopoiesis or leukemia.

Fetal hematopoietic tissue, liver, spleen and marrow, at a stage of development and viability suitable for administration to patients, is difficult to acquire. The opportunity obtained in this case gave rise to some optimism for reasons presented in the discussion. However, an infection established prior to irradiation could not be controlled and led to death of the patient.

A word of caution should be given concerning the intravenous administration of spleen or liver cells. Fatal reactions have been observed in several dogs following intravenous administration of spleen cells after passage through a net of 120 microns square. The cause of this reaction has not yet been determined with certainty, but excessive thromboplastic activity and micropulmonary emboli of clot and cells are suggested by the postmortem histologic studies. In this case the fetal tissue was passed through screens down to 43 microns in size and washed thoroughly before being resuspended in 90 ml. TC-199 and 5% human albumin. The patient had no reaction to the administration, and sections of the lungs at postmortem 9 days later showed no embolus. Administration was slow, about 45 minutes for 65 ml. of suspension and was discontinued when a tendency to clumping was detected in the residual fluid.

Case 12. This 61-year-old man had a left pneumonectomy in December 1956 because of carcinoma of the lung. In April 1957 a tumor of the left posterior chest wall was dem-
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ons trated by biopsy to be metastatic carcinoma of the lung. A few days thereafter he was given a total of 0.4 mg. of nitrogen mustard per Kg. of body weight in a two-day course. This was followed by a period of improvement in his chest pain. Two months later the chest pain recurred and increased in severity. Accordingly, it was decided to give him a larger dose of nitrogen mustard and to follow this with bone marrow infusion. From July 2 through July 6 he received 0.2 mg. of nitrogen mustard per Kg. of body weight each night for a total dose of 1.0 mg./Kg.

On the first and second day after nitrogen mustard the patient was given a total of 7.4 billion nucleated marrow cells. This marrow had been obtained three months previously from a patient dying of congestive heart failure. Eight ribs were removed under sterile conditions. The marrow was prepared and frozen in glycerol as previously described. It was then preserved at -80 C. until being thawed rapidly at 37 C. immediately prior to use. The glycerol concentration was reduced by the addition of hypertonic dextrose and progressive dilution as previously described. With the bone marrow the patient received a total of 6 Gm. of glycerol. Both the patient and the marrow donor were type A, Rh positive. The marrow donor was E+ and the recipient was E-. There was no reaction to the administration of the marrow.

The patient's white blood cell count was 11,500 when nitrogen mustard was started. It was 9,200 on the last day of nitrogen mustard administration. On the third day after nitrogen mustard it was 1,288 and on the fifth day 66. The patient died on the sixth day after the administration of nitrogen mustard.

Postmortem examination showed widespread metastatic carcinoma of the lung. The bone marrow showed scattered metastatic lesions. The remainder of the bone marrow was acellular except for scattered plasma cells. The spleen showed a complete absence of normal lymphoid follicles. However, there seemed to be a few reforming germinal centers about some of the vascular channels. The lymph nodes showed almost complete obliteration of the normal lymphoid architecture. Both spleen and lymph nodes showed numerous plasma cells.

Comment: This patient received 1.0 mg. of nitrogen mustard per Kg. followed by the intravenous administration of 7.4 billion marrow cells. He died six days later without evidence of repopulation of the marrow spaces.

Successful marrow transplantation in the mouse after nitrogen mustard has been achieved, but the dosage of drug required is toxic and difficult to manage. Nitrogen mustard evidently destroys erythropoietic tissue, but the recipient's immune mechanisms may not be damaged to an equal degree. In the light of present knowledge, x-ray seems preferable to nitrogen mustard as an agent for inducing tolerance to homologous bone marrow. The above case report is included as an example of another clinical failure with this radiomimetic drug.

DISCUSSION

A brief review of the general subject of total-body irradiation and marrow replacement may be in order as a background for discussion of the clinical events above reported. Exposure to ionizing radiation is followed in man, as in other animals, by difficulties in cell division. The processes of cellular reproduction are more sensitive to biochemical changes induced by radiation than are prosaic matters of day-to-day function. As a result, the clinical course of radiation injury in the lower lethal range of whole-body exposure becomes an expression of the physiologic consequences of impaired cell division. Damage is most apparent in those tissues where rapid division and a short cell life are the normal order. At higher radiation dosage, levels higher than those under consideration here, acute cell death and injury to the central nervous system complicate the picture.

