

Radiation Damage to Mouse Testis Cells from [^{99m}Tc] Pertechnetate

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The radiation dose and the biologic damage to mouse testis from intravenously administered [^{99m}Tc] pertechnetate were studied. The dose was measured for penetrating and nonpenetrating radiations from Tc-99m, using calibrated thermoluminescent dosimeters and calculations from the uptake of the nuclide in the testis, and was found to be 4.9 rads per mCi of Tc-99m. The biologic damage was measured by the decrease in the number of sperm heads in the testis, counted both by hemacytometer and by Coulter counter. In preliminary experiments using external gamma radiation from Cs-137, the number of sperm heads reached a minimum 29 days after irradiation. Twenty-nine days after injection of 5.8 mCi of Tc-99m, which gives 28 rads to the testis, the number of sperm heads decreased to 70% of control. The biologic effect corresponds to that seen after 40 rads of gamma radiation from Cs-137. The damage to mouse testis cells from internally administered Tc-99m as measured in an in vivo system appears to be at least as significant as that from external gamma irradiation, if not more so.

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As the use of radioactivity in diagnostic and therapeutic procedures increases, there is growing concern about the radiation doses to the gonads produced by internally administered radiopharmaceuticals. It is known that some of the spermatogenic cells of the testis are extremely radiosensitive (1). In addition, the only cells transmitting their mutations to future generations are the germinal cells of the gonad. Therefore, the study of the radiation effects on the testes is extremely important. Because of difficulties involved in measuring the gonadal dose in man, we have approached the problem by studying the mouse because of its availability as an experimental animal and because the effects of radiation on spermatogenesis are best characterized in this species. We have used one radiopharmaceutical, [^{99m}Tc] pertechnetate, which is widely used in nuclear medicine procedures, but we intend to extend this work to other radio-labeled compounds. We have quantitatively measured

the total radiation dose to the testis from this intravenously administered radionuclide, and the radiation damage to the spermatogonia.

MATERIALS AND METHODS

Radiopharmaceuticals. [^{99m}Tc] sodium pertechnetate was obtained as a sterile, pyrogen-free isotonic sodium chloride solution, pH 7.0.

Mice. The animals used, C₃Hf/Bu mice, were 7-11 wk old at the time of irradiation, with an average weight of 30 g. They were killed either by electrocution (dosimetry studies) or by cervical dislocation (biologic studies).

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Concentration of pertechnetate in the testes. We injected 100 μ Ci of sodium pertechnetate in a volume of 0.3 ml into the tail vein of each mouse. The animals were killed at 30 min or 6 hr and the testes were placed in counting vials containing 1 ml of concentrated nitric acid. The total administered activity was measured by comparison with an aliquot of the injection solution.

Another set of experiments was performed with higher activities. The 30-min and 6-hr points were repeated as above and also by injecting 5 mCi Tc-99m per mouse.

In-vivo dosimetry of penetrating radiations from [^{99m}Tc] pertechnetate. Thermoluminescent dosimeters (TLD) used to measure the penetrating radiations of Tc-99m were glass-encapsulated LiF (TLD-100) powder. These dosimeters were 12 mm in length, diameter 1.4 mm. The glass was 0.2 mm thick, which is sufficient to exclude the nonpenetrating radiation.

Dosimeter response was measured after boiling for 5 min, using a TLD reader†. The following is the calibration equation relating dosimeter response, TL, to dose: Rads = (TL + 0.02392)/0.0678.

Two methods were used for implantation of the TLDs. In both, the mice were anesthetized with pentobarbital. In the first group of 12 mice, a 2-cm incision was made in the scrotal area so that the TLD could be inserted within the tunica vaginalis, the membrane that encloses the testis, and the skin was closed by stitching. This procedure failed to restrain the implanted TLDs, and only 4 of the 12 dosimeters were found inside the tunica vaginalis 24 hr after implantation. A different implanting procedure was therefore used for a second group of eight mice. With this group, TLDs were placed just under the skin in the scrotal area.

