Homografts of Bone Marrow in Dogs After Lethal Total-Body Radiation

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LIFE-SAVING HOMOGRAPHS of bone marrow after lethal whole-body irradiation usually succeed in rodents but fail in dogs. Recently we reported a successful and life-saving homograft of marrow after 1,200 roentgens of total-body irradiation in a beagle. Success was attributed to the following procedures: (1) use of a donor and a recipient with a close genetic relationship (litter-mates), (2) use of a supralethal dose of irradiation (1200 r over a three day period), and (3) splenectomy and administration of ACTH to the recipient prior to irradiation. It was felt that splenectomy, ACTH and the supralethal dose of x-ray were necessary to inhibit vigorous immune reactions that normally make homotransplantation impossible in the canine. The intensity of host-donor reactions may have been further reduced by the use of a female litter-mate as the marrow donor. Studies with skin grafts have indicated an occasional relative histo-compatibility between litter-mates in this species.

The present report describes studies on 27 dogs. An attempt is made to evaluate the relative importance of the procedures listed above. In addition a follow-up account is given of the subsequent clinical course and autopsy findings in the dog previously reported (dog 1, table 1).

METHODS

The animals studied were beagles, 6 weeks to 18 months old, relatively pure-bred but not inbred. Twenty-five were males; two were females (17 and 18, table 1). The dogs were purchased from outlying farms and confined in a local veterinary kennel 10 to 14 days before use. Dogs to be irradiated were treated for worms with Vermiplex. Immunization against distemper and hepatitis was attempted by administration of a formalin-killed virus preparation (5 ml. of Virogen D-H). Irradiation was given with a General Electric MaxiMARK Unit, operating at 250 kv. and 10 Ma. with a half-value layer of 2.2 mm. of copper, and a target-source distance of 100 cm. The conditions used to achieve uniform whole-body irradiation were previously described. A dose of 400 r measured in air was given on the first day. Dog 14 received 200 r on the second day. All other dogs received 400 r on the second day. In the case of animals receiving more than 800 r an additional...
Bone marrow homografts in dogs after lethal X-ray

125 to 400 r was given on the third day. Marrow from female donors was given intravenously on the third day. A single donor was used for each recipient.

Marrow for intravenous infusion was obtained, using aseptic technic, from femurs, tibiae and humeri of anesthetized and exsanguinated donors. In some instances additional marrow was obtained from the ribs and vertebral bodies. The marrow was removed by curetting and was suspended in TC 199* containing 5 to 10 per cent normal dog serum. The marrow suspension was passed through successively finer stainless steel screens, 32, 62, and 88 per inch mesh, respectively. Bone spicules were removed by the screens and by decantation. The time elapsed from death of the donor to infusion of the cells into the recipient was approximately one hour.

All irradiated dogs were started on antibiotics on the day of marrow administration. For the first week they received the following antibiotics daily: penicillin, 300,000 units orally; terramycin, 100 mg. orally; and streptomycin, 250 mg. intramuscularly. During the second week they received penicillin, 300,000 units orally and chloromycetin 100 mg. orally daily. Throat and stool cultures were obtained frequently. After the second week dogs with infections were given antibiotics chosen on the basis of the sensitivity pattern of the organisms present.

Splenectomy was performed on six dogs two weeks before irradiation. These dogs also received ACTH, 10 units intramuscularly, twice daily, beginning five to seven days before irradiation and continuing for several days after irradiation and marrow transplantation.

Complete autopsies with histologic studies were performed on all dogs. Bone marrow from the ribs, vertebral bodies and a femur was examined histologically.

Results

Survival period of control dogs not given marrow.—Six dogs were given radiation, 600 to 1200 roentgens, and no infusion of bone marrow. Despite treatment with antibiotics these animals died in 6 to 10 days of the usual postirradiation syndrome of acute marrow failure: leukopenia, thrombocytopenia, petechial and gross hemorrhages in mucosal and serosal membranes, and a serosanguinous bacterial pneumonia.

Survival period of dogs with marrow transplants.—Twenty-one dogs were irradiated, 800 to 1,200 roentgens, and given an infusion of fresh bone marrow. Sixteen showed evidence of recovery of marrow function. Their average period of survival was 33 days. One animal lived 109 days. The usual cause of death in dogs with successful marrow transplants was one of the common canine infectious diseases: distemper, with or without superimposed bacterial pneumonia, hepatitis contagiosa canis, or leptospirosis canicola.