After whole-body irradiation in the range of 300 to 700 roentgens, death is primarily caused by marrow failure. The inability of primitive cells to divide
leads to cessation of production of the circulating formed elements: platelets, leukocytes and erythrocytes. Bleeding and infection follow. Important associated injuries to other tissues of high mitotic activity are the weakening of the intestinal barrier by damage to its mucosa and the destruction of lymphopoietic centers in lymph nodes and spleen. Destruction of the latter paralyzes immunologic defense. The loss of formed elements (leukocytes) and a lower concentration of molecular defense elements, immune globulins and properdin, produce a prostrate host in whom foreign agents of all types flourish: bacteria, yeasts, even engrafted tissues. It is this latter fact, the liberal growth of homografts, particularly homografts of normal marrow, that has pointed the way to clinical management of the postradiation syndrome.

Experiments on animals have shown that the tissues of the irradiated subject may be seeded by intravenous infusion with an adequate number of fresh or preserved marrow cells. These cells "home" to their respective normal histologic sites and multiply. Over a period of time, one to several weeks, they restore marrow function and more gradually and perhaps less adequately they restore the lymphoid defenses: lymph nodes, spleen, Peyer's patches. Most interestingly, they restore a defense system that now bears the imprint and the password of the donor. His tissues—skin certainly, and presumably and by analogy, kidney, endocrine glands and other organs—are now accepted by the altered host. Thus, by a process of irradiation followed by marrow transplantation, the recipient becomes a chimera producing and tolerating cells of the blood type of the donor and in general recognizing his tissues as friendly.

The degree of friendly recognition is, however, a relative thing. At some levels of acceptance, too little radiative destruction of the host's defenses or too foreign a graft leaves cause for immunologic reaction. Three immunologically distinct situations may be distinguished. In one, the defenses of the host are inadequately depressed by radiation. The primary reaction is then that of the host against antigens present in the graft. In a percentage of instances the reaction is effective. Repair is slow and a delayed death from wasting disease and infection follows. The reaction of the host against the graft is avoided when heavier dose of radiation is used in preparation for engraftment. But then a second situation presents itself. Immunologically mature and reactive cells of lymphoid type are present in the marrow of some species in effective number. Billingham and others have shown that these cells in the mouse are capable of reacting against the tissue antigens of the tolerant host. Lymph nodes and spleen seeded and partially repopulated by them are burned out by this destructive reaction. The result is an immunologic cripple with an inadequate lymphoid system incapable of reacting effectively to outside antigens, bacteria, etc. Again there is chronic infection, wasting disease and death in a few months. Circumvention is possible by substituting for adult marrow the hematopoietic elements of sufficiently immature fetuses. In the adequately irradiated recipient infusion of hematopoietic cells of fetal liver is followed by a good recovery of circulating blood elements and no delayed foreign bone marrow reaction. The well-irradiated host does not react against
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the graft. The immature and tolerant graft does not react against the host. Any lymphoid cell present in the infusion of this fetal "marrow" is sufficiently immature to have the capability of actively acquiring tolerance to host antigens.35

For completeness, a third situation may be outlined. With isologous animals of an inbred strain it can be shown that the addition of a few splenic cells to the infusions of marrow hastens the return to normal of the histologic appearance of the spleen and lymph nodes of irradiated animals.23 Evidently, despite the presence of some immunologically mature cells capable of adverse reaction in homologous transfers, adult marrow in the rodent is deficient in the type of cell required for prompt restitution of lymphoid areas after radiative destruction. In other words, marrow is erythropoietic and myelopoietic but inadequately lymphopoietic. This third potential cause of immunologic crippling is then simply a failure of adequate repopulation of lymphoid areas by either host cells or donor cells. It is due not to foreign marrow reactions but to the fact that marrow is a poor source of cells of the splenic or lymphoid follicle type that are needed for prompt restoration of lymphoid functions.

In the case of man, a solution to the unhappy possibilities above outlined would appear to be: (1) determination of whether immunologically mature and reactive cells of lymphoid type are present in adult human marrow in troublesome number; (2) their removal from marrow used for infusions or the use of fetal hematopoietic tissue lacking mature reactive lymphoid elements; and (3) the addition either to processed adult marrow or to fetal marrow of such tolerant lymphoid elements of immature fetal spleen as may be required for prompt, effective and permanent repair of the lymphoid system and its antibody functions.