Two hours after implantation, pertechnetate was injected into the tail veins of both groups of mice. The activity of Tc-99m was measured using a well-chamber radionuclide calibrator with a stated accuracy of $\pm 10\%$. Corrections were made for any activity remaining in the syringe after injection.

Twenty-four hours after implantation of the dosimeters, the mice were killed, the dosimeters removed and read, and the radiation dose calculated.

External irradiation with Cs-137. Mouse testes were locally irradiated using a Cs-137 source. During irradiation each mouse was restrained in a small plexiglass box to ensure proper placement of the testes in the field. Dose rates of 200 rads/min and 38 rads/min were used (accuracy $\pm 3\%$).

Sperm-head counts. The number of sperm heads [i.e., nuclei of elongated spermatids in steps 12–16 of development (2)] in the testes was determined

by counting in a hemacytometer or by Coulter counting. Testes, with the tunica albuginea intact unless otherwise stated, were weighed and then homogenized in 4 ml of deionized water using a Polytron homogenizer. For Coulter counting, 1 ml of 5% Triton X-100 was added to solubilize debris further. The sample was then sonicated for 60 sec, as described previously (2), to disintegrate all cells and organelles except for the elongated spermatid nuclei. When Coulter counting was performed, the suspension was filtered through an HC 10 Nitex nylon screen with a 10- μ m mesh opening.

In earlier experiments the tunica albuginea was removed before weighing to avoid adding debris from the tunica. A small but variable number of testis cells, however, were removed with the tunica albuginea. In later experiments, therefore, the tunica was not removed.

The concentration of sperm heads was determined in a hemacytometer viewed under a phase-contrast microscope. Four Coulter counting, duplicate 20-fold dilutions in Isoton were made with each sample. The instrument was provided with an aperture 50 μ m in diam \times 60 μ m long, and a Channelyzer II‡. The area under the sperm-head peak was integrated electronically on the Channelyzer. The range of integration spread from seven channels below to 15 channels above the distribution peak. This method maximizes the counting of sperm heads in the included channels and excludes most background caused by debris.

RESULTS

Tc-99m concentration in the testis. Uptake studies for pertechnetate were performed. The percent of injected activity per gram of testis at different

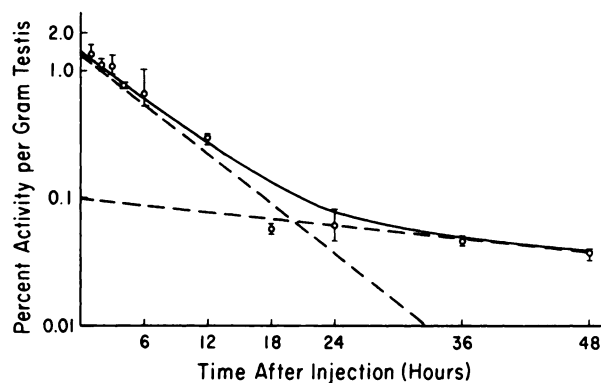


FIG. 1. Percent of injected activity per gram of mouse testis after intravenous [^{99m}Tc] pertechnetate. For each point, corrections for physical decay have been made. Each point shows mean and range for between three and ten mice. Data points were fitted by two exponential components having slopes corresponding to biologic half-times of about 5 and 32 hr.

TABLE 1. CONCENTRATION OF ^{99m}Tc PERTECHNETATE IN MOUSE TESTIS AFTER INJECTION OF HIGH AND LOW AMOUNTS OF ACTIVITY (PERCENT ACTIVITY PER GRAM TESTIS \pm S.E.)

Time after injection	High activity (3.6–5.6 mCi)	Low activity (0.05–0.20 mCi)
30 min	1.37 \pm 0.04 (8)*	1.35 \pm 0.03 (10)*
6 hr	0.58 \pm 0.03 (7)*	0.67 \pm 0.07 (6)*

* Number of mice used is given in parentheses.

times after injection was calculated (Fig. 1). The maximum activity occurs at about 10 min after injection and is 1.43% per gram of testis.

