BIOLOGICAL EFFECTS OF RADIATION FROM SIMULATED ^{238}Pu POWER SOURCES IN DOGS

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MASTER

Biological effects of radiation from simulated ^{238}Pu power sources are being studied using the Labrador Retriever as the experimental animal. The simulated sources consist of a combination of ^{252}Cf (to provide the neutron component of a 30 watt ^{238}Pu source) and ^{90}Sr - ^{90}Y Bremsstrahlung (to provide the additional photon flux needed). Sources are placed in the center of a spherical stainless steel capsule (333 ml volume) and the capsule is implanted in the left paralumbar fossa between the internal and external abdominal oblique muscles. Sources have been implanted which deliver 1, 5, 15, or 70 times the radiation dose expected from a 30 watt ^{238}Pu power source, and dose rates to various organs from these sources have been measured and calculated. A total of forty-eight dogs have been implanted to date. The maximum total accumulated dose in a single dog has been 37,000 Rad at 1 cm from the surface of the implantation capsule.

Clinical evaluation of implanted dogs has revealed no alterations in any of the parameters measured except for a decreased total circulating lymphocyte count and a cessation of sperm production in the 70X animals.

Six of the forty-eight animals have been killed (2-70X, 2-15X, and 2-blanks). Post-mortem examination has revealed a complete cessation of spermatogenesis and a striking reduction in lymphocyte population of the spleen and mesenteric lymph nodes in the 70X animals. Similar, though less severe lesions have been seen in 15X dogs. In addition, one 70X dog developed a mast cell sarcoma at the implant site and the 15X and 70X dogs killed after one year showed a reduction in numbers of megakaryocytes and erythropoietic elements of the bone marrow in the vicinity of the implant.

These preliminary results indicate that mammalian organisms may be able to tolerate the radiation dose incident with the use of ^{238}Pu power sources for major cardiac assist devices.

INTRODUCTION

Over the past few years, considerable attention has been focused on the feasibility of using a radioisotope fueled power source for circulatory

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support systems. A number of radionuclides have been considered as possible fuels; however, it is now felt that ^{238}Pu is probably the isotope of choice for such applications.¹ Current concepts regarding the use of nuclear energy sources to power such systems include estimates that approximately a 30-50 watt plutonium-238 source might be necessary to provide sufficient power over about a ten-year period of useful life. One of the major questions concerning the eventual use of such devices in the human population regards the possible radiation hazard from such sources. We are currently investigating the biological effects of radiation from nuclear power sources which might be used to power an artificial heart.

MATERIALS AND METHODS

A. Animal Model

Large dogs were selected as the animal to be used in this study. In an attempt to reduce variability purebred Labrador Retriever dogs are being used; these animals weigh approximately 30-40 kg when mature and are hence roughly one-third to one-half the size of a standard man. Since mature human beings would be the most likely candidates for implantation of such devices all animals have been allowed to mature to at least one year of age before being introduced into the study.

A spherical stainless steel capsule, 333 ml in volume, has been used as the basic implantation device. The sphere is hollow and contains a small central cavity, accessible by a screw plug, for the placement of radiation sources. A stainless steel cap is cemented over the threaded plug after placement of sources in the central cavity. The unit is then covered with medical grade silicone rubber (Silastic Medical Adhesive Type A) and sterilized under ethylene oxide before implantation.

Since it is the concensus that the most likely site for implantation

of a power source in the human being would be the abdominal cavity, an abdominal site has been chosen for our studies. A pocket between the internal and external oblique muscle in the left paralumbar fossa is used for placement of the implantation capsule. A radiograph of a loaded implantation device in place in the left flank of a Labrador Retriever is shown (Figure 1).

B. Radiation Source

Because of the undesirable heat associated with the use of a ^{238}Pu source a mock source has been devised which provides the same radiation characteristics as plutonium, but has no accompanying heat. The radiations of biological concern from ^{238}Pu are photons and neutrons.² The composite source consists of ^{252}Cf to provide the neutron component and ^{90}Sr , ^{90}Y Bremsstrahlung sources to spike the photon flux of the ^{252}Cf up to that of ^{238}Pu .