Summary of results in dogs given marrow (table 1, Groups A, B, C).—Group A: Irradiated Dogs Receiving Marrow from Litter-Mates. Thirteen dogs were given litter-mate marrow in doses of 0.46 to 8.6 billion cells after lethal total-body irradiation (table 1, Group A). One of these, dog 2, died on the fifth day, of diarrhea and dehydration, before marrow function returned. In five other dogs of this group the marrow transplant functioned poorly (table 1, dogs 9, 10, 11, 12, 13). Formed elements returned to the blood but at subnormal levels. The marrow was cellular to a degree, however, as indicated in the estimates (table 1). Four of the five with inadequate marrow function

*Difco Laboratories, Detroit, Mich.
<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Age</th>
<th>Relationship of Marrow Donor to Recipient</th>
<th>Number of Marrow Cells</th>
<th>Dose of X-ray (r)</th>
<th>Splenectomy and ACTH</th>
<th>Success of Marrow Transplant (Based on Blood Counts)</th>
<th>Cellularity of Marrow (% of Normal)</th>
<th>Leukocyte Count (Peripheral)</th>
<th>Period of Survival after Infusion (days)</th>
<th>Cause of Death</th>
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<tbody>
<tr>
<td>1</td>
<td>1 yr.</td>
<td>litter-mate</td>
<td>8.6</td>
<td>1,200</td>
<td>yes</td>
<td>good</td>
<td>100+</td>
<td>70,000</td>
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<td>2</td>
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<td>80–100</td>
<td>23,000</td>
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<td>5</td>
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<td>80–100</td>
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<td>7</td>
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<td>59</td>
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<td>9</td>
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<td>6.97</td>
<td>925</td>
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<td>Weeks</td>
<td>Relationship</td>
<td>Platelets</td>
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<td>177</td>
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<td>122</td>
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*These estimates are based on the reappearance of platelets, leukocytes and reticulocytes in the peripheral circulation.

†The hemorrhage in these dogs was associated with thrombocytopenia and manifested by petechial and gross hemorrhages in mucosal and serosal membranes.
died of hepatitis or distemper. Two had both hepatitis and distemper and the fifth died of hemorrhagic pneumonia associated with a low platelet level.

Group B: Irradiated Dogs Receiving Marrow from Mother. Four dogs received marrow from their mother (table 1, Group B). Three had successful transplants and one did not. The latter died on the eighth day, of pneumonia and hemorrhage.

Group C: Irradiated Dogs Receiving Marrow from Unrelated Donors. Five dogs received marrow from donors that were not related to them (table 1, Group C). One, dog 20, had a successful marrow transplant. This dog had a splenectomy and ACTH before irradiation and was given 1,200 r and a large dose of marrow, 12.45 billion cells. After making an excellent recovery the animal suddenly became ill and died on the thirty-first day. Postmortem examination showed severe interstitial nephritis consistent with *Leptospirosis canicola*.

Two dogs in Group C, 21 and 22, showed peripheral leukocyte counts suggestive of a return of marrow function (1,500 to 3,000 leukocytes per cu.mm. on the ninth day postirradiation). By the thirteenth day these counts had fallen to 100 to 200 per cu.mm. At the time of death, several days later, postmortem examination showed no evidence of marrow regeneration. Although these two animals lived slightly longer than did controls, their deaths were typical of failure of marrow function after irradiation.

**Correlation between degree of marrow recovery and period of survival.**—Repopulation of marrow spaces by transplanted cells was not an all or none phenomenon. It varied in degree in different marrow sites in the same animal. The estimates of marrow cellularity at autopsy given in table 1 are composites of histologic estimates of the per cent of normal cellularity at several sites in each animal.

The longer the dog survived the more cellular was the marrow; or, perhaps, the more cellular the marrow, the longer the dog survived. In six dogs surviving less than 22 days, the average of the estimates of marrow recovery was 27 per cent. In eight dogs surviving 22 to 37 days, the average was 72 per cent. The two dogs surviving 59 and 109 days, respectively, had hyperplastic marrows.

**Hematopoietic recovery in irradiated dogs with marrow transplants.**—Photomicrographs of marrow in dogs with successful transplants are shown in figures 1, 2, 3 and 4. In general the return of cellularity in marrow was slower in dogs than in mice. In dogs with minimal marrow recovery, the marrow elements were seen in small, scattered foci. Often these foci contained 5 to 10 cells of the same type suggesting nests of similar cells derived from the implantation of a single cell or from the recovery of a single survivor. A nest of megakaryocytes is seen in figure 1.

