Marrow Transplants in Lethally Irradiated Dogs
Given Methotrexate

By E. Donnall Thomas, John A. Collins, Emery C. Herman, Jr.
and Joseph W. Ferreee

Dogs exposed to 600 to 1200 r of whole-body radiation usually die in 10
to 12 days of marrow failure. Those exposed to 1200 to 2000 r die somewhat sooner, their deaths being accelerated by the fluid and electrolyte loss
that accompanies damage to intestinal epithelium. Between 1200 and 2000 r
destruction of immunologic defense is sufficient to permit transplantation of
foreign marrow. Below 1200 r, grafts of homologous marrow are rarely accepted, but grafts of autologous marrow succeed quite well.

Irradiated dogs with successful marrow grafts frequently survive the immediate post-radiation period provided their fluid losses are compensated by
replacement therapy. After a convalescence of several weeks or months, long-term survivors appear essentially normal.1 Gastrointestinal function is good,2
blood values are within normal limits, and even fertility may return.3

The satisfactory state of these survivors is a stimulus to renewed efforts to
increase their number. At present, survival with homologous grafts is below
10 per cent, with autologous4 above 90 per cent. In the homologous division, many dogs fail to survive because their grafts of marrow are not entirely successful. Frequently the grafts fail to “take” adequately, or they “take” but are later rejected. Other grafts succeed but their hosts succumb to secondary syndromes: wasting, infections, graft versus host reactions.

Studies in rodents and preliminary experience in dogs1 have suggested that
the antimetabolite Methotrexate may be useful in promoting graft acceptance5,6 and in limiting graft versus host reactions.7 This report describes recent experiences with Methotrexate and homografts of marrow in dogs receiving 1200-1600 r of whole-body radiation.

METHODS

Forty-four dogs are included in this study. Forty-one received marrow infusions following irradiation. Thirty-two dogs were beagles and 12 were mongrels. All were six months to one year of age. All were housed in an isolation kennel8 for at least one month prior to irradiation. Most were not immunized against distemper or hepatitis. Negative antibody titers indicated absence of these viruses from the isolation unit.8 Because of a limited supply of unvaccinated animals, nine dogs previously immunized against hepatitis, distemper and leptospirosis were used, but only after an isolation period of one month. All were de-wormed a week or more prior to radiation.

Radiation was given from dual Co60 sources.9 Target source distances were

From the Mary Imogene Bassett Hospital (affiliated with Columbia University), Cooperstown, N. Y.


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source A and 236 cm. for source B. Dose rates were 4.2 to 4.4 r per minute. Doses are expressed as mid-point air dose. The dogs were irradiated individually in an aluminum cage 40 x 60 x 45 cm. with walls 1.5 mm. thick. They were not anesthetized during radiation.

The first 20 dogs of this series received replacement of fluid and electrolyte losses according to clinical estimate of need. Because five of these dogs died of gastrointestinal complications, it was decided to initiate therapy before dehydration occurred. The remaining dogs received 25 to 75 ml. per kg. of a balanced salt solution* twice daily from the first through the fifth day post-radiation. Only one dog of this group died of gastrointestinal complications.

The recent demonstration of immunologically potent cells in the circulating blood has occasioned concern that these cells may be responsible for some marrow graft failures. Accordingly, in the experiments reported here, an attempt was made to avoid, but not to evaluate, this problem. Under pentobarbital sodium anesthesia and sterile conditions, the jugular vein and carotid artery of the donor dog were cannulated. A vivipерfusion was then carried out by running a balanced salt solution into the vein and removing blood from the artery at the same rate until heart action stopped, usually after an exchange of three to four blood volumes over 10 to 15 minutes. The hemoglobin of the effluent blood was always less than 1.0 Gm. per cent at the end of this procedure.

At the end of perfusion, and under sterile conditions, marrow was removed from the femori, humeri, sternum, ribs, vertebral bodies and iliac crests. The marrow was suspended in aliquots of TC-199† containing 20 per cent autologous serum. The marrow was then passed through stainless steel screens of 300 and 200 μ square and given intravenously to one or more recipients. The usual time from death of donor until administration to recipient was two hours. Yields varied from 7.2 x 10⁶ to 45 x 10⁹ nucleated marrow cells, the average being 20.3 x 10⁹. Marrow was infused on the first day post-radiation. Two dogs (396, 397) received marrow on the third day after radiation.