The percent uptake of the nuclide at the dose level planned for future experiments was measured to see if there were any differences in uptake at higher activities (Table 1). None was found.

Dose to testes from radiations of ^{99m}Tc pertechnetate. The dose to the testes from penetrating radiations was measured by thermoluminescent dosimeters and the rad/mCi ratio was calculated for each mouse. For the four Group 1 mice in which the TLD remained inside the tunica vaginalis, the average rad/mCi was 2.67 ± 0.06 s.e. For the second group, in which the TLD was implanted under the scrotal skin, the average rad/mCi ratio was 2.10 ± 0.05 s.e. The average figure for the first group was 27% higher than for the second group because the TLDs were located more internally in the first group. The 2.67 rad/mCi value was used in dose calculations as the TLD was closer to the testes in Group 1.

The dose from nonpenetrating pertechnetate radiations was calculated from the uptake data and based on the methods developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (3). The dose was calculated as follows: $D = A \Sigma \Delta_1 \phi_1 / m$, where D is the average absorbed dose (rads), A is the cumulated activity ($\mu\text{Ci-hr}$), Δ_1 is the equilibrium absorbed-dose constant (gram-rad/ $\mu\text{Ci-hr}$), ϕ_1 is the absorbed fraction, and m is the mass of the target organ (g). The cumulated activity was determined from the data of Fig. 1 to be $10.0 \mu\text{Ci-hr/mCi}$ of injected Tc-99m. The $\Sigma \Delta_1 \phi_1$ for nonpenetrating radiations was 0.0362 (4) and the average mass of two mouse testes was 0.161 g. We thereby obtain a value of 2.25 rads/mCi for the dose to the testes from nonpenetrating radiations.

The total dose to a mouse's testes from 1 mCi administered activity is therefore 4.92 rads.

Sperm-head count in testis as a function of time after irradiation. In order to determine the time after

irradiation when the number of sperm reaches a minimum, mice were killed at different times after receiving 80 rads of radiation from Cs-137 (Fig. 2). Testis weights declined to a minimum of 68% of control then increased slowly. The sperm-head count was more sensitive and reached a minimum level of only 20% of control at 29 days after irradiation. The recovery was still incomplete at the 45th day.

This kinetic study was performed using only one dose of radiation. The kinetics of spermatogenesis, however, are not altered by radiation doses of 100 rads (5,6). Therefore, the minimum sperm-head count should occur at 29 days independent of radiation dose.

Sperm-head count as a function of gamma radiation. The response of the testis to Cs-137 radiation was investigated by giving different doses and measuring sperm-head counts and the testis weights 29 days after radiation (Table 2). The relative testis weights, and number of sperm heads as a function of control values for the two experiments, were averaged and are plotted in Fig. 3. No consistent changes in testis weight were observed with doses up to 20 rads. At 40 rads there was a consistent decline in testis weight, and at 60 and 80 rads the decline was clearly significant. Statistically significant declines in sperm-head count were routinely observed at doses of 20 rads and above. By hemacytometer counting, the dose corresponding to 50% survival (LD_{50}) is 53 rads.

There are differences between the data obtained by hemacytometer and Coulter counting. The precision of the Coulter is greater, though the values tend to be consistently higher because of the background (debris) count. The amount of debris is

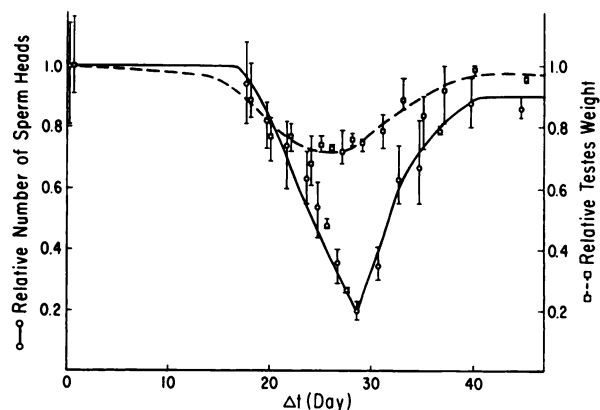


FIG. 2. Relative numbers of sperm heads obtained from testis (lower curve) and testis weights (upper curve) at various times after irradiation of testis with 80 rads of gamma radiation from Cs-137. At various times, three irradiated and three control mice were killed. Each point shows mean (as a fraction of control) and range.

