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RADIOBIOLOGICAL EFFECTS OF ^{110}In VERSUS ^{111}In IN RAT TESTIS

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ABSTRACT

Induction of radiobiological effects after intratesticular (IT) injection of ^{110}In-oxine or ^{111}In-oxine in Wistar rats were evaluated in the present report. These two radionuclides were chosen because of their different energy deposition patterns. ^{110}In is almost a pure β emitter with no Auger electron emission, whereas ^{111}In emits conversion electrons and Auger electrons. The retention of ^{111}In activity in the testis was measured with a scintillation camera and ^{110}In with a collimated HpGe detector. Measurements were performed immediately after IT injection and repeated over several half-lives. Time-activity curves were generated for each animal and these were used for absorbed dose calculations. The resulting D_{37} values for spermhead survival were approximately 1.9 Gy for ^{110}In-oxine, and 2.2 Gy for ^{111}In-oxine.

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INTRODUCTION

Various radionuclides decay by electron capture and/or internal conversion. These events are followed by cascades of Auger and Coster-Kronig electrons. Such cascades involve emission of numerous low-energy electrons, which are of very short range. If these radionuclides are incorporated into the cell nucleus, the short-range electrons locally deposit their energy causing high absorbed doses in the proximity to the DNA (2-4).

The rationale for utilizing mammalian testis as an *in vivo* model to study the effects of these radionuclides is the extreme radiosensitivity of the spermatogonial cells compared to other testicular cells (5-7). Rao *et al.* (8-13) have, in various reports, evaluated the radiobiological effects of Auger electron emitters in the mouse testis. A similar model has been established by our group in rat testis (14). The rodent testis model seems appropriate for further investigation of basic phenomenon (such as geometry, intracellular biokinetics and heterogeneity of radioactivity) crucial for understanding the biological effects of Auger electron emitters (14).

A straightforward way of assessing the radiobiological effects of Auger emitters is to compare their effects with radionuclides of the same element having various energy deposition patterns. Our project consequently aims to use the indium isotopes: ^{110}In, ^{111}In, ^{113m}In, ^{114m}In and ^{115m}In. Indium radioisotopes are of great interest in diagnostic and therapeutic nuclear medicine. In the present report we compare the radiobiological effects induced by intratesticularly (IT) injected ^{110}In-oxine and ^{111}In-oxine.

Earlier, electron microscopy studies of our group indicate that intravenously injected indium radiopharmaceuticals localize in the cell nuclei of the testicular cells (15). Similarly, cell fractionation studies show that the fraction of IT injected indium activity found within the cell nuclei was about 60% 6-24 h post-injection (14). Because ^{111}In has a half-life of 2.8 d it has sufficient time to become intracellularly incorporated and therefore the short-ranged Auger electrons (Table I) should exert the major influence on spermatogonial cell killing. Conversely IT-injected ^{110}In, an almost pure β emitter with a half-life of only 69 min (Tables I,II), mostly decays outside the nucleus.