In dogs that received twice the lethal dose of radiation, rapid recovery of hematopoietic function following infusion of homologous marrow indicated a successful graft. In 19 instances the use of female donors and male recipients permitted positive indication of successful engraftment by the subsequent appearance of female leukocytes in the circulating blood. In three cases, production of red cells of donor type was also observed.

The radiated animals were given penicillin, 500,000 U., and streptomycin, 0.25 Gm., subcutaneously twice daily from the fifth day following radiation until the white blood cell count returned to 5,000 per cu.mm., usually a period of less than 10 days.

Complete autopsies with histologic studies were performed on all dogs. Peripheral blood counts were performed not less than three times per week. Platelet counts were done by the method of Brecher and Cronkite.

**RESULTS**

The question of whether or not transplantation of infused marrow is successful is often difficult to answer. At these levels of irradiation (1200 to 1600 r), the white blood cell count invariably falls to values of 100 to 300 per cu.mm. by the fifth or sixth day (fig. 1). In those dogs receiving marrow, there is a rapid return of the polymorphonuclear white blood cell count to normal values by approximately the 15th day with the platelet count lagging behind by a few days. In some dogs the peripheral counts are normal for the remainder of the dog’s life, donor red cells or leukocytes (female to male) can be identified.

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*Ionosol C-CM (Abbott Laboratories) Na⁺ 138 mEq./L., K⁺ 12 mEq./L., Ca⁺⁺ 5 mEq./L., Mg⁺⁺ 3 mEq./L., Cl⁻ 108 mEq./L., Lactate 50 mEq./L.
†TC-199 Difco Laboratories, Detroit, Mich.
and the marrow is cellular at autopsy. It is obvious that a successful transplant has occurred. In other dogs, the rise in white blood cell count after the sixth day is not permanent. After periods ranging from eight days to 30 days, the count may begin to fall (fig. 2). Once this fall starts it usually continues, and the dog dies with an aplastic marrow. Dogs whose white blood cell counts have returned to values above 1000 per cu.mm. with a subsequent decline have been classified as a "graft rejection". Almost all dogs receiving marrow have shown some rise in white blood cell count after the sixth day. However, in the dogs described as having "no take" of the transplanted marrow, the white blood cell count has not gone above 1000 per cu.mm. The usual range is 500 to 800 cells per cu.mm. A differential count at this time demonstrates 20 to 80 per cent polymorphonuclear leukocytes. It is not possible to say whether this transient cell production is due to a temporary "take" of the transplant with a rather immediate rejection, or whether these cells are produced by maturation of the infused marrow cells without a true proliferation of stem cells.

Group I—Dogs that lived less than 8 days: Seven dogs receiving 1525 to
Fig. 2.—White blood cell count and Methotrexate administration in three irradiated litter-mate dogs with marrow grafts from the same donor. Two rejected the marrow graft, but Dog 392 was living and well 220 days after radiation.

1566 r followed by homologous marrow in doses of 9.3 to 24.0 \times 10^9 nucleated cells died in seven days or less (table 1). This interval is too short to allow evaluation of a successful "take" of the marrow hemograft. Deaths in this interval usually indicate a fatal complication other than bone marrow failure. Five dogs in this group received marrow on the first day post-radiation. They were not given prophylactic fluid therapy. All five died of gastrointestinal complications. Two dogs received marrow on the third day post-radiation. They died of pneumonia due to \textit{B. bronchiseptica}.

\textbf{Group II—Dogs that lived more than 8 days and received no Methotrexate:} 
Six dogs in this group received 1530 to 1566 r followed by marrow infusions of 1.5 to 16.1 \times 10^9 nucleated cells (table 2). Four dogs did not get marrow "takes." Two of these had received less than three billion cells. One dog got a "take" of the infused marrow, but rejection began on the 10th day, and the dog died on the 14th day. One dog (341) received 16 billion marrow cells, had an excellent "take," but died on the 21st day of pneumonia (fig. 3). The average survival in the group was 15 days.

