HOMOLOGOUS BONE MARROW IN THE TREATMENT OF RADIATION INJURY IN MICE*

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In the experimental treatment of lethal total-body irradiation injury in mice by intravenous injection of bone marrow suspensions, most of the work has been carried out with isologous† bone marrow donor animals of the same strain as the irradiated recipient. In these experiments with x-radiation, about 95 per cent 30-day survival was observed. There was no appreciable additional mortality during the next few months. Under similar irradiation conditions the exposed mice receiving homologous bone marrow from donor animals of a different strain showed about 50 per cent 30-day survival with many delayed deaths during the second and third months after irradiation.[1] The nature of the delayed deaths and the clinical features of the disease exhibited by the animals prior to death form the basis of the present report.

MATERIALS AND METHODS

Animals. Male and female LAF_1 mice were used as irradiated recipients; IOI × C_3HF_1 or LAF_1 mice were the donor animals. All irradiated mice were about 3 months old at the time of exposure. The mice were kept 10 to a cage; food and water were always available.

X-Ray Conditions. The irradiation conditions were: 250 kvp, 30 ma, and 3 mm. of Al filter; target-object distance, 80 cm.; dose rate, ~100 r./min.; hvl 0.4 mm. of Cu.

Bone Marrow Preparations. The femur of the donor mouse was severed at both ends and the bone marrow flushed into a small cup by means of a needle and syringe containing Tyrode's solution. The tissue was drawn several times through the needle and syringe to make the suspension. All bone marrow suspensions were administered intravenously.

Necropsy. Gross examinations were carried out on nearly all animals dying in certain experiments and on selected animals in other experi-

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† Isologous bone marrow refers to transplantation within an inbred strain or between genetically homogeneous F_1 hybrids. Homologous transplantation of bone marrow refers to transplantation between inbred strains or between different F_1 hybrids. Heterologous transplantation is used to denote interspecies experiments; e.g., rat to mouse.

ments, as indicated. Tissues for microscopic study were fixed in Zenker's-formol solution or in 10 per cent formalin. The sections were stained with hematoxylin and eosin.

RESULTS

Survival

The pattern of death in one experiment during the first 30 days after irradiation is shown in Table I for x-ray control animals and those treated with isologous and homologous bone marrow. At a dose level of 900 r., x-ray controls rarely survived beyond the 15th day after irradiation. Mortality in mice treated with isologous bone marrow varied from 0 to 10 per cent during the first 30 days after irradiation. The results were generally uniform from experiment to experiment, and the few animals that did die might have died at any time during the 30-day

TABLE I

Effect of Isologous and Homologous Bone Marrow on 30-Day Mortality of Total-Body X-Irradiated (900 r.) LAF_1 Male Mice

No. of mice	Donor animal*	Number of animals dying each day after x-ray																Mortality
		Day	6	7	8	9	10	11	12	13–19	20	21	22	23	24	25	26–30	
																		%
8	None					1	2	4	1									100
15	LAF_1			1														6.6
15	101 × C_3HF_1	1									1		1	1	1	2		46.6

* The bone marrow from one femur given intravenously to each recipient.

TABLE II

Effect of Isologous and Homologous Bone Marrow on Survival of LAF_1 Mice for 100 Days After 900 r. of Total-Body X-Radiation

No. of mice and sex	Donor*	Number surviving at end of each 10-day period											Survival
		Day	0	10	20	30	40	50	60	70	80	90	100	
														%
47 M	101 × C_3HF_1		47	44	28	15	11	9	6	4	3	2	1	2.1
32 F	101 × C_3HF_1		32	27	24	15	10	9	8	5	4	4	3	9.4
35 M	LAF_1		35	33	33	33	33	33	33	33	33	33	33	94.3
28 F	LAF_1		28	28	28	28	28	28	28	28	28	28	28	100.0

* Bone marrow from one femur given intravenously to each recipient.

period. During the first 15 days after irradiation, there were often no more deaths among the mice injected with homologous bone marrow (Table I) than in those treated with isologous marrow. The results, however, varied from experiment to experiment. A large percentage of

mice injected with homologous marrow died during the second 15-day period after irradiation (Table I). These deaths were due to a secondary disease process, as described later, and were not caused by lack of bone marrow regeneration.