TABLE I

Absorbed Energy from ^{110}In in Rat Testis

Radiation	Energy (MeV)	Yield per decay	ϕ	E_{emit} (MeV)	E_{abs} (MeV)	% E_{tot}
γ_1	0.511	1.23	0.12	0.6285	0.00774	1.2645
γ_2	0.6577	0.978	0.12	0.6432	0.0079	1.2942
γ_3	0.8153	0.0028	0.12	0.0023	0.000028	0.00455
γ_4	0.818	0.0079	0.012	0.00648	0.000078	0.01274
γ_{11}	1.126	0.0102	0.011	0.01149	0.000132	0.02154
γ_{13}	1.236	0.0026	0.012	0.003263	0.000038	0.006131
γ_{16}	1.421	0.0042	0.011	0.005982	0.000065	0.0107
γ_{17}	1.476	0.0047	0.011	0.006922	0.000075	0.01227
γ_{19}	1.103	0.0013	0.011	0.002036	0.000022	0.003544
γ_{23}	1.698	0.0027	0.011	0.004653	0.000049	0.007987
γ_{25}	1.783	0.0028	0.01	0.005064	0.000053	0.008584
γ_{26}	1.975	0.0015	0.01	0.002903	0.000029	0.00478
γ_{27}	2.003	0.0013	0.01	0.002544	0.000025	0.004156
γ_{29}	2.129	0.0213	0.01	0.04535	0.000446	0.07290
γ_{30}	2.211	0.0176	0.01	0.03891	0.000378	0.06174
γ_{31}	2.318	0.0131	0.01	0.03037	0.000029	0.04736
γ_{32}	2.2421	0.0054	0.009	0.01302	0.000122	0.01997
γ_{33}	2.444	0.003	0.009	0.007405	0.000069	0.01131
γ_{34}	2.536	0.0024	0.009	0.00596	0.000055	0.00897
γ_{36}	2.746	0.0009	0.009	0.002337	0.000021	0.003391
γ_{37}	2.787	0.0009	0.009	0.002425	0.000021	0.003486
γ_{38}	2.808	0.0055	0.009	0.01539	0.000135	0.02212
γ_{39}	2.818	0.0006	0.009	0.001818	0.000016	0.002584
γ_{41}	2.975	0.0014	0.009	0.004046	0.000035	0.005685
γ_{42}	3.044	0.0013	0.009	0.003988	0.000034	0.005538
γ_{43}	3.078	0.003	0.009	0.009326	0.000079	0.01295
γ_{48}	3.475	0.0065	0.008	0.002241	0.000188	0.03076
γ_{49}	3.597	0.0013	0.008	0.004496	0.000037	0.006098
γ_{50}	3.772	0.0007	0.008	0.002508	0.000021	0.003361
$K_{\alpha 1}$	0.02317	0.15	0.112	0.003476	0.000388	0.06333
$K_{\alpha 2}$	0.02298	0.08	0.114	0.001838	0.000209	0.03410
β_5^+	0.5056	0.0024	1.0	0.001203	0.001203	0.1966
$\beta_{8,9}^+$	0.6426	0.0038	1.0	0.002435	0.002435	0.3979
β_{10}^+	1.015	0.609	0.95	0.6181	0.5872	95.94
$CK_{1,2}$	0.631	0.0027	1.0	0.001678	0.001678	0.2742
A-KLL	0.01917	0.0359	1.0	0.000688	0.000688	0.1124

Energy and yield data taken from Refs. 17-18.

ϕ = absorbed fraction

$\%E_{tot}$ = percent of the total energy absorbed in the rat testis.

E_{emit} = Yield X Energy

$E_{abs} = \phi E_{emit}$

TABLE II
Breakdown of Absorbed Energy in Rat Testis from ^{110}In and ^{111}In

	% of Total Energy Absorbed in the Testis	
Radiation	^{110}In	^{111}In
Photons, X rays	3.1	55.4
β particles	96.5	-
Conversion Electrons	0.3	35.5
Auger Electron	0.1	9.1

By employing radioactive isotopes of the same element (indium), labeled to the same compound (oxine), this model should be able to distinguish between the biological effects of different types of radiation with different energy deposition patterns. In this study, the radiobiological effects of IT injected ^{110}In and ^{111}In were investigated and compared with external X irradiation of the rat testis.

MATERIALS AND METHODS

Animals

Adult male Wistar rats of 7-8 weeks age, weighing 200-250 g, were used (M llegaard Breeding Center Ltd., Denmark). The animals had free access to commercial pellet food and tap water. They were kept under controlled light (12 h light and 12 h darkness) and constant temperature (22°C). Light ether anesthesia was employed during the invasive procedures, *i.e.* IT injections. The rats were maintained in groups of three.

Production of ^{110}In

^{110}In, not commercially available, was cyclotron produced at the Svedberg Laboratory, Uppsala, Sweden. The mother radionuclide ^{110}Sn ($T_{1/2}$ = 4.15 h) is produced by the reaction In (p,xn) ^{110}Sn which has a maximum cross-section of 110 mb at approximately 70 MeV and a practical

yield of 400 MBq/μA-h (16). The ^{110}In produced was eluted in 0.5 ml fractions with 0.05 N HCl. Impurities produced during irradiation of the In target were separated from ^{110}In by the ion exchange column in the generator. The radioimpurity ^{111}Sn ($T_{1/2}$ = 35 min) which decays to ^{111}In ($T_{1/2}$ = 2.81 d) was avoided by waiting 4-5 h between the end of the bombardment and preparation of the generator. Gamma spectroscopy with an HpGe detector was performed to assure radionuclide purity.