The question of numbers of cells required comes into the above considerations and the answer to this question is at present ill defined. From the standpoint of procurement fetal hematopoietic tissue rarely provides more than 2 billion nucleated cells. Aspiration biopsy or a surgically removed rib yields about the same number, and adult cadavers provide 25 to 50 billion. Probably the number of cells infused in our studies are at the lower limits of usefulness, and probably every effort should be made to get into the 25 to 50 billion range. Certainly experiments on animals indicate that the larger the infusion the more prompt and satisfactory is the return of marrow function.1 The experimental data regarding the use of splenic cells as restorers of lymphoid function are less extensive but may be interpreted to indicate a requirement within the range of fetal spleen.

A word might be said about the use of spleen and about the time after irradiation at which marrow in general is best administered. It must be clearly understood that the use of mature spleen or lymph nodes is contraindicated in homologous transfers. This follows from the discussion of the "second immunologic situation" above presented and from the easily demonstrated fact that homologous adult spleen added to isologous marrow produces an early demise (4 to 10 days) in irradiated animals.36 One of the problems with fetal spleen is definition of the stage of immaturity necessary for avoidance of this
type of reaction. This is probably a species variable. Another problem with spleen of any age is its tendency to produce pulmonary symptoms, presumably embolic, despite screening that is quite sufficient for the safe use of marrow. We have killed several dogs in this manner with mature spleen, and in man with fetal spleen we have been rather careful to go down to 43-micron screen and to stop the infusion when a visible tendency to reaggregate made its appearance (case report 11).

The time after radiation when marrow is best administered may be derived from the following considerations. The period of irradiation is best somewhat prolonged. Certainly in the acute leukemic subject too rapid administration of x-ray is apt to be toxic if for no reason other than the sudden rise in uric acid that attends acute and extensive cell destruction. Therefore we have found it advantageous to spread the radiation over a period of two or three days. Cell death and removal during this period leaves the marrow spaces relatively free of debris and perhaps in better shape for re-seeding. Certainly the symptoms of radiation toxicity are minimal with this procedure, and in animals it has been found that equally good early restoration of marrow function is so obtained provided adequate doses of marrow are used. Indeed, as far as the incidence of foreign marrow reaction is concerned, somewhat better late results seem achieved when transplantation is delayed until the third day. Further delay is hazardous since the prime consideration of transplantation is a return of marrow function sufficiently early to avoid fatal bleeding and infection. From the theoretic immunologic standpoint the delayed or third day administration is clearly preferable since time is thereby allowed for deterioration of residual immune mechanisms potentially inimical to the graft. The nature of these mechanisms is obscure, but their existence must be inferred from the fact that the marrow dose requirement of homologous transfers is ten times that of the isologous. Moreover, it is evident that radiation in the range here discussed inhibits mitosis rather than kills cells per se. Time must be allowed therefore for death of unreproducible but living and effective immunologic reactors of short life span, both molecular and cellular. This time requirement is probably the significant factor underlying and explaining the so-called radio-sensitive and radio-resistant phases of postradiative immunologic reaction.

So far we have not been able to distinguish in man the order of importance of the several foreseeable immunologic difficulties above recounted. No subject has yet survived long enough or had sufficient radiation or graft survival to make analysis possible. The complication introduced by working with the leukemic subject is formidable. A return of the leukemic process, as in Case 6, precludes sensible analysis of histologic events relatable to radiation in either lymph nodes or marrow. Experience with individuals other than the leukemic patient would be welcome, for example the uremic patient, for whom radiation, marrow replacement and a kidney graft is a logical therapy.

What we have been impressed by is the general problem of control of bacterial disease in the irradiated subject. It may well be that the rodents used in a majority of earlier studies are special cases of fortunately chosen species.
inordinately resistant to bacterial invasion. Table 1 taken from Pillemer's work\(^{40,41}\) shows the relative antibacterial potency of the properdin system in rats, mice, dogs and men. In rats, antibiotics have little effect in improving mortality rates following LD 50's of radiation.\(^{29}\) The integrity of the natural immunity is too well sustained for antibiotics to be of significant help. In dogs and in man obvious benefit is secured, and in our experience with both dog and man the cause of death both early and late has been sepsis, independent of whether marrow function has been restored or not.