Figure 5 shows the white blood cell counts, and figure 6 the platelet counts in six male dogs that received 800 r and litter-mate marrow (table 1, dogs 3, 4, 5, 6, 7, 8). Maximum depression of leukocyte counts occurred on the seventh to eighth day after irradiation. Platelets reached their lowest levels on the eleventh day. Thereafter recovery was rapid, and normal leukocyte and platelet counts were attained about the fifteenth day. The return of
Fig. 1.—An isolated nest of megakaryocytes in the bone marrow of dog 16 (250 ×).

Fig. 2.—The bone marrow of dog 6. The cellularity of this marrow was estimated to be 50 per cent of normal. A tendency of hematopoietic cells to congregate around bony trabeculae is shown (120 ×).

Fig. 3.—The bone marrow of dog 8. The cellularity of this marrow was estimated to be 75 per cent of normal (120 ×). See figures 7 and 8 to contrast this cellularity with the relative acellularity of the lymph nodes of this animal.

Fig. 4.—The hyperplastic bone marrow of dog 7 (120 ×).

Marrow function in male dogs given female marrow was accomplished by the appearance of leukocytes showing the female sex-chromatin marker in the per cent normal for females,9 figures 5 and 15.

Table 1 lists preterminal white blood cell counts obtained one or two days
Fig. 5.—White blood cell counts in six male dogs (table 1, dogs 3, 4, 5, 6, 7, 8) that received 800 roentgens of whole-body irradiation followed by the intravenous administration of marrow from female litter-mates. The return of marrow function in these male dogs given female marrow was accompanied by the appearance of leukocytes showing the female sex-chromatin marker in the per cent normal for females.

before death. The peripheral leukocyte and platelet counts did not always correlate well with the marrow cellularity observed at autopsy. Several dogs with adequate marrow showed a terminal leukopenia consistent with their viral infections (table 1, dogs 3, 10, 11, 13). Six dogs, however, showed terminal white blood cell counts above 20,000 per cu.mm. The two dogs having the longest survivals developed an extreme leukocytosis. Dog 1 had a white cell count of 68,000 per cu.mm. on the ninety-ninth day, and dog 7 had a count of 54,000 per cu.mm. on the fifty-seventh day. Both animals had very hyperplastic marrows (figure 4).

Differential leukocyte counts on the peripheral blood of twelve normal dogs showed lymphocyte percentages ranging between 10 and 32 per cent (1,000 to 3,500 lymphocytes per cu.mm.). In eight dogs living from 28 to 36 days, differential counts done in the last week of life showed a lymphocyte range of 0 to 4 per cent (0 to 500 per cu.mm.). Dog 7, the only animal with histologic evidence of complete lymph node recovery (figs. 9, 10, 13, 14), showed lymphocyte counts of 5 to 8 per cent (2,200 to 3,800 per cu.mm.).
BONE MARROW HOMOGRAFTS IN DOGS AFTER LETHAL X-RAY

Fig. 6.—Platelet counts in six dogs (table 1, dogs 3, 4, 5, 6, 7, 8) that received 800 röntgens of whole-body irradiation followed by the intravenous administration of litter-mate marrow.

Dog 1 showed lymphocyte counts of 3 per cent on the ninety-ninth day, with an absolute lymphocyte level of 2,052 per cu.mm.

Lymph nodes and spleens in dogs with marrow transplants.—In general, dogs with successful marrow transplants showed little evidence of restoration of cellularity in lymph nodes. The sinusoids were filled with phagocytic cells containing hemosiderin, cellular debris and occasionally large numbers of erythrocytes. Dog 7 showed good lymph node recovery at 59 days, and dog 1 showed partial lymph node recovery at 109 days (see description below). All other dogs showed no evidence of lymph node recovery, regardless of whether or not they had received ACTH. As an example, dog 8 showed marrow recovery at 4 weeks estimated at 75 per cent of normal (fig. 3). Peripheral blood counts were normal. Figures 7 and 8 show a section of a lymph node of this dog. There is a general lack of cellular repopulation. Rare mature lymphocytes and plasma cells are present, but there are no germinal follicles. ACTH had not been given.

Spleens showed occasional aggregates of lymphocytes but no germinal centers. Several contained megakaryocytes. Dog 14 died in 8 days without evidence of marrow recovery. The spleen showed good germinal centers (fig. 11). This dog received only 600 r and no ACTH.