Rat Testis Model

Details regarding the evaluation of the rat testis model, as well as the procedures for intratesticular injection of ^{111}In and testicular X ray irradiation, have previously been described in detail (14) and are only briefly described below. The minimum time necessary for spermatogonial cells to become spermheads has been established to be 7 wk after exposure to ^{111}In-oxine and X rays. Hence, the minimum spermhead count is observed at this time and therefore all spermhead counts were performed 7 wk after the injection of radionuclides or exposure to external irradiation.

The study design is presented in Table III. Seven series were analyzed. All rats were sacrificed and assayed at the 7th wk post-injection. Series 1 and 2 were IT injected with ^{110}In-oxine and ^{111}In-oxine, respectively. The testes of the rats in series 7 were exposed to external X rays (250 kVp). Four series served as controls, *viz.* series 3 (decayed ^{110}In-oxine), series 4 (oxine IT), series 5 (NaCl IT), and series 6 (sham irradiated).

Intratesticular Injections

A series of 12 rats were IT injected with an ^{110}In-oxine activity concentration of 0.02-0.34 MBq/μl (series 1). These results were compared with a previous investigation of 25 animals IT injected with ^{111}In-oxine activity concentrations of 0.17-1.58 MBq/μl (series 2) (14). The injection technique was as follows: A small incision was made distally in the scrotum, and the testis was manipulated to the opening and partly externalized during the injection. The incision was sutured after injection. All radiolabeled and unlabeled compounds were injected centrally into the testis in a volume of 1 X 10 μl or 2 X 10 μl using a microsyringe equipped with a newly grinded 27 gauge (diameter 0.41 mm) needle. During the injection, the syringe was drawn backwards to form an initial "line source" of the injected

radionuclides. The volume injected was approximately 1% of the rat testis mass (1.4 g).

TABLE III
Rat Testis Study Design[a]

Series	Absorbed Dose (Gy)	No. of Animals[b]
1. ^{110}In-oxine, IT[c]	0.15 - 2.6	12
2. ^{111}In-oxine, IT[c]	0.4 - 7.7	25
3. Decayed ^{110}In-oxine, IT[c]	-	4
4. Oxine, IT[c]	-	2
5. NaCl, IT[c]	-	7
6. Sham-irradiated	-	5
7. X ray, 250 kVp	0.48-9.45	28

[a]Series 2 & 4-7 are described in detail elsewhere (14).
[b]All the animals sacrificed the 7th week after exposure, when the minimum number of spermheads is attained.
[c]IT=Intratesticular injection.

External Irradiation with 250 kVp X rays

Local external testicular X ray irradiation was performed with a commercial X ray unit (Siemens, 250 kVp, HVL 2.59 mm Cu) with a dose rate of 0.46 Gy/min. To assure only irradiation of the scrotum, a field of 28 X 38 mm^2 was applied (14). The 28 animals irradiated received a testis dose between 0.48 and 9.45 Gy (series 7). These animals, as well as a series of sham irradiated controls (series 6), were sacrificed after 7 wk.

Production of ^{110}In-oxine

^{110}In has a half-life of 69.1 min and decays to stable cadmium. The mother nuclide ^{110}Sn (in the ^{110}Sn/^{110}In generator) decays to ^{110}In with a half-life of 4.15 h (17,18). As indicated in Fig. 1 and Table I, ^{110}In decays mainly by

β^+ (61%) with an average energy of 1 MeV. Photons of 658 keV (98%) and 511 keV (123%) are also emitted.