The dichotomy between restoration of marrow function and prolonged survival is clearly seen in irradiated normal dogs. After 800 to 1200 r of total-body irradiation in this species active marrow transplants are readily obtained, but the animals succumb to bacterial, viral or parasitic disease in a few months.\(^{3,42,43}\) Their lymph nodes and spleens are not normal and despite grossly increased numbers of circulating polymorphonuclear leukocytes their course continues to be suggestive of that of the agamma or dysgammaglobulinemic patient. Evidently successful transplantation of marrow has not been attended by adequate restoration of immunologic defense mechanisms in these animals.\(^{44}\) The suggestions outlined under (3) above (the use of fetal marrow and spleen) are therefore being carefully explored.\(^{43}\)

The postmortem findings described in the case reports show that a little bacterial action with its attendant capillary damage and hemorrhage goes a long way in the lungs of acutely irradiated terminal leukemic patients. These patients whether irradiated or not are known to have little resistance to bacterial disease. An extensive hemorrhagic pneumonia is the usual end result, with toxemia and anoxemia the immediate causes of death. Critical attention must therefore be given to reverse-isolation precautions, to the management of antibiotic regimen, to the use of steroids and to the use of fresh blood and platelets to combat exudative and bleeding tendencies that compromise effective air space. What additionally may be accomplished with large doses of gamma globulin\(^{45,46}\) or other plasma derivative\(^{21,47}\) remains to be determined. The problem is difficult but not necessarily hopeless (case reports 6 and 10).

The fact that the above two patients survived the immediate post-radiation period while others did not merits comment. These individuals received rather less radiation than did the others, tissue doses of the order of 200 to 300 r in contrast to doses for the remainder of the group of the order of 400 to 600 r. They had a bad time with infection, but marrow function fortunately returned in 2 to 4 weeks and with meticulous attention to antibacterial regimen they managed to make at least a partial recovery. In no one of the others was there a useful return of marrow activity in the limited time that we were
able to keep them alive. The fact that these latter had received heavier dosage of radiation is the probable explanation for the fact that their marrow function failed to return and help them through a difficult period of post-radiative bacterial disease.

Evidence has been presented in rodents to show that radiation in the 400 to 600 r range is apt to be lethal when coupled with marrow transplantation. Below this range there is no permanent acceptance of graft but an early return of host marrow function and a low mortality. Above this range there is early and useful activity in the marrow graft and again a low mortality. In the particular range 400 to 600 r, there is neither a successful graft nor an early return of host marrow function, and the mortality is high. The meager clinical evidence here presented would appear consistent with a similar state of affairs in man and would seem a compelling argument for staying out of the 400 to 600 r range with patients in the future.

The greatest hindrance we have observed to carrying out intelligent studies of total-body irradiation and marrow replacement in man has been the lack of facilities in which radiation may be administered in a sophisticated fashion consistent with the patient's own interest. It is no good using beams of small diameter, multiple exposures and overlapping areas of uncertain dosage. In most instances the patient may be expected to require nice adjustment of ionization effects in the 800 to 1000 r range to secure beneficial clinical effects. Too little x-ray is useless, and an overlap in the intestinal area at this level is lethal. One probable reason why success with marrow transplantation and with the treatment of leukemia has been obtained in the mouse is that the small body size and relatively delicate bony structure of this animal have permitted uniform ionization effects in the 1000 r range with the use of 250 KV photons and single tube sources. From known physical data it should not be expected that similar results will be obtained in man with the usually available facilities.

It is important that uniformity of radiation effect be obtained and obtained simultaneously in all tissues. Overtreating some areas and undertreating others is disastrous in a situation complicated by a ubiquitous malignant cell and a normal radiation requirement for transplantation purposes that is close to the limit of intestinal tolerance. Quadrant radiation, at least at high dosage rates, is not lethal in the dog. Presumably the normal flux of marrow seed through the circulation is adequate for autogenous repopulation. If this be so, the quite evident flux of mitotable leukemic cells precludes irradiation by a technic of divided fields. Optimal radiation would appear to be prolonged and of low rate, uniform and general, calculated to extend over a period and area sufficient to catch each cell at its most radio-sensitive and vulnerable time in the mitotic cycle. What might be accomplished by interrupted periods of radiation deserves exploration. J. B. Murphy long ago outlined problems now bedevilling us, including the effect of adult spleen in the tolerant host. In an interesting study he showed that repeated sublethal exposures to total-body irradiation produced paralysis of immune response without loss of marrow function. This again suggests that marrow function is more easily restored after radiation than is lymphoid function, whether the restoration be
autologous and autogenous as in his experiments or homologous or isologous as in more recent studies. Account should be taken of recognized differences in autogenous rates of regeneration in pertinent tissues in schedules of total-body irradiation suggested for man. Stereotyped procedures and premature conclusions are certainly to be avoided in this ill-explored field.