\textbf{Group III—Dogs that received 5 mg. of Methotrexate every other day for 10 days:} Five mg. of Methotrexate every other day for 10 days (total 25 mg.) produced signs of toxicity in our dogs: lethargy, anorexia and weight loss. However, no dog has died as a result of this treatment. Accordingly, an at-
temp was made to evaluate the effects of this dose schedule when initiated at various times after radiation and marrow transplantation.

Data on fifteen dogs are given in table 3. One control dog that did not receive marrow is included. Treatment with Methotrexate was initiated from three to 14 days after radiation exposure and continued for 10 days, unless death occurred sooner.

Dog 340 was started on Methotrexate 11 days after radiation. A good marrow “take” was evident by the 7th day post-radiation (fig. 4). The customary fever occurred in the second week. Appetite was lost while the drug was administered, but there was no adverse effect on the white blood cell count or the platelet count. The dog was in good condition throughout the first two months post-radiation. In the third month weight loss occurred and progressed except during a two week period when the dog was given Lipomul* intravenously. Death with “secondary syndrome,” inanition and infection, occurred on the 116th day post-radiation.

Three litter-mates (392, 389 and 388) received aliquots of marrow from the same donor (fig. 2). Their course of Methotrexate was started on the sixth day post-radiation. All had good marrow “takes.” Two began to reject their marrow grafts after Methotrexate was discontinued and died shortly thereafter. The third dog (392) is living and well 229 days post-radiation.

In the group of 15, the four dogs that did not get a marrow “take” lived an average of 14 days. The 11 dogs that did get a marrow “take” lived an average of 60 days, and two are still living.

**Group IV—Dogs that received 1 mg. doses of Methotrexate for prolonged**
periods: Observations were made on a group of dogs that received a slightly lower dose of radiation combined with a longer course of Methotrexate administration (table 3). Eleven dogs were given 1 mg. of Methotrexate three times per week starting before or shortly after radiation and continuing for one to two months. Two received 1500 r and nine received 1200 r. White blood cell counts are shown in figure 5.

Five dogs died 36 to 40 days after radiation. Three rejected the marrow graft and showed a progressive decline in white cell and platelet counts prior to death. Two died of intercurrent infection with normal white blood cell counts.

Four dogs survived beyond three months. Three of these are still living. Two are in good health and appear to have weathered the period of "secondary syndromes." The third has evidence of pancreatic insufficiency.2

Figure 1 shows the white blood cell counts of two dogs given 1250 r. Dog 401 received 15.5 billion nucleated marrow cells from an unrelated donor on the day following radiation. Dog 407 received no marrow. Dog 401 is living and well 201 days after radiation. Dog 407 died in 13 days.

General Observations

Figure 6 shows the marrow dose, marrow "take" and duration of survival for all dogs that lived more than one week. Five of 10 dogs given less than
MARROW TRANSPLANTS IN IRRADIATED DOGS