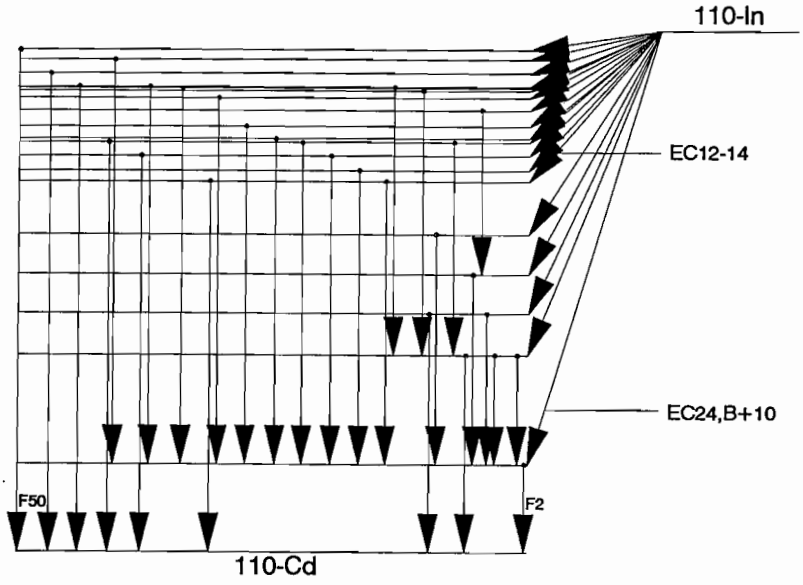

FIG. 1. Decay scheme for ^{110}In (half-life = 69.1 min). Main transition lines are indicated (β^+10 - 61%, EC24 - 27%, EC12-14 - 6%). Transitions with probabilities less than 1% are not indicated in the figure.

Absorbed Energy in the Rat Testes from ^{110}In

Table II gives the main contributions to the absorbed dose to the rat testes. The organ is assumed to have a mass of 1.438 g, a shape averaged of 1:2:4 ellipsoid and sphere, and uniform distribution of ^{110}In.

Labeling Procedure and Quality Control for ^{110}In-oxine

The procedures in Ref. 1 were employed. ^{110}In was eluted from the generator as a chloride solution in 0.05 N HCl. The activity was eluted in 0.5 ml fractions, which were separately measured for activity content. Fractions containing the main part of the activity were pooled in a polypropylene centrifuge tube (15 ml). The chloride solution was neutralized with an appropriate volume of 0.1 N NaOH. A buffer of 0.3 N sodium acetate,

pH 5.5, was added (0.2 ml) to the solution and mixed. A volume of 50 µl of oxine dissolved in ethanol, with a concentration of 1 mg/ml, was added and mixed. The labeled ^{110}In-oxine is lipophilic, while unlabeled ^{110}In chloride is not. By adding chloroform and mixing it well, the labeled part may be extracted in the chloroform. The chloroform phase was transferred to a new tube and evaporated to dryness. The ^{110}In-oxine was dissolved in ethanol, measured for activity, and evaporated to a quarter of the desired final volume. Physiological saline was added to form a 25% ethanol solution. Activity concentrations of 19-335 MBq/ml were thus achieved. The fraction of ^{110}In not labeled to oxine was negligible.

Retention of ^{110}In-oxine in Rat Testis

Because we have previously demonstrated a great variability of the indium elimination from the rat testis (14), the retention of ^{110}In in the testis for each animal was measured with a collimated HpGe detector. After IT injection, the slightly anesthetized animal was placed in a horizontal Perspex tube and the root of the tail fixed in a slot. After adjustment of the front end of the tube, the animal was unable to move. The animal was placed 2 m away from the detector. Apart from the testes, the rat was collimated with a 40 mm thick lead shield. ^{110}In emits high energy photons (658 keV) which are faintly attenuated in the animal. Repeated measurements were performed without anesthesia. Between the measurements, the animal was free to move in its cage. The fraction of injected radioactivity retained in the testis was followed over a period of up to eight hours post-injection. Using efficiency calibrations for the detector geometry, the activity in the testis was calculated. After correction for physical decay of the nuclide, the biological retention of activity was calculated.

Retention of ^{111}In-oxine in Rat Testis

The radiopharmaceutical employed was ^{111}In-oxine ($T_{1/2}$ = 2.8 d) (Mallinckrodt Diagnostica, Peten, Holland) dissolved in sodium chloride with a specific activity of 1.58 MBq/µl (30 mCi/ml) (14). A stock solution of 8-hydroxyquinoline (Sigma Chemical Co., St. Louis, MO) for the control (series 4) was prepared in the same manner.