Observations on two dogs that survived for several months.—Dogs 7 and
Fig. 7.—Lymph node of dog 8. There are no lymphoid follicles (40 ×).

Fig. 8.—Higher magnification of the lymph node shown in figure 7 (100 ×).

Fig. 9.—Lymph node of dog 7 showing normal lymphoid follicles (40 ×).

Fig. 10.—Higher magnification of a lymphoid follicle shown in figure 9 (110 ×).

1 (table 1) are of particular interest because of their long periods of survival. Dog 7 received 400 r of whole-body irradiation on each of two successive days, 800 r total. On the third day he was given 1.86 billion cells from a female litter-mate. The success of the graft was attested by a prompt return to the peripheral blood of all three formed elements: leukocytes, platelets and reticulocytes. The female symbols on the leukocyte curve of figure 15
Fig. 11.—Low-power photomicrograph of the spleen of dog 14 showing lymphoid follicles (30 ×).

Fig. 12.—Liver of dog 7 showing irregular areas of necrosis (135 ×).

Fig. 13.—Ileum of dog 7 showing normal mucosa and normal lymphoid follicles (30 ×).

Fig. 14.—Higher magnification of a lymphoid follicle shown in figure 13 (90 ×).

indicate the appearance of leukocytes of female type. Dog 7 was in good health from the fifteenth through the fortieth post-irradiation day (fig. 16). He was active, eating well and gaining weight. He then appeared ill, food intake decreased, ascites developed, and he died on the fifty-ninth day. In the last week of life leukocyte, platelet and reticulocyte counts were elevated.

Postmortem examination showed the bone marrow to be hyperplastic (fig. 4). The liver was enlarged and firm, and an irregular mosaic pattern of yellow and red linear markings was present externally. This pattern extended into the parenchyma. Microscopically the dark red areas were foci of liver degeneration and necrosis without preferential localization to any particular lobular area and without inflammatory response (fig. 12). The cytoplasm
Fig. 15.—White blood cell counts (WBC), reticulocyte counts (retics) and platelet counts on dog 7. This male dog received 800 roentgens of whole-body irradiation followed by the intravenous administration of 1.86 billion nucleated marrow cells from a female litter-mate. The female symbols on the leukocyte curve indicate the appearance of female-type leukocytes.

of surrounding parenchymal cells showed varying degrees of vacuolization and hyaline degeneration. The sinusoids in some areas of degeneration were thrombosed. The liver lesions resembled those of hepatitis contagiosa canis. Inclusion bodies, however, were not identified in the liver or in other organs. It is not known whether the marrow donor in this case had been immunized against hepatitis. The spleen, lymph nodes and intestine showed complete recovery of lymphoid tissue with normal follicles containing germinal centers (figs. 9, 10, 13 and 14). The dog had not received ACTH.

Dog 1 survived for 109 days after receiving 1,200 r and bone marrow. Autopsy revealed a hyperplastic bone marrow. There was a severe, chronic, but also active, bronchitis and bronchiolitis with metaplasia of the mucosa and extension of bronchiolar epithelium into the alveoli. There were foci of active pneumonia as well as organizing pneumonia. Some alveoli were filled with macrophages containing iron pigment and abundant lipid material. Although the bronchiolar changes suggest distemper, inclusion bodies were not found in the lungs or elsewhere.

The exocrine portion of the pancreas of dog 1 was atrophic, and showed an interstitial inflammatory reaction (fig. 18). This process was not seen in other dogs, and there was nothing to indicate its etiology. The spleen had been
removed and although operative injury to the blood supply of the pancreas was considered as a possible causal factor, it was believed very unlikely.

Sections of lymph nodes and intestine of dog 1 showed incomplete regeneration of lymphoid tissue, with aggregates of lymphocytes suggesting follicles. There were no true germinal centers. This dog had received ACTH.

Miscellaneous autopsy findings.—Focal necrosis of the liver was seen in 10 of 21 dogs given marrow. In three of these, typical inclusion bodies of hepatitis contagiosa canis were identified in the liver and other organs. The liver lesions in dog 7 have been described. In six other dogs (1, 3, 4, 15, 21, 22) there were multiple foci of necrosis scattered throughout the liver lobules (fig. 17). The areas were small, comprising 10 to 30 liver cells in various stages of degeneration. Some contained fat, whereas others contained “hyaline” material. Varying degrees of nuclear degeneration and necrosis were also present. Some foci contained an infiltration of polymorphonuclear leukocytes. Bacteria were not identified in the lesions. Focal glomerular changes in the kidney of the type seen in generalized infections were not present.