During the second and third months after irradiation, mice treated with homologous bone marrow continued to die. Table II shows the results obtained in a series of experiments. In both male and female

TABLE III

Long-term Survival of Irradiated Mice Treated with Homologous Bone Marrow

Experiment no.	No. of mice and sex	Post-irradiation (900 r.) treatment and time*	Post-irradiation survival†	
			No. of mice	No. of days
1	4 M	Marrow‡	2	316
2	17 F	Marrow	2	217
3	15 M	Marrow	1	204
4	17 F	Marrow; streptomycin on days 44–53	6	190
5	9 F	Marrow	4	167
6	10 M	Marrow; streptomycin on days 3–24	1	163
7	10 F	Marrow; streptomycin on days 4–30	3	142
8	10 F	Marrow on day 1	7	107
9	10 F	Marrow on day 2	8	107
10	10 F	Marrow on day 3	4	107
11	10 F	Marrow on day 4	1	107

* Bone marrow on day 0 unless otherwise stated.

† As of August 8, 1956.

‡ Marrow from 4 femurs in experiment 1; in all others, 1 femur.

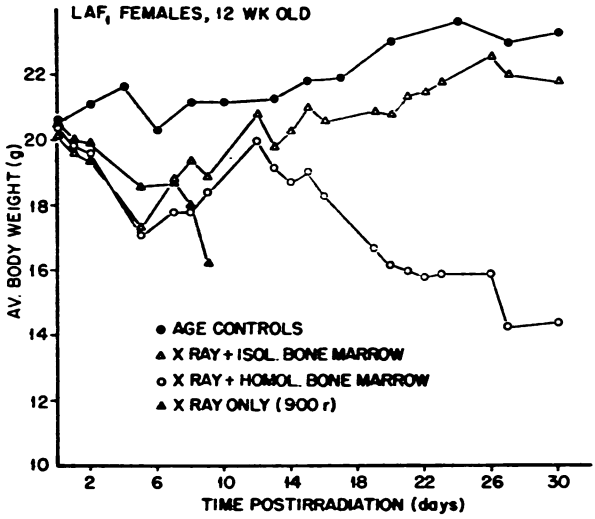
mice, 100-day survival was rare after injection of homologous bone marrow, in sharp contrast to the high percentage of survival in mice treated with isologous bone marrow (Table II). Selected homologous bone marrow experiments in which the animals lived longer than 100 days are shown in Table III.

Appearance and Body Weight

Mice treated with homologous bone marrow closely resembled the isologously treated animals for the first 2 weeks after exposure. During this period the untreated, irradiated mice died of the irradiation syndrome. The body-weight response after bone marrow treatment is shown in Text-figure 1. Mice injected with isologous and homologous bone marrow showed a nearly parallel decline in average body weight

and recovery during the first 2 weeks after irradiation. In the second 2 weeks, the isologous animals continued their recovery; and the average body weight of the homologous mice showed a secondary decline during which many of the mice died.

In the second 2 weeks after irradiation, or later, most of the mice treated with homologous bone marrow had marked ruffling of hair, the skin became atrophic, and a yellow, scaly dermatitis developed. Partial



Text-figure 1. Response of body weight in irradiated mice treated with isologous and homologous bone marrow.

epilation often appeared, and the hair was easily pulled out. Radiation-induced graying of hair was well developed in isologous animals by 30 days after irradiation but was absent or markedly reduced in homologous mice unless they lived for prolonged periods.

A few of the sick animals described consumed a normal amount of food, but lost much weight. Normally formed feces were eliminated. During this same period the isologous mice resembled age controls except for the growth of gray hair (Fig. 1).

Gross Necropsy Findings

Gross necropsy examinations were performed on 33 males that died between the 13th and 92nd days after 900 r. and homologous bone marrow treatment. Necropsies were performed also on 24 similarly treated female mice that died on the 6th to 95th days after irradiation. Since there was no marked difference in the findings in males and

females, the observations apply to both sexes. The most striking feature at necropsy was emaciation; many animals weighed only 11 to 15 gm. This was true for nearly all animals examined, whether death occurred early or late. Dermatitis was noted in most of the mice examined but not necessarily in those that died very early. Graying of hair did not appear except in patches even in mice that died 90 days after irradiation. Emaciation was associated with loss of adipose tissue in subcutaneous areas and other sites. Marked atrophy of thymus, lymph nodes, and Peyer's patches characterized the necropsy findings in nearly every mouse. The spleen was normal in many mice and was occasionally hyperplastic. In many mice, localized hemorrhagic lesions were found in the wall of the gastro-intestinal tract at specific anatomical areas. Seven of the 24 females examined showed this lesion, and 16 of the 33 males showed 18 discrete hemorrhagic lesions in the wall of the gastro-intestinal tract. In the females, three of the hemorrhagic lesions were located in the wall of the pylorus; and four were in the wall of the cecum and colon. Two of the pyloric lesions produced acute gastric obstruction and dilatation. The hemorrhage at the pylorus sometimes extended into the adjacent omentum and pancreas. The mucosal surface of the pylorus was often ulcerated, but perforation was not found. In the cecum, the hemorrhage sometimes involved the ileocecal valve and produced obstruction of the small bowel. The 18 hemorrhagic lesions in the males were associated with the pylorus in 12 instances, 5 of which produced acute obstruction, and with the cecum and colon in 6 instances. The ascending, transverse, and descending colon were less frequent sites of mural hemorrhage. Generalized purpuric manifestations of the type associated with the radiation syndrome were not observed. The hemorrhagic lesion occurred in mice that died 20 to 60 days after irradiation.