The retention of ^{111}In in each testis for each animal was measured with a scintillation camera (Maxi Camera I, General Electric, equipped with a medium energy parallel hole collimator). The retention of ^{111}In in the testis

was followed by performing 2 min accumulations to obtain images during the early hours after the IT injection, and then regularly (1-4 times per day) up to 13 days. For each animal, a region of interest (ROI) was selected over the scrotum, and the area was corrected for the background and the dead-time of the detector. The activity content in each testis could then be calculated employing a calibration constant of 194 s^{-1} MBq^{-1}. Time-activity curves were generated for each testis. The biological clearance for all the testes in all the animals are plotted during the time interval used for the absorbed dose assessment. An enlarged plot for the first 6 h is given in Fig. 3.

Determination of Spermhead Count

The spermhead count was performed according to the technique introduced by Meistrich *et al.* (5) and further elaborated by Rao *et al.* (8). The elongated nuclei of late spermatids of the mouse and rat are resistant to sonication, whereas spermatogonial and other cells in testicular homogenates are disrupted. Consequently, the method is appropriate for isolation and counting of spermheads. After the animal was sacrificed, both the testes were removed, weighed, homogenized (Ultra-Turrax TP18/2) in 10 ml deionized water for 20 s, and sonicated for 60 s (Ultrasonicator 4712-2, 40W, Cole-Parmer Instrument Co., Chicago). The spermheads from each testis were counted (200-500) in a hemocytometer (Bürker chamber) using a phase contrast microscope. The term "relative spermhead survival" implies a quotient between the number of spermheads exposed to radiation and the corresponding series of controls, *viz.* ^{110}In-oxine/decayed ^{110}In-oxine; ^{111}In-oxine/oxine; and X ray 250 kVp/the sham irradiated group, respectively.

Activity Distribution in the Testis

The distribution of the activity in the testis after the IT injection was checked with autoradiographic techniques. Briefly, after IT injection the testes were embedded in carboxymethyl cellulose, frozen and sectioned with a microtome (14). The freeze-dried sections containing radioactivity were placed on X ray film to produce autoradiographic grains. To investigate the influence on the distribution of the injected volume, controls were made with a staining agent. Fifteen minutes after IT injection of 10 µl, 20 µl, or 50 µl of Evans Blue, testes were dissected and frozen. After sectioning, photographs were taken.

RESULTS

Biokinetics of the Radiochemicals

The rat testicular time-activity curves for ^{110}In-oxine demonstrated a biological elimination of almost 10% within the first hour after IT injection (Fig. 2), but subsequently the clearance became much slower. After 4-5 h post-IT injection, almost 90% of the activity was retained in the testis with almost negligible elimination. These results were further confirmed by measuring alternatively the testes and the rest of the animal with the collimated HpGe detector. Less than 10% of the IT injected activity was found in the rest of the body during the time of investigation.

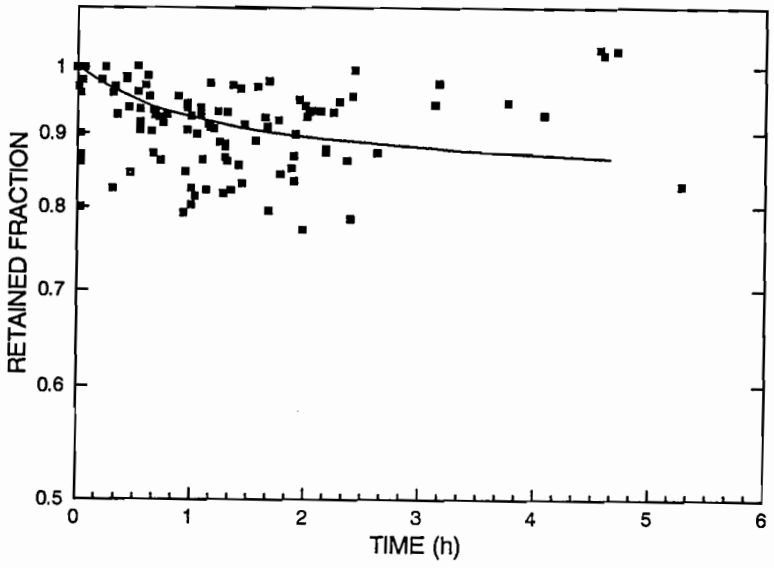

FIG. 2. Biological elimination during the first 6 h after intratesticular injection of ^{110}In-oxine. Activity is corrected for physical decay.