Attempts to correlate liver lesions with other factors were unsuccessful. All animals with lesions were adults except dog 15. There was no correlation with radiation dose (800 r to 1,200 r), or with period of survival 12 to 109 days. Some dogs with lesions had received ACTH; about half had not. Other drugs administered had also been received by dogs that did not show liver necrosis. Half of the dogs with liver lesions had intrapulmonary hemorrhage, but half did not. Spleens had been removed from three.

The liver lesions somewhat resembled those described by Congdon in seven of 57 mice receiving homologous marrow. But the lesions in the dogs were
smaller and less numerous. The lesions also resembled the focal liver necrosis associated in man with generalized infection, but seen relatively uncommonly in the dog.

Mucosal hemorrhages in the gastrointestinal tract were conspicuous in dogs with generalized hemorrhagic phenomena. Other gastrointestinal lesions were qualitatively similar to those described in other studies. The changes observed were less marked than would be expected from a single dose of radiation of equal size, 800 to 1,200 r). Dog 20 showed ulcerations of the ileum invaded by a yeast, Candida.

**Discussion**

From the above observations it appears reasonable to draw one or two conclusions. First, marrow grafts between closely related beagles, such as litter-mates or mothers and offsprings, are almost always successful following 800 to 1,200 roentgens of total-body irradiation. Further, the successful transplants prevent the acute deaths usually seen at 10 days from marrow failure after this amount of radiation. The period of survival following transplantation is 2 to 10 times greater than that of control animals not given marrow. Moreover, the causes of death in this group are common canine infectious diseases rather than failure of marrow function.

Transplants of marrow between unrelated dogs appear more difficult to achieve than those between related dogs, but they also are possible. One successful graft was obtained in a rather incomplete series of 5 attempts. This report is incomplete in the sense that the effects of splenectomy, administration of ACTH and the dose of marrow may not be properly evaluated.
BONE MARROW HOMOGRAFTS IN DOGS AFTER LETHAL X-RAY

in so limited a study. These measures do not appear of critical importance in securing grafts between litter-mate beagles. Further studies will be required to determine whether these measures are helpful when transplants between less closely related animals are attempted. It is perhaps significant that the one successful graft from an unrelated donor was obtained with the coincidental use of ACTH, a large dose of marrow and splenectomy.

In this study we have used 800 to 1,200 roentgens of total-body irradiation, an amount of radiation that should be well beyond the LD$_{100}$ d. range for dogs. No attempt has been made to define the LD$_{100}$ d. range in this study, but it is assumed from the work of others and from a few preliminary experiments that the LD$_{100}$ d. is around 400 to 600 roentgens.$^{5,4,13}$ The reported unsuccessful attempts to secure marrow homografts in dogs have been associated with radiation at the LD$_{100}$ d. level.$^{2}$ We have stayed away from this range and have increased the dose of irradiation beyond the LD$_{100}$ d. in an attempt to secure adequate depression of immunologic response and a permanent acceptance of the marrow homograft.$^{14}$ By giving the radiation in a series of three daily exposures, the acute toxicity of a single large exposure has been avoided, and by waiting until the third day before administering marrow it may be that time has been allowed for the deterioration of deleterious responses that have been injured but not immediately destroyed.

One of the major problems has been that of keeping the dogs alive after successful marrow transplantation. The graft is successful. It grows female cells in a male recipient, but the host dies. He dies of infectious disease, and he dies usually in a few weeks. At death circulating formed elements and marrow function appear adequate but spleen and lymph nodes show little evidence of return to normal. Their cellularity is markedly subnormal, lymphoid follicles are absent, and the normal architecture is not present. The failure to restore lymphoid structures and resistance to disease may be the result of too much x-ray or of a foreign marrow reaction,$^{14-16}$ or it may be that in the dog, marrow is a poor source of cells of the type needed to repopulate lymph nodes and splenic follicles.$^{17}$ Congdon and co-workers have shown that even in the mouse the repopulation of lymph nodes and spleen is markedly accelerated by the addition of splenic cells to the marrow infusions used to induce recovery after lethal irradiation.$^{18}$ The possibility should be considered that in the dog infusions of marrow effectively restore only marrow. In such case lymphoid cells of the tolerant$^{19}$ fetal type may be necessary to restore lymphoid functions and a normal resistance to endemic infections.$^{20,21}$ We are currently attempting to validate this hypothesis by adding elements of fetal lymphoid tissue to infusions of adult marrow.$^{22,23}$