TABLE 2. MEAN TESTIS WEIGHTS AND SPERM-HEAD COUNTS, 29 DAYS AFTER IRRADIATION, IN CONTROL AND Cs-137-IRRADIATED MICE AT DIFFERENT DOSES*

Experiment A. Tunica albuginea removed				
Dose (rads)	No. of mice	Testis weight (mg) (Mean \pm s.e.)	Sperm heads $\times 10^{-6}$	Sperm heads $\times 10^{-6}$
			2 testes Coulter counter (Mean \pm s.e.)	2 testes hemocytometer (Mean \pm s.e.)
0	15	131 \pm 4	23.3 \pm 1.3	29.3 \pm 0.6
5	9	145 \pm 9	23.7 \pm 0.3	25.9 \pm 1.7†
10	9	149 \pm 11†	23.8 \pm 0.4	30.3 \pm 2.5
20	9	142 \pm 18	20.0 \pm 1.5	24.3 \pm 2.0‡
40	6	130 \pm 4	18.2 \pm 0.7†	18.4 \pm 1.8‡
60	6	110 \pm 20†	12.2 \pm 1.0‡	10.4 \pm 1.6‡
80	6	101 \pm 16‡	9.4 \pm 0.1‡	6.9 \pm 1.2‡

Experiment B. With tunica albuginea				
Dose (rads)	No. of mice	Testis weight (mg) (Mean \pm s.e.)	Sperm heads $\times 10^{-6}$	Sperm heads $\times 10^{-6}$
			2 testes Coulter counter (Mean \pm s.e.)	2 testes hemocytometer (Mean \pm s.e.)
0	15	190 \pm 3	34.6 \pm 1.1	41.1 \pm 1.6
5	9	176 \pm 6†	32.9 \pm 1.5	40.0 \pm 1.6
10	9	176 \pm 4†	29.1 \pm 1.5†	34.3 \pm 2.3†
20	9	184 \pm 4	29.4 \pm 0.8†	29.9 \pm 2.4‡
40	6	179 \pm 2†	24.1 \pm 1.6‡	29.6 \pm 0.9‡
60	6	164 \pm 5‡	16.0 \pm 0.8‡	19.5 \pm 0.7‡
80	6	157 \pm 3‡	13.6 \pm 0.6‡	16.0 \pm 0.1‡

* In each experiment five groups of three mice each were used as controls; three groups of three mice each received 5, 10, and 20 rads; and three groups of two mice each received 40, 60, and 80 rads.

† Significantly different from control at $p < 0.05$.

‡ Significantly different from control at $p < 0.01$.

essentially the same at the various doses; therefore, at high doses of radiation a higher proportion of the Coulter counts result from debris (Fig. 4).

Sperm-head count as a function of injected activity of [^{99m}Tc] pertechnetate. The effect of radiation from injected pertechnetate on mouse testis was determined by measuring testis weights and sperm-head counts (Table 3, Figure 5). Testis weights are significantly decreased (to 92% of control) after injection of 5.76 mCi of the nuclide. The sperm-head counts show more significant decreases, to 70–80% of control values, after injection of either 5.20 mCi or 5.76 mCi of Tc-99m pertechnetate.

DISCUSSION

In this study we have developed a new method for rapidly and sensitively quantitating the effects of radiation on spermatogenesis. We counted testicular sperm heads rather than epididymal sperm, because the latter is subject to hormonal perturbation (7).