The human body is thick and the density differences of its soft and bony tissues are appreciable. The thickness causes a significant absorption of radiant energy and a difference in intensity of radiation effects on the near and far sides of the exposed body. Turning critically ill patients for periods of hours in front of a single beam to secure uniformity is not often feasible. Multiple sources (at least two) of high energy photons spread in large beams to include the entire body continuously have appeared to be the appropriate physical solution. Figure 2 is a diagram of a facility at present under construction for these purposes. Figure 3 shows the uniformity of general radiation, lines of isodosage, to be obtained with two opposed Cobalt units. The uniformity will be better in the installation diagramed with a two-meter distance between each source and the midline of the patient lying in the centrally placed bed.

High energy photons, 1 MEV, knock electrons from the outer orbits of atoms they strike and impart to them considerable speed. These Compton electrons in turn knock out other electrons from other atoms and these secondary electrons are the essential ionizing agents. The energy spectrum of the Compton electrons liberated by high energy photons is sufficiently broad to induce uniform ionization throughout soft tissue contained in bony cavities. The energy spectrum of electrons liberated by 250 KV photons is not. Figure 4 shows the approximation of uniformity in soft tissue within and without bony cavities that is obtained with photons in the 0.5 to 1 MEV range. The net result with two Cobalt units (1 MEV photons) each at 2 meters from midline of the patient is a uniformity of effect that begins to approximate the conditions known to be successful in mice.

Finally, a word in general might be said about the treatment of leukemia. Despite success in animals and palliative effects in some instances in preliminary crude trials in man, total-body irradiation can scarcely be touted as an optimal treatment. Its effect on normal and neoplastic tissue are too indiscriminate to be attractive as a solution to the problem of neoplasia or to the associated problem of homograft tolerance. Moreover, some leukemias seem rather radio-resistant and their requirement may exceed the limits of tolerance of the intestinal mucosa. Chemotherapy, oncolytic virology, or some similar specific approach through the emergent immunology of cancer retains our affection. Studies of the type herein discussed have merit only in their usefulness to certain present-day patients and their welcome provision of a basic knowledge of radiation effects in man.

CONCLUSION

The immediate biologic problem after whole-body irradiation is the management of infection. For understandable reasons infection is a particularly difficult problem in the terminal leukemic patient with whom we are most apt
Fig. 2.—Facility for simultaneous uniform irradiation of the entire human body with high energy photons of Cobalt⁶⁰.

(1) Cobalt⁶⁰ Teletherapy Unit, Picker X-ray Company, C 1000. This is a usual rotational teletherapy unit with an additional special collimator to give a 2-meter broad beam at a distance of 2 meters as indicated in the diagram. The collimator is fitted with a variable lead filter to regulate dosage rates.

(2) Cobalt⁶⁰ Unit, Picker X-ray Company, C 700. A low specific activity Cobalt⁶⁰ unit for general radiation studies fitted with special collimator as in (1) above.

(3) The usual table for positioning patients receiving usual rotational teletherapy treatment over limited areas with Picker unit C 1000. This is moved aside and the rotational head directed away from its shield when the unit is used for total-body radiation.

(4) A narrow bed, 36 inches wide and 2 meters long, for patients receiving irradiation of the entire body at dosage rates of 10 to 200 r per hour and total dosages of 200 to 1000 r, with units 1 and 2 operating as opposed balanced beams as indicated in the diagram.

(5) Viewing portal.

(6) Control panel.

(7) Heavy concrete walls providing radiation shield for operating personnel (cross-hatched).

(8) Entrance maze.

to work. Moreover the problem persists after marrow function has been re-established. Leukocytes from active marrow regeneration or from successful marrow grafts are not in themselves adequate antibacterial defenses. Considerable evidence indicates that infusions of marrow do not restore satisfactory function in irradiated lymph nodes and spleens. Marrow is ery-
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Fig. 3.—Isodose curves obtained by combining two Co** fields in opposition 16 cm. apart. The individual fields (dotted) are for a 5 x 5 cm. field at TSI 80 cm. (From Johns, H. E.: X-rays and teleisotope gamma rays. In Hine and Brownell: Radiation Dosimetry. New York, Academic Press, Inc., 1956, chap. 12, pp. 532-594.)

thrompoietic and myelopoietic but insufficiently lymphopoietic for these purposes, even when the difficulties of foreign marrow reaction are circumvented by adequate irradiation and the infusion of tolerant material. Evidently something more must be done and suggestions for so doing are given.