SUMMARY

Twenty-two dogs (20 males and two females) were uniformly exposed over their entire surfaces to supralethal irradiation: 800 to 1,200 roentgens of 250 kv. x-rays measured in air at mid-body position. On the third day and after the last exposure, these irradiated animals were given infusions of normal bone marrow. The marrow for their infusions was taken from female
litter-mates, from mothers or from unrelated dogs. Evidence for a return of marrow function and for a successful marrow graft was evaluated on the basis of: (1) the reappearance of formed elements: platelets, leukocytes, and reticulocytes, in the peripheral circulation; (2) the appearance in males of leukocytes bearing the sex-chromatin marker of the female donor; (3) prolonged survival, as compared to six irradiated control animals that were not given marrow; and (4) cellularity of marrow spaces and histologic evidence of marrow function at autopsy.

It was found that marrow transplants usually succeeded after 800 to 1,200 roentgens of total-body irradiation when the infused marrow was taken from litter-mate sisters or from mothers (15 successes in 17 attempts). Marrow transplants between unrelated animals appeared more difficult but were not impossible. One success was obtained in five attempts, and this success was achieved with the coincidental use of splenectomy, ACTH and a large dose of marrow.

Dogs with successful transplants lived longer than did control animals; in this series two to 10 times as long. When they died, they died of common canine infectious diseases and not of marrow failure. Distemper, hepatitis and leptospirosis, with or without superimposed bacterial respiratory disease, were the common causes of death.

The lymph nodes and the splenic follicles of irradiated animals had, in most instances, not regained normal histologic appearance at the time of death from these infectious diseases. The working hypothesis is advanced that infusions of marrow repopulate marrow spaces in the canine after irradiation but are poor sources of the type of cell needed to restore lymphoid function and immunologic effectiveness in lymph nodes and spleen.

**SUMMARIO IN INTERLINGUA**

Vinti-duo canes (20 masculos e 2 femininas) recipiva uniformemente super le integre superficie del corpore un dosage supraletal de radiation: 800 a 1,200 roentgens de radios X de 250 kv, mesurate in aire a un position medie-corporal. Le tertie die e post le exposition final, iste animales irradiate recipiva infusiones de medulla ossee normal. Le medulla pro le infusiones esseva prendite ab femininas del mesme lectiera, ab lor matres, o ab canes non consanguinee. Evidentia de un retorno del function del medulla e de sucesso in le graffo del medulla esseva evalutate super le base de (1) le reaparition de elementos formate—plachettas, leucocytos, e reticulocytos—in le circulation peripheric, (2) le apparition in masculos de leucocytos marcate con le chromatina sexual del donator feminin, (3) un superviventia prolongate in comparation con le sex irradiate animales de controlo que non recipiva medulla, e (4) le cellularitate del spacios medullar e, al necropsia, evidentia histologic de medulla functionante.

Il esseva constatate que graffos de medulla es generalmente successose post un dosage de 800 a 1,200 roentgens de irradiation del corpore total quando le medulla infundite es prendite ab sorores del mesme lectiera o ab matres (15 successos in 17 tentativas). Transplantationes de medulla inter animales
non consanguinees esova plus difficile sed non impossibile. Un successo esova obtenite in 5 tentativas. Iste successo esova obtenite con le uso coincidente de splenectomy, ACTH, e un grande dosage de medulla.

Canes con graffos successoses superviveve per periodos plus longe que le animales de controlo. Quando illos moriva, illos moriva del commun morbos infectos canin, e non de fallimento del medulla. Le causas usual del morte esova maladia de Carré, hepatitis e leptospirosis, con o sin un superimponite morbo bacterial respiratori.

Al tempore del morte ab iste morbos le nodos lymphatic e le folliculos splenic del animales irradiate non habeva, in le majoritate del casos, re-attingite lor normal apparentia histologic. Le hypothese tentative es proponite que infusiones de medulla servi a repopular le spatios medullar in le ossos canin post irradiation, sed que illos es povre fontes del typo de cellula que es necessari pro restaurar le function lymphoide e le efficacia immunologic in le nodos lymphatic e in le splen.

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