Another lesion was discovered in the liver in four of the females and in three of the males (Fig. 2). In these, the organ showed a diffuse, often uniformly granular or mottled appearance from the capsular surface. On cut surfaces, the fine or coarse alteration in the parenchyma extended through all lobes. The larger focal lesions (about 2 to 3 mm.) had red centers and white margins, and the intervening tissue had a translucent or gelatinous appearance. More common in the liver than this change were single and multiple yellow abscesses or white areas of necrosis of varying size. These were seen in 6 of the females and 15 of the males; in some, the livers showed no gross abnormalities. In a few mice, abscesses were observed in other organs, primarily the

kidneys and lungs. Some mice showed no gross changes at death other than the emaciation, dermatitis, and atrophy of lymphatic tissues. The bone marrow could not be accurately characterized by gross observation but appeared to be normal.

Microscopic Findings

Tissues from 25 male animals that died 18 to 92 days after 900 r. and homologous bone marrow treatment and from 31 female mice that died 6 to 95 days after similar treatment were examined microscopically. The changes were not significantly influenced by the sex of the animals.

Bone Marrow. The degree of cellularity was estimated on sections through the femur or sternum. Four plus was considered normal. Table IV shows the results.

TABLE IV

Bone Marrow Cellularity at Necropsy of Mice that Died 6 to 95 Days after 900 r. and Treatment with Homologous Bone Marrow

No. of mice and sex	Cellularity of bone marrow				
	++++	+++	++	+	±
25 M	11	10	4	0	0
31 F	22	4	2	2	1

Mild or moderate congestion was the most common cause of reduction in cellularity. Occasional focal areas with loss of blood-forming cells were seen, some of which showed fibrin deposits. In rare instances, foci of necrosis of blood-forming cells were noted. Plasma-cell collections and eosinophilic granulocytes were present in some sections. Granulocyte formation was often increased at the expense of erythropoiesis, presumably in response to the purulent and suppurative inflammations that were often present in other organs. The changes in the bone marrow showed no special relation to time of death. In approximately one half the animals, the bone marrow was considered normal except for the increased granulopoiesis. No abnormality in the formation of megakaryocytes was observed.

Spleen. In two animals, the white pulp was partially intact; in all others, the lymphocytic elements were not present, and only the framework of the white pulp remained. It usually contained some plasma cells. In many animals, an occasional individual splenic nodule was replaced by a dense pink-staining material (Fig. 3). Sometimes the arteriole in the white pulp was obliterated.

The red pulp contained all phases of blood cell formation. However,

formation of blood cells was often markedly reduced. Infiltration of plasma cells was usually present, sometimes to a very marked degree. Some spleens showed erythrophagocytosis. Focal areas of necrosis of blood-forming cells were seen in a few sections. Often, patchy areas in the red pulp were replaced by fibrinous deposits or had undergone fibrosis. None of the spleens could be considered normal.

Lymph Nodes. The brachial and inguinal lymph nodes were always atrophic. In the more extreme cases, the normal architecture was obliterated (Fig. 4). The capsule was thickened. The cortex and medulla were replaced by dense fibrous connective tissue, usually infiltrated by plasma cells and containing pigment-laden macrophages. In some instances, the medullary sinuses were discernible. Blood-forming cells were present in a few lymph nodes.

Thymus. Extreme simple atrophy was present in all cases.

Liver. The unique lesion affecting the entire parenchyma seen in the gross examination consisted of foci of simple necrosis of the hepatic cord cells resembling tiny infarcts (Fig. 5). In some of the cases, there was no inflammatory cell reaction; but when it was present, it usually contained plasma cells in addition to other cells associated with the repair of necrotic foci. Small foci of extramedullary hematopoiesis were present in the portal areas in several animals. Metastatic hepatic abscesses from thrombo-pylephlebitis were observed in several mice. The inflammatory processes, when present, did not differ from those expected in otherwise normal mice.