In order to obtain some information as to the radiation levels needed to produce effects, and yet not to make the number of animals included in the project excessively large, sources that produce the same radiation flux as would be expected from a 30 watt ^{238}Pu source (nominal, or 1 X sources) as well as sources which produce five times the radiation level that would be expected from such a source (5 X sources) have been used. In addition, some animals have been implanted with either 15X or 70X sources.

The dose rates from the various source configurations used in this study have been measured and/or calculated using data from studies in water phantoms and Labrador Retriever cadavers and compared with data from dosimetry studies of ^{238}Pu sources.³ A comparison of the dose rates from our source configurations with that of a 30 watt plutonium source is shown (Table 1). It can be seen that the dose from a nominal composite source is almost identical to that of the equivalent plutonium source. Dose rates to various organs and surfaces from a 70 X source are also given (Table 2).

C. Experimental Protocol

Animals have been implanted in four groups of twelve dogs each. Each group consists of four large source dogs, four small source dogs, and four blanks consisting of dogs implanted with capsules containing no radiation sources. A summary of the four groups implanted to date is shown (Table 3). At least one more group of dogs has yet to be implanted.

A number of physiological parameters have been routinely monitored on all dogs used in this study in order to maximize the probability of detecting any changes in function which might occur as the result of the radiation involved. Every dog used in the project has been submitted to a battery of clinical tests repeatedly before implantation so that a statistical evaluation of his normal range can be made. The same tests are then run periodically on each dog after implantation. Any alterations can be compared to the normal values obtained in the particular animal before implantation as well as to the population normal. A list of the routinely monitored parameters with the colony normals for each is shown (Table 4).

When killed, all animals, experimentals and controls, are subjected to an extensive postmortem examination. The examination consists of three phases: (a) gross inspection of organs and tissues; (b) histological examination of all lesions observed during gross necropsy (in addition to specifically radiosensitive organs and tissues regardless of gross appearance); (c) radiographic examination of the entire skeleton.

RESULTS

A total of forty-eight dogs have been implanted to date (Table 3). Group I dogs were implanted in October and November 1969, Group II in September and October 1970, Group III in December 1970 and January 1971, and Group IV in June and July 1971. The anticipated kill dates for these animals are also shown (Table 3). However actual kill dates may be changed depending upon

clinical results observed.

Results of clinical testing of animals in the study have indicated changes in only two of the parameters under surveillance. Both of these changes have occurred only in the large source dogs of Group I i.e. 70 X animals. Beginning about 2-3 months after implantation, total lymphocyte counts were observed to decrease from the preimplantation normal of about 2000 per cubic millimeter of blood. The decrease continued over the next year until the lymphocyte count had fallen to approximately 50% of the control value, where it has remained since that time. Secondly, examination of semen collected beyond three months after implantation from the male 70 X animals revealed a virtual absence of spermatozoa in the ejaculate. No consistent change from the normal has been observed in any of the other animals at this time.

Of the forty-eight animals implanted to date only six have been killed. The six animals killed comprise half of Group I animals i.e. two 70 X animals (1 after three months and 1 at one year after implantation), two 15 X animals (1 after four months and 1 at one year after implantation), and two blanks (both at one year after implantation).

Post mortem examination of these animals was performed as outlined. One of the most striking lesions was seen in the lymphoid tissue. There were severe reductions in the lymphocyte populations of the white pulp of the spleen in the 70 X animals. Similarly there were reduced populations of small and medium lymphocytes in the mesenteric lymph nodes of the two 70 X animals and in the 15 X dog killed after one year. In these animals there was an almost total ablation of the germinal centers of the lymph nodes.

All four of the irradiated male dogs had gonadal lesions. These consisted of altered cell populations within seminiferous tubules, with morphologic evidence of reduction and qualitative change in spermatogenic sequences. In

three dogs there appeared to be graded sub-normal levels of spermatogenesis while in one animal (a 70 X dog killed after 1 year) there was a complete cessation of spermatogenesis. In addition, an intratubular seminoma was found in the testes of one 15 X dog. Since this lesion occurs quite frequently in the dog its presence cannot be interpreted as a radiation effect.