The different cell types within the seminiferous tubules have very different sensitivities to ionizing radiation (8,9), the most sensitive being the differ-

entiated spermatogonia (Types A₁, A₂, A₃, A₄, In, and B). After irradiation of the testes, the various cells progress with normal kinetics. Thus, by counting the sperm heads at various times, we are sampling the survival of a group of cells in a given earlier stage. Since only the differentiated spermatogonia are killed by 80 rads, we would not expect to observe any drop in sperm counts until they became sperm. A decline to a minimum at about 28 days is predicted from the kinetics of spermatogenesis in unirradiated mice (6) and the steps of spermatid development represented by the sperm heads (2). These expectations are in agreement with the present data. We find, however, an LD₅₀ of 53 rads for the overall survival of the differentiated spermatogonia—a value much greater than those expected from Oakberg's data (8): 21 rads for In and B type spermatogonia and 33 rads for A type spermatogonia. This difference in LD₅₀ may be because we are sampling all phases of spermatogonial cell cycle in our experiments, while Oakberg may have been looking at limited parts of the cycle.

The advantage of using sperm-head assay is its simplicity and sensitivity. The method is easier than histologic counts (1,5,8) and is more sensitive than testis weight. Testis weight (10) and DNA determination (11) have disadvantages in that nongerminal cells cannot be measured at higher doses.

It appears that the irradiation from pertechnetate has a greater effect on the testicular cells than external gamma radiation. The number of sperm heads

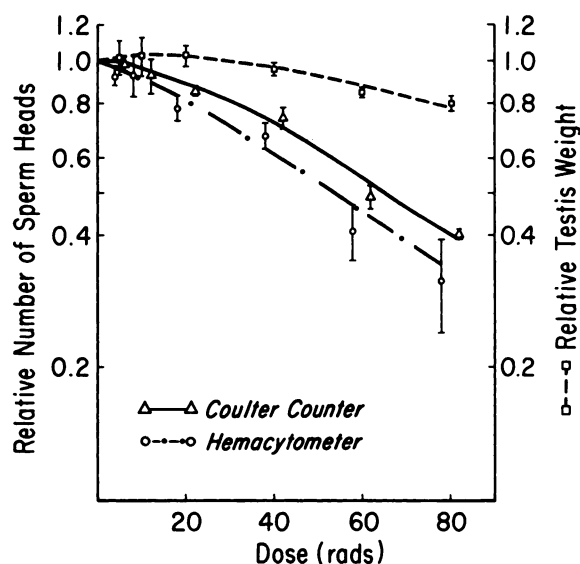


FIG. 3. Testis weights, and relative numbers of sperm heads obtained from testis, 29 days after different doses of Cs-137 radiation. Slight horizontal displacement of data points from their original positions is for clarity. Each point shows mean and range of the two experiments reported in Table 2.

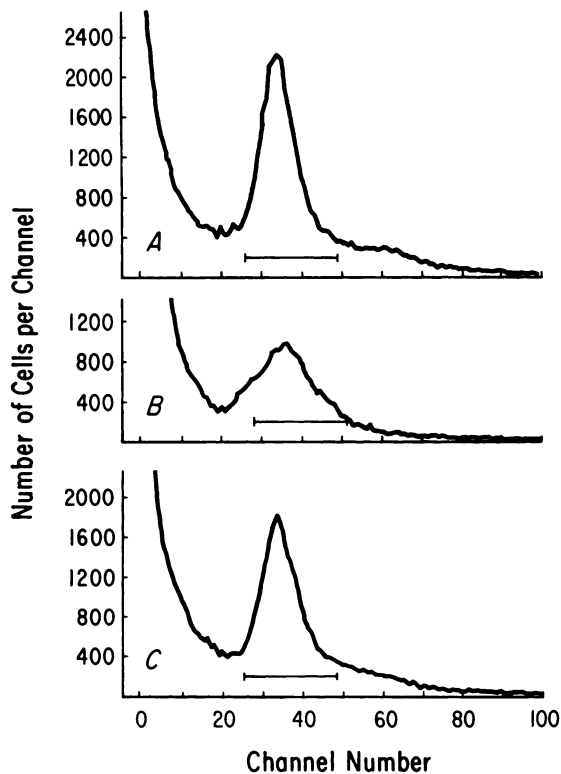


FIG. 4. Volume distribution of sperm heads counted on Coulter counter. Horizontal bars indicate channels included in counts of sperm heads. (A) Control group; (B) 29 days after 40 rads from Cs-137; (C) 20 days after injection of 5.76 mCi of Tc-99m.

decreases to 70% of control after injection of 5.76 mCi of Tc-99m, which we calculate to deliver about 28 rads to the testes. To produce the same effect, gamma radiation from Cs-137 must deliver 40 rads. This discrepancy can be explained by several factors.