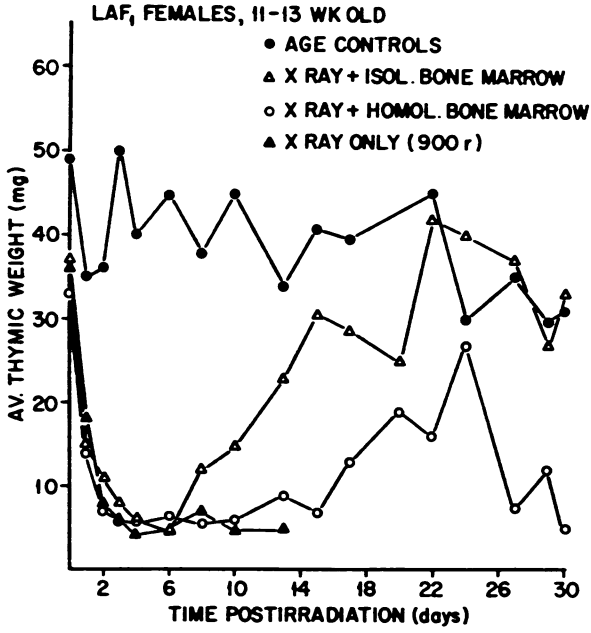
Stomach and Intestine. On microscopic examination, the hemorrhagic lesions at the pylorus or in the large intestine consisted of necrotic, ulcerating mucosal lesions with extensive bacterial growth and suppurative inflammation. Extensive recent hemorrhage into adjacent tissues was almost invariably present. Septic thrombosis of vessels in the wall of the pylorus or large intestine accompanied the lesion.

Adrenal Gland and Kidney. Usually, microscopic examination showed these organs to be normal. A few kidneys showed embolic abscesses or septic thrombi in blood vessels in the hilum. In one female mouse that died 64 days after irradiation and homologous bone marrow treatment, necrosis of erythropoietic cells was observed in most of the glomeruli of both kidneys.

Lungs. About one third of the mice showed inflammatory lesions in the lungs. These varied from purulent bronchitis and lobular pneumonia to septic emboli that rarely formed abscesses. Large collections of plasma cells around blood vessels and bronchi were observed in a few of the lungs with inflammatory lesions.

Data Obtained on Mice Sacrificed at Intervals after 900 r. and Treatment with Homologous Bone Marrow

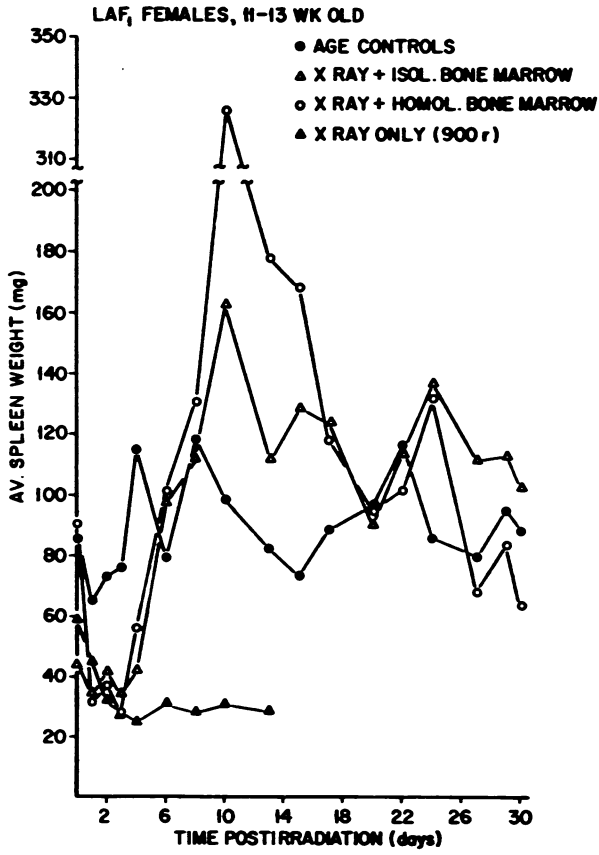
A group of 30 LAF_1 female mice that received 900 r. and homologous bone marrow were sacrificed at intervals of 1 to 3 days on days 0 to 30. Equal numbers of un-irradiated normal mice and irradiated mice receiving isologous bone marrow were also sacrificed. Fourteen mice given 900 r. of total-body radiation without additional treatment were sacrificed on days 0 to 13. Organ weights were obtained on thymus and spleen, and histologic sections were taken at selected intervals on thymus, spleen, and lymph nodes. Text-figures 2 and 3 show the data