The retention of ^{111}In-oxine activity in the testes for each animal was measured up to 34 times throughout the time used for assessment of the absorbed dose to the testis (Fig. 3). The decrease of activity was rapid during

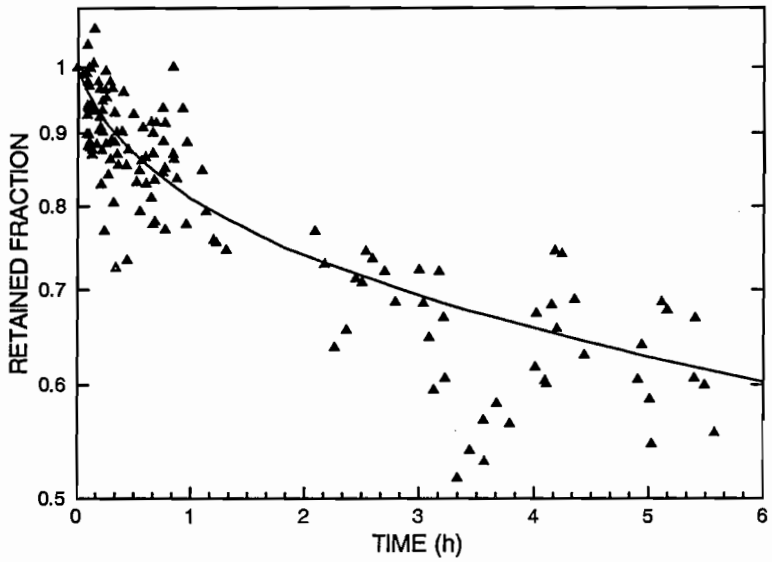

FIG. 3. Biological elimination during the first 6 h after an intratesticular injection of ^{111}In-oxine. Activity is corrected for physical decay.

the first 6 h, but became much slower. At the end of the time interval for the absorbed dose calculation (13 d), the retention was approximately 50%.

Activity Distribution in the Rat Testes

As can be seen in Fig. 4a, the activity is heterogeneously distributed. The distribution of Evans Blue is similar to the autoradiograph (Fig. 4a) at low injection volumes (Fig. 4b), but becomes more homogeneous the larger the injected volume (Figs. 4b-d).

Radiobiological Effects: Spermhead Survival

The spermhead count in the controls, series 3 (decayed ^{110}In-oxine), series 4 (oxine) , series 5 (NaCl) and series 6 (sham irradiated) showed 279, 294, 281 and 264 million per testis respectively, which revealed no significant difference. The relative spermhead survival count assessed at the 7th wk post-exposure, as a function of absorbed dose to the testis subsequent to local external irradiation or IT injection of the radiochemical, showed (Figs. 5-7) a

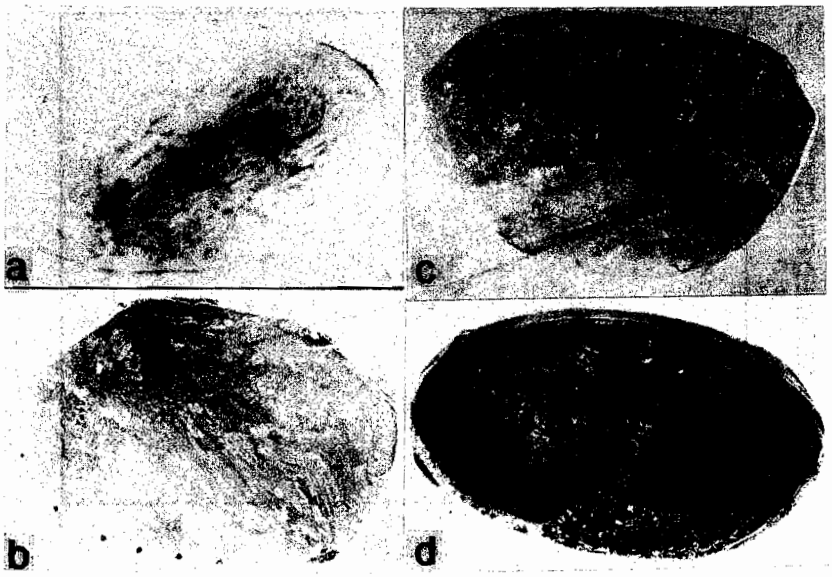

FIG. 4. a) Activity distribution in the testis, 30 min post-injection of 10 µl ^{111}In-oxine. Distribution of Evans Blue in rat testis 15 min after IT injection of b) 10 µl, c) 20 µl, and d) 50 µl.