In the two blank and two 15 X animals, the implantation capsule was surrounded by a thin capsule of dense fibrous connective tissue 0.5 - 1 mm thick with an incomplete inner lining of mesothelioid cells. On the outer surface of the fibrous capsules was a loose meshwork of areolar tissue which suspended the device between the muscle layers. Tissues immediately adjacent to the capsule seemed quite normal in all respects. The connective tissue layer surrounding the implantation capsule in the 70 X dog killed after three months was intensely reactive; this was interpreted as due to chronic infection since a fistula had developed in this dog shortly before it was terminated.

The implantation site of the 70 X dog killed after one year was also intensely reactive. The inferior aspect of the connective tissue capsule was distorted by a large spherical nodule (approximately 5 cm in diameter) which proved histologically to be a mast cell sarcoma. The nodule was intimately adherent to the capsule, but the overlying skin was not attached. In addition to the nodule, much of the tissue capsule was infiltrated with nests of anaplastic mast cells, and a metastasis was present in the ipsilateral lumbar lymph node.

Technically satisfactory marrow specimens were available from the four dogs killed after one year. The 15 X and 70 X dogs showed an altered cell population characterized by a reduction in megakaryocytes and erythropoietic elements and an apparent predominance of large, relatively immature, and undifferentiated cells. These changes occurred on the marrow of bones

immediately adjacent to the implantation capsule.

DISCUSSION

Assuming a mid-abdominal dose of roughly 300 mrad/hr (extrapolated from Table 2), the mesenteric lymph nodes and spleen probably received a dose of about 630 rads in three months which was sufficient to cause the decreased population of lymphocytes and atrophy of lymphoid germinal centers seen in the 70X dog killed at this time. Such changes were also seen after one year or 2400 rad but were not significantly greater in severity at this time than at three months. Similar, though less severe lesions were seen in the 15 X animals.

The testicular lesion amounted to almost complete cessation of spermatogenesis in the 70 X animal killed at three months after implantation and complete aspermatogenesis in the 70 X dog killed after one year. The total dose to the testes during three months was 140 rads while after one year the total accumulated dose was 570 rads assuming a dose rate of 65 mrad per hour. Such changes would probably be expected from such a dose at a daily dose rate of approximately 1.5 rads.⁴

Of great interest is the mast cell tumor found in association with the connective tissue capsule in the 70 X dog killed at one year. This region (within 1 cm of the implant surface) received a total dose in the neighborhood of 18,000 rad during the year of implantation. It is true that mast cell tumors occur frequently in dogs, and it might be argued that the occurrence of the tumor in this animal is fortuitous. However, the tumor did show some unusual characteristics, specifically: 1) mast cell tumors are rare in the Labrador Retriever⁵; 2) spontaneous mast cell tumors arise almost without exception in the dermis, or deep layers of the skin, while the tumor in question had no association with the skin; 3) the tumor metastasized and this occurs only rarely in cases of spontaneous mast cell tumor; and 4) the

tumor arose at the site of maximum radiation dose. Because of these special features it is felt that this tumor may be an example of radiation carcinogenesis; however, no definite conclusions can be made on the basis of this one case.

The decreased level of erythropoietic elements and megakaryocytes in the marrow of the lumbar vertebrae immediately adjacent to the capsule was caused by a dose of approximately 170 rads in the 15 X dog and 750 rads in the 70 X dog killed after one year.

Only one other group has conducted studies similar to the one in progress at our laboratory.^{6,7,8} Their results to date are very similar to the results reported here. However, they have detected fewer pathological changes than seen in the current study. This is probably due to the fact that their sources are in the probable range of 1 X to 5 X and pathological data are given for animals killed after two years. Based on our results, two years may be too short a time period for the accumulation of sufficient dose for distinct biological effects from sources in this dose rate range.