Text-figure 2. Response of thymic weight in irradiated mice treated with isologous and homologous bone marrow.

for weight of thymus and spleen. Microscopically, the thymus showed massive necrosis within 24 hours in all irradiated groups. In the control irradiated group, the animal examined on day 10 showed slight regeneration of thymocytes in cortex and medulla. On day 10, the mouse treated with isologous marrow showed nearly normal architecture with a wide cortex filled with thymocytes. The mouse treated with homologous bone marrow on day 10 showed only slight regeneration of thymocytes. At successive intervals, the thymuses of isologous marrow-treated mice continued to enlarge, having by 10 days reconstituted the normal architecture of the organ. At 15 days, the thymus of the mouse

injected with homologous bone marrow had a normal architecture in one lobe, but part of the other lobe was without a normal cortex. On days 22, 27, and 29, the cortex was irregular with reduction in thymocytes; the sharp corticomedullary junction was no longer discernible.



Text-figure 3. Response of splenic weight in irradiated mice injected with isologous and homologous bone marrow.

These findings along with the organ-weight data on the thymus show that partial regeneration after treatment with homologous bone marrow occurs but is followed by secondary degeneration during the fourth week after irradiation.

Marked destruction of the red and white pulp of the spleen occurred in all irradiated groups in the first 24 hours after irradiation. Slight regeneration of lymphocytes in the white pulp of the irradiation controls appeared and remained in this state throughout the observation period. No regeneration took place in the red pulp.

The white pulp in the mice treated with isologous marrow showed

slight regeneration very early. Enlargement and germinal-center formation were present on day 10, and a normal state was reached by day 22. As would be expected, marked regeneration of blood-forming cells in the red pulp had begun by day 4 in the isologous animals and continued to increase thereafter.

Normal white pulp was not regenerated in the mice injected with homologous bone marrow. During the first 2 weeks after irradiation, blood cell formation from the red pulp encroached on the atrophic white pulp. The animal sacrificed on day 15 showed fibrinoid degeneration of two adjacent splenic nodules and infiltration by plasma cells. The number of blood-forming cells in the red pulp near these nodules was markedly reduced. The animal sacrificed on day 8 showed a focal area of reticulo-endothelial cell proliferation. Hyaline degeneration or fibrinoid necrosis in the white pulp was seen also on days 17, 24, and 29. On day 29, however, the remainder of the white pulp had a nearly normal content of lymphocytes. The red pulp in the mice treated with homologous marrow showed massive hyperplasia of blood-forming elements of all phases, paralleling that seen in the mice injected with isologous bone marrow. These changes were reflected in the weight of the spleen (Text-fig. 3). The drop in splenic weight to normal levels during the third and fourth weeks after irradiation reflects the normal reduction in blood-forming cells in the red pulp in mice treated with both isologous and homologous bone marrow.

In the three irradiated groups, microscopic examination of the lymph nodes showed massive necrosis of lymphocytes during the first 24 hours after exposure. Slight regeneration of lymphocytes occurred in relation to the original germinal centers in the irradiated control group. These were present on day 1 after irradiation and persisted as the lymph nodes became smaller and smaller on subsequent days.

The lymph nodes of the mice treated with isologous bone marrow did not differ appreciably from those of the x-ray control mice until day 10. Lymph nodes of the animal sacrificed on this day showed extensive formation of granulocytes in the medullary cords. On day 15, marked accumulation of lymphocytes around the cortical nodules was present. Formation of granulocytes persisted in a reduced amount. Gradual resumption of the normal architecture of the lymph node began between the 15th and 29th days after irradiation.

The lymph nodes in the mice treated with homologous bone marrow did not return to a normal state microscopically. They showed the same findings as the other two groups for about 8 days after irradiation. Formation of granulocytes was minimal compared to that seen

in the lymph nodes of mice treated with isologous bone marrow. Proliferated reticulo-endothelial cells, plasma cells, and scattered multinucleated giant cells were the most striking histologic features in the lymph nodes on day 10. These changes persisted for about 1 week. On day 24, progressive fibrosis of the lymph nodes was taking place with a marked reduction of all other cell types. At subsequent intervals, fibrous atrophy had occurred in nearly all lymph nodes examined.