dose dependent response curve. The relative spermhead survival for all the series exposed to ^{110}In-oxine, ^{111}In-oxine and the X ray irradiation showed a two-component exponential decline. Based on these curves, the D_{37} (*i.e.* the absorbed dose, where 37% of the initial number of spermheads remained) was established. Analyses of the survival data gave a D_{37} of approximately 1.9 Gy for ^{110}In-oxine, 2.2 Gy for ^{111}In-oxine, and 1.2 Gy for 250 kVp X rays. In addition, the decrease in relative testis weight showed a dose related response curve with corresponding D_{37} values of 5.8 Gy, 5.3 Gy and 6.5 Gy, respectively.

DISCUSSION

In the mouse testis model, Rao *et al.* (8-10,12) have established the radiobiological effects of low-energy electron emitting radionuclides. Besides measuring the spermatogonial survival, Rao *et al.* (11,13) also have examined other radiobiological models in the mouse, *e.g.* measuring spermhead abnormalities (13) and oogenesis (11). The results of all three radiobiological

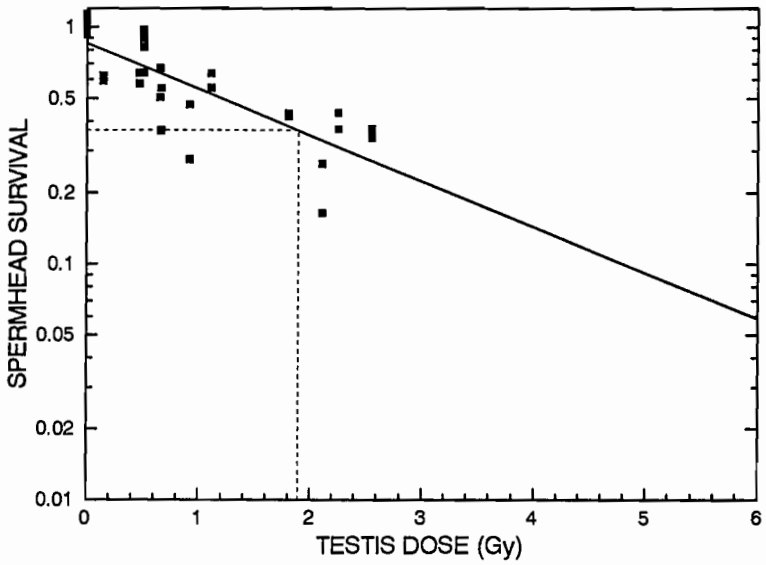

FIG. 5. Relative spermhead count as a function of absorbed dose to rat testis from intratesticularly injected ^{110}In-oxine.

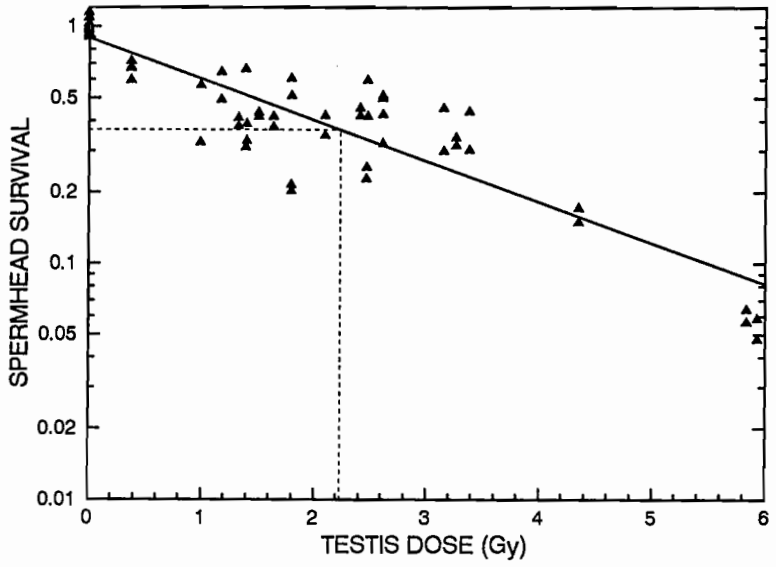

FIG. 6. Relative spermhead count as a function of absorbed dose to rat testis from intratesticularly injected ^{111}In-oxine.

