Selective Sterilization of Young Female Mice by Radioiodine Transmitted Through the Mother's Milk. (20484)

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It has been established that ionizing radiations, whether from an x-ray source or from some isotope, may bring about the sterilization of animals if they are subjected either to large single or small chronic exposures(1-3, 6,8). Young mice of the C_{57} strain showed reduction in ovogenesis but no effect on spermatogenesis following injections of radioiodine (Gorbman—personal communications). Speert *et al.*(7) injected pregnant mice with radioiodine to determine the onset of fetal thyroid function, and found effects on the fetal gonad. Radioiodine readily passes from the nursing mouse to its litter young by way of the milk and there is a progressive increase in the relative amount of radioiodine previously injected into the nursing mouse, found in the suckling litter young. By 48 hours as much as 86% of the retained radioiodine is found in the litter members and only 14% in the mother(4,5).

It seemed of importance to determine the differential sensitivity of the ovary and the testes of the newborn mouse as it might be affected by radioiodine injected into the mother and transferred to the suckling young by way of the mammary glands.

Materials and method. The female mice used in this study were of the Swiss albino stock, each of which had previously delivered a normal litter. They were time-mated so as to litter simultaneously, and 37 litters were selected. The mice with small but normal litters were chosen so that there would be no milk shortage to the suckling young. In other words, there was available to them milk *ad libitum*. The 37 litters were treated as in Table I.

TABLE I.

Litters	Males	Females	Total	Post-partum age, days	I^{131} inj., μc
9	16	19	35	5	300
7	10	11	21	5	600
8	23	13	36	15	300
5	18	5	23	15	600
8	13	18	31	Controls	

The radioiodine was in the form of sodium iodide (NaI^{131}) received from the Pile at Oak Ridge and diluted so that each cubic centimeter contained 400 μc of active radioiodine. The dose levels used were 300 and 600 μc per single injection. The isotope was injected subcutaneously into the nursing mouse which was then returned to its litter. Sixteen mice were injected when the litter young were 5 days of age and 13 when their young were 15 days old. It is known that by the fifteenth day there is maximum milk production by the nursing mouse. Eight control females were injected with an amount of nonradioactive elementary iodine comparable to that of the higher dose levels of the isotope used. The shavings in all cages were discarded at 24 and 48 hours post injection to avoid any possible external contamination from excreted iodine and the mice were given the usual care of our animal quarters. At weaning time (4 weeks) the sexes were separated, members of one litter being kept separate from the members of other litters.

At 2 month intervals, beginning at 2 months of age and continuing until the mice were 10 months of age, about 10 mice from each of the 5 categories were selected at random and tested against normal stock for fertility. Each female was tested consecutively against 2 males for 5 days each, and each male was tested against 2 stock females. These same experimental mice were not again tested for fertility until all others, similarly treated, had been tested. At the termination of the experiment when the mice were 10 months of age, all living mice were fertility-tested.

Observations and experimental data. Table

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TABLE II. Fertility Tests.*

	I^{131} treatment of mother									
	5 days postpartum				15 days postpartum				Controls	
	300 μc		600 μc		300 μc		600 μc			
Age, mo.	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2	5/6	4/4	5/5	4/5	2/5	5/5	5/5	6/6	3/3	5/5
4	3/4	2/4	3/4	1/4	4/5	5/5	5/5	4/6	6/6	4/4
6	5/5	2/5	3/4	0/5	5/5	2/5	5/5	3/6	6/6	5/6
8	4/4	3/4	4/4	0/4	4/4	4/5	3/3	3/6	3/3	4/4
Totals	17/19	11/17	15/17	5/17	15/19	16/20	18/18	16/18	18/18	18/19
%	90	65	88	29	79	80	100	89	100	95
Final test at 10 mo.	15/16	4/19	6/8	0/11	21/23	7/13	14/17	0/5	29/30	31/36
%	94	21	75	0	91	54	82	0	97	86

* The data are given in this manner: Fertile/total tested; hence fertility percentage can be determined directly.

II presents the fertility data of the entire experimental series. For practical reasons tests were not made on all animals every 2 months, but by random sampling and without duplication of animals until all had been tested, the data are considered to be representative.