Attempts to Influence the Delayed Homologous Bone Marrow Reaction

The reaction occurred at all doses of homologous bone marrow administered from 1/32 of the marrow from one femur to a 16-femur bone marrow dose. It developed at all levels of exposure from 600 through 1200 r. but did not develop at exposures from 200 to 500 r. It was not definitely prevented by use of older (6-months-old) irradiated recipients or by administration of homologous fetal blood-forming tissues. The fetal homologous blood-forming tissues, however, may cause less delayed reaction than adult homologous tissues. It was not prevented by chemical protection (S,2-aminoethylisothiuronium·Br·HBr), gonadotrophin, hydrocortisone, diphenhydramine hydrochloride, estrogen, or streptomycin administration under the experimental conditions used. Mixtures of isologous and homologous bone marrow did not prevent the delayed homologous reaction unless excess isologous bone marrow (3:1) was in the mixture. The most promising results in our efforts to circumvent the delayed reaction were seen in mice given homologous bone marrow on day 1 or 2 after irradiation instead of day 0, the usual time for injection. Fifteen of 20 female mice treated in this manner survived 107 days after irradiation (Table III). They resembled mice treated with isologous bone marrow and were gaining weight.

Discussion

The delayed reaction was not observed in the first report on the use of homologous* bone marrow in the treatment of total-body irradiation injury in mice.[2] Loutit[3] noted that spleen homogenate transplantation between strains of mice enhanced 30-day survival but that delayed deaths beyond the 30-day period occurred in the treated mice. He suggested that host iso-antibodies developed that killed the graft and the host animal. Delayed deaths after the 30-day observation period

* In some of the early literature on the use of bone marrow and spleen in the treatment of irradiation injury, the term homologous was used to indicate intrastrain transplantation; now referred to as isologous. Heterologous transplantation was used to indicate interstrain as well as interspecies transplantation.

have now been observed with homologous bone marrow treatment by several investigators.[1,4,5]

The occurrence of delayed deaths of this type in heterologous bone marrow treatment; i.e., rat bone marrow to the lethally irradiated mouse, was reported also.[6,7]

It is clear that the delayed homologous reaction is caused by the homologous bone marrow since, at sublethal radiation exposure (650 r.), only the homologous bone marrow-treated mice develop the reaction. It was not seen in the mice treated with isologous bone marrow or in the untreated-irradiated controls that survived the 650-r. exposure.[1] The amount of radiation administered was also important. Below 600 r., homologous bone marrow injection did not cause the delayed reaction.

An important feature in the pathogenesis of the delayed homologous bone marrow reaction or in the delayed heterologous bone marrow reaction is the proliferation of the foreign bone marrow cells in the irradiated host. Evidence to support the idea that proliferation occurs has been accumulated by several investigators.[8-14]

The delayed foreign bone marrow reactions can be interpreted as evidence of a hypersensitive state resulting from a chronic *in vivo* tissue antigen-antibody reaction.[11,15] In this reaction, however, the host animal is not able to destroy significant numbers of the proliferating foreign bone marrow cells, as evidenced by the nearly intact bone marrow in most of the mice at necropsy. Presumably, the main antibody-producing tissues, the spleen and lymph nodes, are exhausted in the presence of such extreme stimulation. Lesions in these tissues are compatible with this interpretation. An alternative suggestion is that the donor bone marrow cells also transplant the donor type immune mechanism and that this reacts against host tissue antigens and brings about the delayed reaction. The mechanism is not yet settled.

The thymus in mice treated with homologous bone marrow showed a partial, temporary recovery followed by a secondary, simple atrophy. This organ did not show the reactive changes seen in lymph nodes and spleen. Failure of homologous and heterologous bone marrow treatment to allow thymic regeneration after multiple total-body irradiation exposures was reported by Hirsch *et al.*[16] Under the same conditions, treatment with isologous bone marrow caused complete regeneration of the thymus. The effect of treatment with foreign bone marrow on the prevention of radiation-induced thymic lymphosarcoma has not been determined. The secondary atrophy of the thymus in

the present work may be related to the emaciated condition of the animals at necropsy rather than to a failure of the foreign bone marrow to allow its complete regeneration.

The dermatitis seen grossly and the specific lesions of the liver and gastro-intestinal tract cannot be satisfactorily explained at the present time. Nutritional disturbances and severe stress reactions as well as possible allergic phenomena were considered. The failure to develop normal amounts of gray hair after recovery from irradiation injury indicates failure of hair growth and is believed to result from the total metabolic disturbance. The later disturbance in the presence of a nearly normal food intake was not investigated. The structure of the thyroid gland was normal.