Table 3.—Dogs Receiving Five Mg. of Methotrexate Every Other Day for Ten Days

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Weight (kg.)</th>
<th>Radiation Dose (r)</th>
<th>Marrow Dose (Mg.)</th>
<th>Methotrexate (day started)</th>
<th>Marrow Take</th>
<th>Marrow Reaction</th>
<th>Day of Rejection</th>
<th>Survival (days)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>335</td>
<td>9.1</td>
<td>1584</td>
<td>14.4</td>
<td>14</td>
<td>no</td>
<td>—</td>
<td>—</td>
<td>18</td>
<td>Hemorrhage &amp; infection</td>
</tr>
<tr>
<td>340</td>
<td>7.7</td>
<td>1565</td>
<td>15.8</td>
<td>11</td>
<td>yes</td>
<td>no</td>
<td>116</td>
<td>116</td>
<td>Terminal jaundice</td>
</tr>
<tr>
<td>356</td>
<td>7.5</td>
<td>1534</td>
<td>3.1</td>
<td>11</td>
<td>yes</td>
<td>no</td>
<td>49</td>
<td>49</td>
<td>Fungus infection</td>
</tr>
<tr>
<td>348</td>
<td>9.5</td>
<td>1566</td>
<td>14.4</td>
<td>9</td>
<td>yes</td>
<td>yes</td>
<td>9</td>
<td>16</td>
<td>Gram-neg. septicemia</td>
</tr>
<tr>
<td>349</td>
<td>10.0</td>
<td>1566</td>
<td>2.8</td>
<td>9</td>
<td>no</td>
<td>—</td>
<td>14</td>
<td>14</td>
<td>Gram-neg. septicemia</td>
</tr>
<tr>
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<td>1510</td>
<td>21.0</td>
<td>9</td>
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<td>no</td>
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<td>41</td>
<td>Pneumonia (B. bronchisepticus)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver necrosis</td>
</tr>
<tr>
<td>385</td>
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<td>1525</td>
<td>0.4</td>
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<td>no</td>
<td>—</td>
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<td>13</td>
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</tr>
<tr>
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<td>1561</td>
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<td>9</td>
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<td>yes</td>
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<td>23</td>
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<td>1536</td>
<td>4.2</td>
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<td>—</td>
<td>13</td>
<td>13</td>
<td>Hemorrhage</td>
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<td>392</td>
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<td>1530</td>
<td>9.9</td>
<td>6</td>
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<td>229*</td>
<td>229*</td>
<td>Gram-neg. septicemia</td>
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<tr>
<td>388</td>
<td>12.5</td>
<td>1525</td>
<td>9.9</td>
<td>6</td>
<td>yes</td>
<td>yes</td>
<td>23</td>
<td>23</td>
<td>Gram-neg. septicemia</td>
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<td>398</td>
<td>7.7</td>
<td>1561</td>
<td>9.4</td>
<td>5</td>
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<td>no</td>
<td>27</td>
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<td>Pneumonia</td>
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<td>22.3</td>
<td>3</td>
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<td>18</td>
<td>18</td>
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<td>14.2</td>
<td>1506</td>
<td>24.3</td>
<td>3</td>
<td>yes</td>
<td>no</td>
<td>22</td>
<td>22</td>
<td>Gram-neg. septicemia</td>
</tr>
<tr>
<td>387</td>
<td>12.5</td>
<td>1515</td>
<td>Control</td>
<td>8</td>
<td>—</td>
<td>—</td>
<td>12</td>
<td>12</td>
<td>Hemorrhage</td>
</tr>
</tbody>
</table>

*Living.

five billion nucleated marrow cells had “takes.” Of these, none lived beyond 49 days. Seventeen of 21 dogs given nine billion or more marrow cells had “takes.” Seven lived beyond 90 days. Despite the scatter of points it is evident that the likelihood of a successful marrow graft increases with increasing amount of marrow administered. Ten billion cells appear to be a minimum dose for consistent results.

Four irradiated dogs with transplants of homologous marrow developed jaundice in the last day or two of their lives while dying of infections. Two of these dogs (393, 394) died of B. bronchisepticus pneumonia. Acute liver necrosis was found at autopsy. One dog (356) died with a generalized infection of Candida parapsilosis. Autopsy disclosed bile stasis caused apparently by yeast infection in duodenal wall and papilla of Vater. Two dogs (340, 406) died of mixed infections with gram negative organisms. Focal liver necrosis was found at their autopsies, but only dog 340 showed jaundice. Jaundice has been reported as a complication of the period of secondary syndromes. We have not been able to recognize liver disease as a specific manifestation of graft versus host reaction.

Anemia (hemoglobin below 10 Gm. per cent) not associated with external bleeding occurred in but one animal in this study (Dog 468). The marrow infusion in this instance totaled only 1.6 billion cells. The white blood cell count did not rise above 5000, and platelets did not rise above 100,000. Ashby counts had shown a rise in erythrocytes of donor type until the 16th day post-radiation and then a fall. Failure of adequate marrow implantation appears a likely cause of the anemia observed.
It was anticipated that Methotrexate, as an antimetabolite and marrow depressing drug, would interfere with the active growth necessary for repopulation of the marrow by the infused marrow cells. This was found not to be the case. For example, rapid marrow regeneration was observed in three dogs (fig. 2) started on a moderately toxic dose of Methotrexate on the sixth day post-radiation (fifth day after marrow administration) and in two dogs started on the third day (table 3).