The chief physical problem in studies of whole-body irradiation in man is the setting up of radiologic facilities in which simultaneous homogeneous ionization effects may be obtained in the rather large human body. Until this matter is in hand it may be difficult to assess the immunologic problems underlying success and failure of marrow transplants in our species. Similarly, assessment of the control of leukemia by radiation and marrow transplantation must await application of sophisticated methods of irradiation. Suggestions for appropriate physical arrangements and the reason for them are given.

Follow-up on Case 10

Dr. A. R. Jones of the Blood Grouping Laboratory in Boston kindly performed quantitative determinations of the Duffy A (+) cells in this patient's blood using a new technic (Jones, A. R., and Silver, S.: The detection of minor erythrocyte populations by mixed agglutinates. Blood 13:763, 1958). The results were as follows: 61st postirradiation day, 3.3% Duffy A (+) cells; 107th postirradiation day, less than 0.02% Duffy A (+) cells.

It is apparent that by the 90th postirradiation day the patient's circulating cells were all of her own original type. From this we conclude that the transplanted marrow was no longer functioning, at least in terms of red cell production. We do not know whether the transplanted marrow functioned in the immediate postirradiation period.

On the 99th postirradiation day a 2 x 2 cm. full-thickness skin graft was transplanted to the patient from her sister, the marrow donor. This skin transplant had a 100% "take" and is still in place on 203rd postirradiation day. Evidently a striking degree of tolerance exists between the patient and her sister. This may be (1) an exceptional instance of prolonged survival in closely related individuals; (2) tolerance induced by her disease, leukemia; (3) tolerance induced by the whole-body irradiation and marrow transplantation.

On the 128th postirradiation day leukemic cells were again detected in the patient's
Fig. 4.—Ionization in soft tissue inside bone cavities for radiation generated at 80 KV, 200 to 250 KV, and 0.5 to 1.0 MEV compared with that in soft tissue outside bone (Tissue Valve). (From Spiers, F. W.: Brit. J. Radiol. 22:521, 1949.)

Peripheral blood. On the 134th postirradiation day a marrow aspiration showed a hyperplastic marrow with all normal elements present. About 20 to 30% of the marrow cells were undifferentiated blast cells.

From the 135th day postirradiation to the 161st, the patient received usual doses of 6-mercaptopurine. Response was mediocre and for this reason 1.9 billion nucleated marrow cells from the original donor were given to the patient on the 183rd postirradiation day. On the 180th day the appearance of joint pains led to the reinstitution of steroid therapy. On the 203rd postirradiation day the patient remains clinically well except for intermittent joint pains. The blood picture shows a normal hemoglobin and total white cell count, but 6% blast cells are present. The skin graft remains intact.

We do not know how to evaluate the roles currently played by her original irradiation and bone marrow infusion, her subsequent steroid therapy, her more recent infusion of normal marrow without preliminary radiation and the course of 6-mercaptopurine.

**SUMMARY**

Case reports of 5 patients with acute leukemia receiving total-body irradiation and intravenous infusion of normal marrow are presented. An eight-month follow-up on a previously reported patient with chronic leukemia is included and a review of an individual receiving nitrogen mustard and marrow is presented for comment.

Of several patients reported in this and in a previous communication only two may be said to have obtained significant clinical benefit. Potential reasons
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for this incidence of improvement are advanced and the general subject of total-body irradiation and marrow replacement in man is discussed. Pitfalls and problems biologic and physical and the theory of their circumvention are analyzed.

SUMMARIO IN INTERLINGUA

Es presentate reportos del casos de 5 patientes con leucemia acute, recipiente irradiation del corpore total e infusion intravenose de medulla normal. In plus, observationes ulterior pro un periodo de 8 menses es presentate in le caso de un previemente descripte patiente con chronic leucemia, e commentos es offerite relative al caso de un individuo tractate con mustarda de nitrogeno e medulla.

Inter le varie patientes reportate in iste e in un previe communication, solmente duo obteneva grados significative de beneficio clinic. Le rationes potential de iste basse incidentia de melioration es presentate, e le thema general del irradiation del corpore total e de reimplaciamiento del medulla in humanos es discutite. Problemes e difficultates de character biologic e physic e le teoria de lor circumvention es analysate.

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Irradiation of the Entire Body and Marrow Transplantation: Some Observations and Comments

E. DONNALL THOMAS, HARRY L. LOCHTE, JR. and JOSEPH W. FERREBEE