First, there are possible sources of error in the Tc-99m dosimetry studies. The dose to the testis from penetrating radiations measured using TLDs might underestimate the dose the testis gets from contained Tc-99m. This underestimate of dose is at most 0.16 rads per mCi of Tc-99m, as calculated from the uptake data assuming a spherical testis, which would add at most 3% more to our calculated values of total dose to the testis. Moreover, the total dose to testis from penetrating radiation may be higher than that measured from TLDs located on the surface of the testis. Such error is unlikely since the TLDs were randomly placed on different sides of the testis and the standard deviation in the measurements is only 4%.

Second, the radiopharmaceutical—and hence the dose from nonpenetrating radiations—may not be evenly distributed in the mouse testis. The barriers to penetration of Tc-99m to the spermatogenic cells include the walls of the blood capillaries and the myoid cells that surround the seminiferous tubules (12). The nuclide would then be concentrated in the interstitial spaces, and the cells on the periphery of the seminiferous tubules, such as the spermatogonia, would be receiving more radiation than expected. The inhomogeneity is most important for the radiation from low-energy electrons, which have a range of about 5 μm in soft tissues. Another barrier is the tight junctions connecting adjacent Sertoli cells (12). The spermatogonia lie outside this barrier, which possibly results in more radiation to spermatogonia. In the case of another radiopharmaceutical, Pu-239 citrate, it has been reported that about 90% of the radioactivity is distributed in the interstitial space of

TABLE 3. MEAN TESTIS WEIGHTS AND SPERM-HEAD COUNTS, AFTER 29 DAYS, IN CONTROL AND Tc-99m-INJECTED MICE*

No. of mice	Activity injected (mCi)	Calculated† dose (rads)	Testis weight (mg) (Mean ± s.e.)	Sperm heads × 10 ⁻⁶	
				Coulter counter (Mean ± s.e.)	hemocytometer (Mean ± s.e.)
18	Control (uninjected)		178.8 ± 1.3	30.9 ± 2.1	42.9 ± 0.7
6	Control (injected with Tc-99m pertechnetate decayed for 5 days)		184.2 ± 4.7	35.3 ± 0.7‡	40.8 ± 0.2
6	1.69	8.3	183.1 ± 0.9	32.6 ± 1.2	43.0 ± 2.4
6	2.68	13.2	184.2 ± 0.1	29.2 ± 2.8	40.5 ± 2.5
6	5.20	25.6	174.9 ± 1.1	24.7 ± 4.6§	31.1 ± 2.0§
9	5.76	28.3	164.3 ± 1.8§	22.0 ± 0.8§	29.6 ± 1.0§

* Three groups of two or three mice each were used for each dose point; six groups of three mice each were used as controls; and two groups of three mice each were given decayed dose material 5 days old.

† 1 mCi = 4.92 rads.

‡ Significantly different from control at p < 0.05.

§ Significantly different from control at p < 0.01.