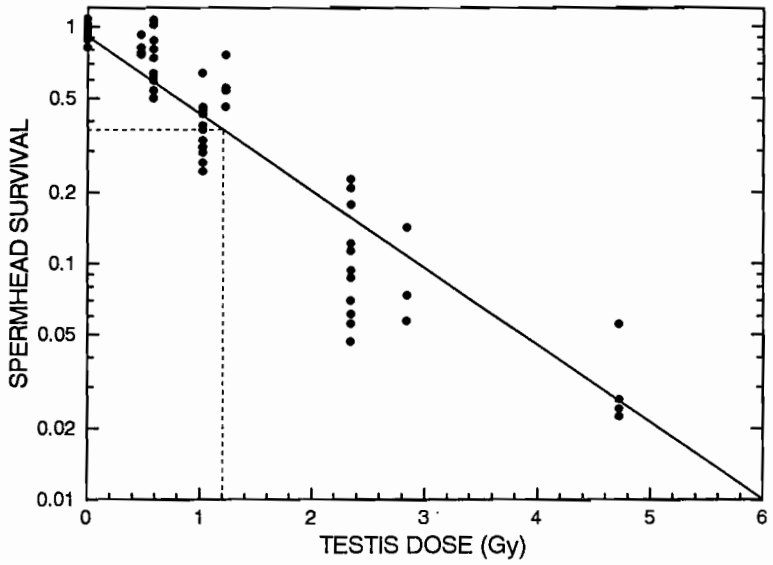

FIG. 7. Relative spermhead count as a function of absorbed dose to testis subsequent to local external irradiation with 250 kVp X rays.

models have been consistent with each other. The investigations have shown great differences in D_{37} values between the various radiopharmaceuticals employed.

By employing two different radioactive isotopes of the same element *viz.* ^{110}In and ^{111}In, labeled to the same chemical (oxine), the rat testis model might discern the biological effects of different types of radiation with different patterns of energy deposition. In all of our experiments, the spermhead survival showed a dose-dependent response curve. The data also suggests that spermhead survival is a much more sensitive radiobiological model than decrease of the testis weight.

The absorbed energy distribution in the testis from the relatively high-energy charged particle radiation of ^{110}In is much more homogeneous than that of ^{111}In which only exposes the region in close proximity to the injection channel (14). Although only a minor part of the testis was exposed to ^{111}In, the biological effect was almost equivalent to the effect of ^{110}In. This is

perhaps due to the nonuniform distribution of the radiochemicals in the testis (Fig. 4a) which only results in local irradiation of the testis along the line injection for ^{111}In. Whereas the energetic β particles emitted by ^{110}In irradiate the testis somewhat uniformly. In that event, the biological effects of the ^{111}In Auger electrons may have been underestimated in spite of similar experimental results for both radionuclides. The Evans Blue stain studies with different injection volumes (Figs. 4b-d) suggest that an injection volume of 50 µl would provide a more uniform distribution of radioactivity in the rat testis. This injection volume for the rat testis (1.4 g in weight) would be more consistent with the 3 µl injection for the mouse testis (0.1 g in weight) used by Rao *et al.* (8-10). Although our present studies involve only a 10 µl injection volume, our future studies will employ 50 µl volumes. This technique should provide better delineation between the radiobiological effects of Auger and β emitters and also help establish reliable RBE values compared to external X ray values.

It should also be pointed out that, in contrast to the mouse testis (10), a large fraction (55.4%) of the energy deposited in the rat testis by ^{111}In is from photons and X rays. This low-LET component, in conjunction with the conversion electron component (35.5%), may contribute to masking the high-LET type effects of the Auger electrons observed by others (10).

Finally, we believe that the larger rat testis model might be a useful supplement to the more radiosensitive, but smaller, mouse testis model for scrutinizing different patterns of energy deposition by incorporated radionuclides.

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