Delayed mortality in lethally irradiated mice that received homologous spleen treatment was investigated by Barnes and Loutit.[17] They reported a chronic diarrhea and weight loss as the prominent clinical features of the disease preceding death. No specific lesions were noted at necropsy. Trentin[18] also found no specific lesions at necropsy to explain the delayed deaths in homologous and heterologous bone marrow-treated irradiated mice. Some of the lesions reported by Denko[5] at necropsy of irradiated mice treated with homologous bone marrow resemble those described in the present paper. The extent to which these apparently specific changes depend on the strains of mice used has not been determined.

Some aspects of the delayed homologous bone marrow reaction resembled certain features of parabiosis intoxication in rats[19] and also the syndrome seen in germ-free guinea pigs.[20] The near-total absence of normal lymphocytic tissue in these mice probably favored the development of some of the secondary purulent and suppurative inflammatory conditions. The possibility that prolonged absence of lymphocytic tissue by itself might give rise to a metabolic disorder was considered but not investigated.

The few animals that survived for prolonged periods (Table III) demonstrated the feasibility of preventing or circumventing the delayed foreign bone marrow reaction. It is obvious that such an achievement with persistence of the foreign bone marrow cells would have important implications for the homotransplant problem.

Summary

The 30-day survival of lethally irradiated LAF_1 mice receiving homologous bone marrow intravenously was often comparable to the survival of those receiving isologous bone marrow; however, most of

the mice treated with homologous bone marrow subsequently died of a secondary disease. The histologic changes in the lymph nodes and spleen were compatible with an immunologic tissue reaction. The lesions in the liver, gastro-intestinal tract, skin, and the general state of the mice at the time of death suggested a severe metabolic disturbance, presumably initiated by the immune reaction if not actually a part of the reaction. A few animals survived 107 to 316 days and, in general, resembled isologous bone marrow-treated mice at these intervals.

The ability of a few mice to escape the delayed homologous bone marrow reaction suggests the feasibility of attempts to circumvent the reaction if proper experimental conditions could be found.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. The animal at the top of the picture was a normal LAF_1 mouse at 4 months of age. The middle animal was an LAF_1 mouse of the same age that received 900 r. and isologous bone marrow 30 days before the picture was taken. Graying hair over most of the body can be seen. The animal at the bottom of the picture was an LAF_1 mouse that received 900 r. and homologous bone marrow 30 days before the picture was taken; it was small, had ruffled hair, and showed very little graying.

FIG. 2. Formalin fixed specimen of liver in a mouse that died 66 days after 900 r. and injection of homologous bone marrow.

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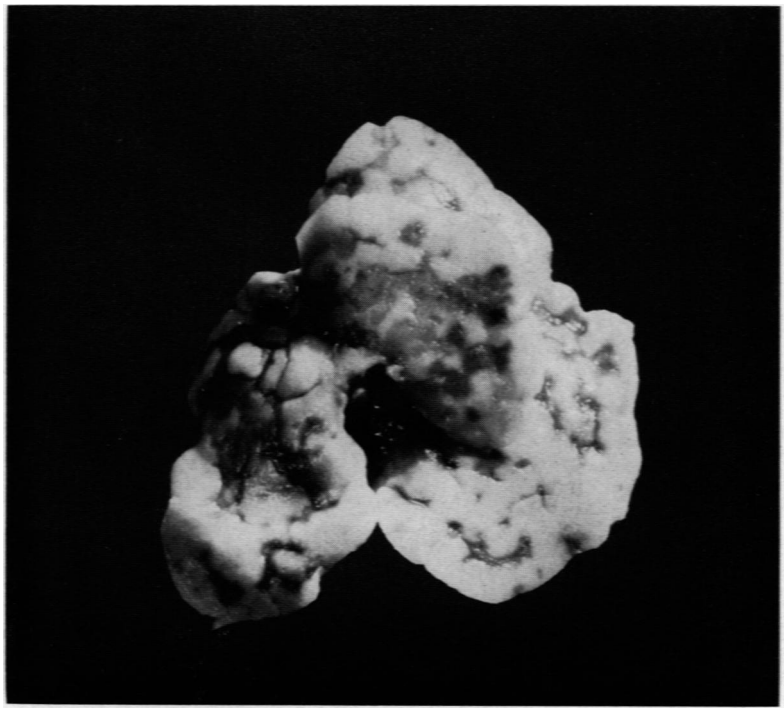