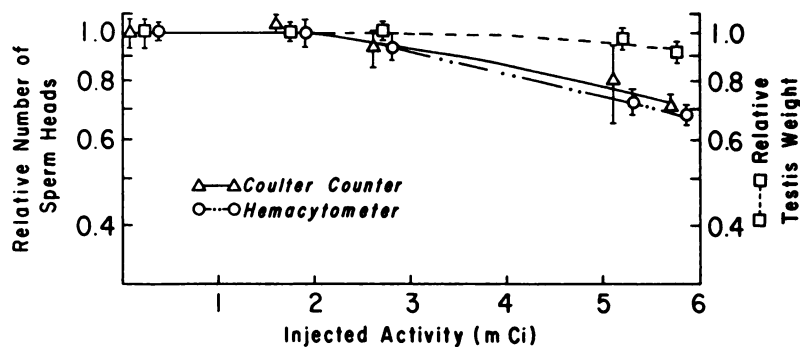


FIG. 5. Testis weights, and numbers of sperm heads obtained from testis, vs. injected doses of [^{99m}Tc] pertechnetate. Ordinates are calculated from Table 3 and presented as a fraction of control values. Slight horizontal displacement of data points from their original positions is for clarity. Each point represents mean and standard error of values.

mouse testis, which results in increased radiation to the spermatogonia (13).

A third factor is that the relative biologic effectiveness (RBE) of low-energy electrons (10 keV) is about 2. Some 14% of the dose from nonpenetrating radiations (6% of the total dose) comes from electrons with energies below 10 keV, thus possibly enhancing the overall RBE by about 6%.

Other differences between the external gamma radiation and internal radiation are not expected to produce different biologic effects. Furthermore, the radiation from Cs-137 was localized, whereas Tc-99m was distributed throughout the body. There are no significant differences to the testis, however, between localized and total-body radiation (10). Moreover, we do not expect any dose-rate effect, since a reduction of the dose rate from 86 to 0.009 rads/min, with total dose of less than 300 rads, had no effect on spermatogonial killing in the mouse (8). The initial dose rate after administration of 5.76 mCi of Tc-99m was calculated to be 0.12 rads/min, compared with the Cs-137 dose-rates of 200 rads/min and 38 rads/min.

The data obtained from the mice can be used to estimate the dose to human testis from 1 mCi of intravenously administered [^{99m}Tc] pertechnetate. The concentration of Tc-99m in the mouse testis is only 43% of the average concentration in the body, and the biologic half-time of this radionuclide in the mouse testis is about 5 hr. Assuming similarity, the dose to human testis for a 70-kg man should be 0.9 mrad from nonpenetrating radiations ($\Sigma\Delta_i\phi_i \text{ N.P.} = 0.0362$) and 0.3 mrad from penetrating radiations ($\Sigma\Delta_i\phi_i = 0.0125$) for a testis weight of 38 g (3,4,15). To calculate the dose from penetrating radiations that the testis would get from other organs of the body, we assumed a uniform distribution of the nuclide throughout the body. According to reciprocity theorem (3), the dose to body from the 1 mCi of radioactivity concentrated in the testis must equal the dose to the testis from the same amount of radioactivity distributed throughout the body. In this cal-

culcation the biologic half-time of Tc-99m in the human body was taken as 48 hr (16), so the effective half-time is 5.33 hr. The $\Sigma\Delta_i\phi_i \text{ P.}$ ($b \leftarrow t$) equals 0.1408 (4,15). The calculated dose is then 15.5 mrad. We must consider, however, that in the case of the mouse, the actual measured values with TLD were 2.4 times those calculated on the assumption that the emitter was uniformly distributed throughout a cylinder-shaped body (17). Accordingly we suspect that the above figure for dose to the human testes from other organs of the body is an underestimate, most likely because of greater concentration of Tc-99m in nearby organs, such as the bladder. With these qualifications, we calculate the total dose to human testes to be 16.7 mrad from 1 mCi of intravenously administered [^{99m}Tc] pertechnetate. Our data compare well with a reported value of 10 mrad/mCi (18). Thus, 20 mCi used clinically will give $20 \times 16.7 = 334$ mrad. This value must be taken into account when evaluating the possible harmful effects of diagnostic procedures that use pertechnetate.

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FOOTNOTES

† EG&G 2010A Programmer TLD Reader, Goleta, Cal.

‡ Model ZBI Counter, Coulter Electronics, Hialeah, Fla.

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**1ST ANNUAL MEETING ON GENERAL RADIOPHARMACEUTICAL SCIENCE
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