**Discussion**

Early studies in this laboratory on whole-body irradiation and marrow transplantation in the dog were complicated by a high incidence of canine distemper and hepatitis. These diseases were observed in dogs with marrow homografts despite proper prior immunization of both donors and recipients, presumably because of the inadequate immune response associated with graft versus host reactions. The use of healthy dogs and the provision of a kennel permitting effective isolation has eliminated the problem of viral disease. The problem of susceptibility to infection in these animals remains. Studies are continuing directed at control of bacteria and fungi and improvement in general hygiene.
Table 4.—Dogs Receiving One Mg. of Methotrexate Three Times Per Week Before or Near Time of Radiation *(Days Before Radiation Indicated by −, After Radiation by + )*

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Weight Kg.</th>
<th>Radiation Dose (r)</th>
<th>Marrow Dose (x10³)</th>
<th>Methotrexate Day started</th>
<th>Marrow Day stopped</th>
<th>Marrow Take</th>
<th>Marrow Rejection</th>
<th>Day of Rejection</th>
<th>Survival (days)</th>
<th>Cause of Death</th>
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<td>1275</td>
<td>9.9</td>
<td>−35</td>
<td>+65</td>
<td>yes</td>
<td>no</td>
<td>−</td>
<td>99</td>
<td>Gram neg. septicemia</td>
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<td>446*</td>
<td>6.7</td>
<td>1518</td>
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<td>−5</td>
<td>+48</td>
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<td>no</td>
<td>−</td>
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<tr>
<td>441</td>
<td>8.6</td>
<td>1515</td>
<td>control</td>
<td>−4</td>
<td>+8</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>10</td>
<td>Hemorrhage and infection</td>
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<td>+35</td>
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<td>no</td>
<td>−</td>
<td>39</td>
<td>Weight loss, gram-neg. septicemia, focal liver necrosis</td>
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<td>1260</td>
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<td>no</td>
<td>−</td>
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<tr>
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<td>control</td>
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<td>−</td>
<td>−</td>
<td>−</td>
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<td>yes</td>
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<td>1251</td>
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<td>+11</td>
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<td>−</td>
<td>−</td>
<td>13</td>
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<td>−</td>
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<td>—</td>
<td>—</td>
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<td>1551</td>
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<td>no</td>
<td>—</td>
<td>27</td>
<td>Liver necrosis and pneumonia <em>(B. bronchisepticus)</em></td>
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</tr>
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*Living.
†Methotrexate dose was 2.5 mg.
‡Methotrexate dose was 5.0 mg.
Fig. 5.—White blood cell counts in 11 dogs that received 1.0 mg. of Methotrexate three times a week before or at the time of radiation and for one to two months after radiation. Death of seven animals is indicated by a cross.

The series reported here is too small to permit final conclusions regarding the usefulness of Methotrexate in securing and maintaining satisfactory transplants of foreign marrow in irradiated dogs. A larger series with standardized and improved supportive treatment, using infusions of marrow containing more than 10 billion cells, is in progress. The preliminary efforts described demonstrate a high incidence of satisfactory “takes,” a low incidence of rejections, and an encouraging number of long-term survivors among the animals given the drug.

SUMMARY

This report describes 41 dogs that received 1200–1600 r of whole body irradiation followed by infusions of homologous marrow. The clinical and hematologic events in these animals are described.

Five dogs given Methotrexate following irradiation lived beyond four months and appeared to have survived the period of secondary syndromes.

SUMMARIO IN INTERLINGUA

Iste reporto describe 41 canes que recipeva 1200 a 1600 r de irradiation del corpore integre, sequite per infusiones de medulla homologe. Le evenimentos clinic e hematologic in iste animales es describite.

Cinque canes, tractate con Methotrexato post irradiation, viveva plus que quatro menses e pare haber supervivite al periodo del syndromes secundari.
MARROW TRANSPLANTS IN IRRADIATED DOGS

Fig. 6.—Marrow dose and duration of survival in all dogs living beyond seven days. ⊙ indicates that the dog is living.

ADDENDUM

Dogs 401, 446, 392 and 384 are still living and well 80 days beyond the period indicated in the table. Dog 451 was sacrificed on the 124th post-irradiation day to serve as a marrow donor in another experiment.

ACKNOWLEDGMENT

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