Results obtained to date from this study, though preliminary, are encouraging. It should be emphasized that all clinical and pathological changes seen have been in 15 X or 70 X animals. No functional changes have been discerned in 1 X or 5 X animals. It is true that the 15 X and 70 X animals have been implanted for a longer period of time than any of the other dogs and have accumulated a much larger total dose. However, clinical changes were seen in the high dose rate animals at a much earlier time (3 months) than in the lower dose animals some of which have now been implanted for one and one-half years. Because of the relatively low dose rate in the 1 X and 5 X animals, long term studies i.e. five to ten years will probably be necessary in order to detect possible subtle changes such as life-shortening and shortening of incidence times for various tumors.⁹

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TABLE 1

Dose Rate in Tissue (H_2O) from Simulated Sources Implanted in Labrador Retriever Dogs Compared to Estimated Dose Rate from 30 Watt Plutonium-238 Source (Electro-refined metal) under Similar Conditions

Source Contents	Total Dose Rate (mrads/hr) at Given Distance from Surface of Capsule (cm)			Factor above Nominal
	<u>1</u>	<u>5</u>	<u>10</u>	
0.373 μ g Cf 500 mCi Sr	1991	602	225	72
0.0745 μ g Cf 100 mCi Sr	398	120	45	14.4
0.373 μ g Cf 30 mCi Sr	158.4	46.5	16.7	5.7
0.0745 μ g Cf 6 mCi Sr	27.6	8.1	2.9	1
^{238}Pu 30 Watt	28.2	8.6	3.2	

TABLE 2

Approximate Dose Rates to Various Sites and Surfaces
 from a 500 mCi ^{90}Sr Bremsstrahlung Source and a
 0.373 μg ^{252}Cf Source in an Implantation Capsule

<u>Site</u>	<u>Distance to surface of capsule (cm)</u>	<u>mrads/hr</u>
Internal:		
descending colon	3	1123
spleen	6	470
liver	19	60
(L) iliac plexus	5	592
(R) iliac plexus	15	225
cecum	16	194
(R) kidney	17	194
Surface:		
(L) flank, over capsule	0.5	1532
(R) flank	16	112
lower dorsum	15	88
mid abdomen	7	225
anterior testis (front)	15	90
posterior testis (rear)	18	42
(L) popliteal space	15	28
(R) popliteal space	21	36
(L) eye	67	1.7
(R) eye	68	2.1
thyroid	51	27
(L) costal	24	35
(R) costal	27	18
sternum	27	22
upper dorsum	27	12

TABLE 3

Total Accumulated Dose at 1 cm from Surface of Capsule in Labrador
Retriever Dogs Implanted with Simulated 30 watt ^{233}Pu Power Sources

Group #	Sources (X nominal)	No. of Dogs	Implant Year	Accumulated Dose at 1 cm from Surface (Rads)	Kill Year
I	70X	4	1969	37,300	?
	15X	4	1969	7,450	?
	Blanks	4	1969	-	?
II	5X	4	1970	1,820	1972
	1X	4	1970	350	1972
	Blanks	4	1970	-	1972
III	5X	4	1970	1,365	1975
	1X	4	1970	260	1975
	Blanks	4	1971	-	1975
IV	5X	4	1971	680	1974
	1X	4	1971	130	1974
	Blanks	4	1971	-	1974

TABLE 4

Physiological Parameters Monitored in Labrador
Retriever Colony

<u>Parameter</u>	<u>Normal Value</u>	<u>Units</u>	<u>S.D.</u>
Blood studies			
Total WBC	12863	per mm ³	1791
Packed cell volume	43	%	3.3
Differential WBC			
Bands	0.2	%	0.3
Segmenters	62	%	5.6
Lymphocytes	25	%	3.7
Monocytes	7	%	1.1
Eosinophils	6	%	4.0
Serum Electrolytes			
Sodium	173.7	meq/L	10.5
Potassium	7.1	meq/L	0.8
Calcium	11.0	mg %	0.6
Serum Proteins			
Total protein	6.4	gms %	0.6
A/G ratio	1.50	-	0.26
Serum Enzymes			
SGOT	42	S-F U/ml	13.5
SGPT	46	S-F U/ml	18.6
Serum Lipase	0.4	S-T U/ml	0.2
Prothrombin Time	9.8	seconds	0.8
Blood Sugar	82	mg %	9.0
Blood Urea Nitrogen	18	mg %	2.0
Serum Creatinine	0.94	mg %	0.17
Sperm Count	302.000	per mm ³	197357

FIGURE 1

Radiograph of stainless steel implantation capsule, with contained ^{252}Cf and ^{90}Sr sources, in place in the left paralumbar fossa of a Labrador Retriever dog.