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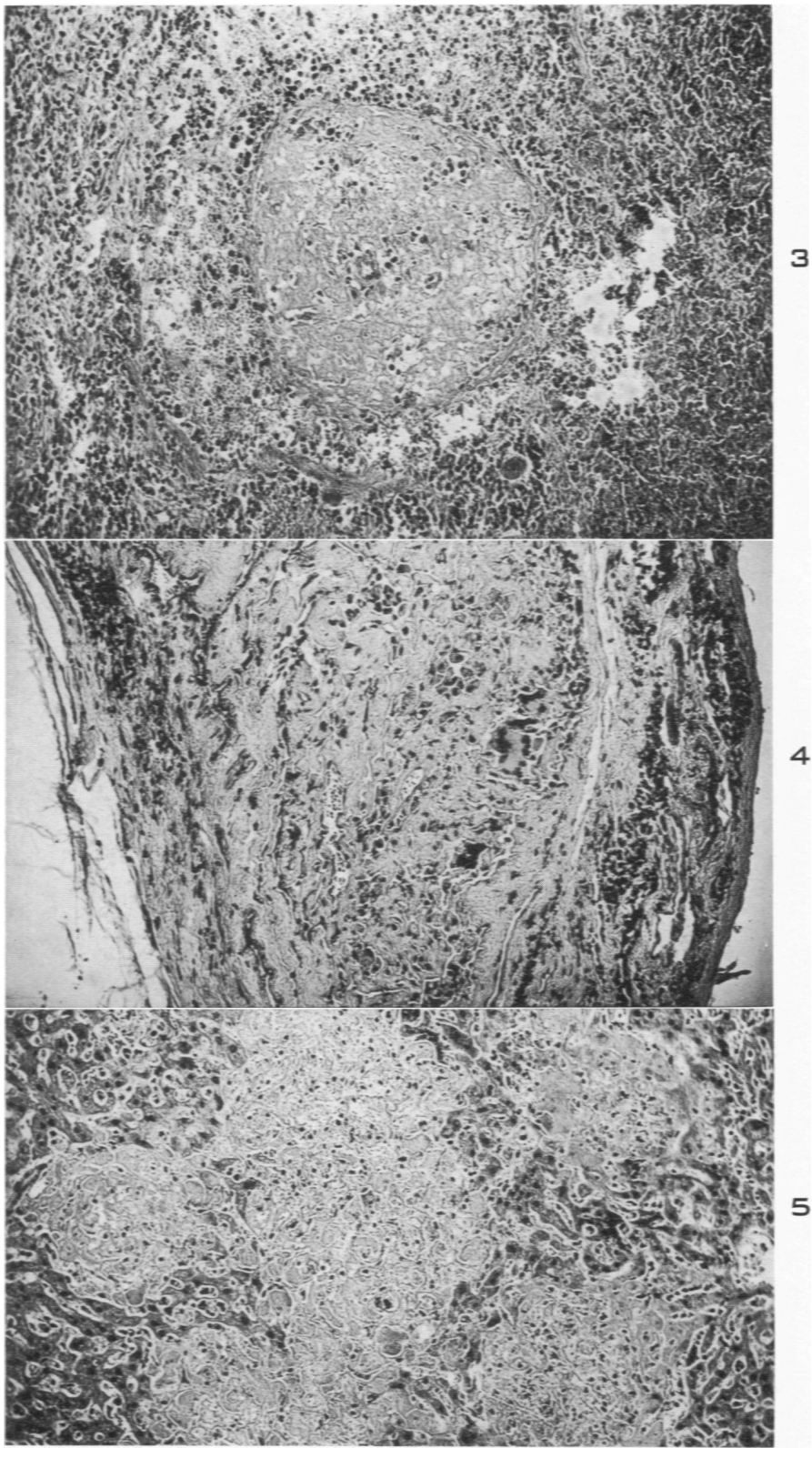
FIG. 3. Fibrinoid degeneration of a splenic nodule in an LAF_1 mouse sacrificed 15 days after 900 r. and homologous bone marrow. Hematoxylin and eosin stain. × 145.

FIG. 4. Fibrosis and multinucleated giant cell reaction in the inguinal lymph node of an LAF_1 mouse that died 64 days after 900 r. and homologous bone marrow. Hematoxylin and eosin stain. × 145.

FIG. 5. Simple necrosis in the liver of an LAF_1 mouse that died 33 days after 900 r. and homologous bone marrow. Hematoxylin and eosin stain. × 145.



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