With regard to the male offspring it is readily apparent that the fertility level is unaffected by any dose or time of treatment used. The lowest fertility value of 79% for males from 300 μc mothers injected on the 15th day is counterbalanced by the final test of the entire group of 23 animals which showed 91% fertility. The highest exposure of 600 μc I^{131} to the mother never reduced male offspring fertility below 75%. This figure was derived from the 10 month survivors of exposure on the 5th day postpartum. It is safe to conclude, therefore, that the male offspring subjected to radioiodine from the mother's milk is radioresistant with regard to its reproductive activity.

The data from the female offspring are, however, quite different. Sterility is evident as early as 4 months of age in mice exposed at 5 days post partem to either level of radioiodine injection of the mother. Those exposed at 15 days showed some sterilization by 4 months at the higher level and by 6 months at the lower level of injection of radioiodine. The overall fertility percentage for the period of 8 months indicates that the young ovary is more radiosensitive at 5 than at 15 days post partum. The smaller dose of 300 μc of radioiodine at 5 days reduced the fertility more (65% fertile) than the 600 μc dose at 15 days postpartum (89% fertile). This occurred in spite of the fact of greater milk production on the part of the mother. If one examines the final data of all remaining females at the termination of the experimental period, it is further evident that 600 μc of I^{131} to the mother at either the 5 or the 15 day postpartum period results in complete sterilization. This means that not only is the overall fertility reduced in the female, but the reproductive life span is likewise reduced. At the termination of the experiment 86% of the control females were still fertile.

Discussion. The reasons for the hypersensitivity of the young ovary as opposed to the young testes to the damaging effect of high and concentrated exposures to ionizing radiations from radioiodine have not been determined. It is very likely that the developing ovary and testes are not at the same stage of maturation at the time of radiation insult. However, this fact has been established for the fetal and adult mouse and the experimental evidence reported here substantiates the thesis for the newborn, receiving its exposure from maternal milk.

The question is raised with regard to a possible indirect effect on the suckling young when the mother is subjected to a large dose of radioiodine. There is no doubt but that either dose used would eventually ablate the mother's thyroid gland. Such radiation damage of the nursing mouse in no way alters her ability to suckle her young, to produce milk, or to survive for the duration of the experi-

ment. The young mice are weaned at the same time as are the controls, and there is no outward evidence of functional or structural damage of any of the mice.

There is also the question of possible irradiation of the suckling young by the temporary radioactive mother. She certainly emits both beta and gamma radiations. This, no doubt, obtains for a very short period immediately after the injection but there is evidence that the relative amount of radioiodine shifts in favor of the litter young very rapidly (4,5). Further, even though the mother might be a considerable source of radiation for a short time, this does not detract from the thesis that the ovaries are more radiosensitive than are the testes. It would be difficult to postulate selective exposure of the sexes.

It has been shown(4) that the amount of I^{131} passing to any suckling litter member never exceeds 5% of the amount injected into the mother. This means that no more than 30 μc of I^{131} reached any of the young mice tested. Even this amount is rapidly reduced by excretion and decay. It can be stated, therefore, that the ovaries at 5 days appear to be more radiosensitive to an exposure of no more than 30 μc of I^{131} than do the ovaries at 15 days postpartum. This occurs in spite of the further fact that more milk is available to the suckling young on the 15th day.

Finally, the absolute amount of injected radioiodine into the adult has been shown to drop from 100% in 4 hours to 90% in 24 hours and 20% in 48 hours, due to excretion and to decay(4). If a comparable reduction rate occurs for the suckling young, the maximum concentration of 30 μc received by any suckling member was reduced in 48 hours to a maximum of 6 μc. The duration of irradiation of the tissues of the newborn mice is not long. Nevertheless, it seems evident that the gonads of the young newborn female mouse must be very sensitive to ionizing radiations from radioiodine, expressed in reduced fertility as early as four months of age.

Summary and conclusions. 1. Ovaries of young newborn mice are very sensitive to ionizing radiations from radioiodine administered to the mother and reaching the young through the milk. The testes of litter mate male mice are very radioresistant under the same conditions. 2. A single injection of a nursing mouse with 600 μc of I^{131} reduced fertility in the female offspring by four months and made all female offspring sterile by 10 months while controls were 86% fertile. Litter mate males were never reduced to less than 75% fertility. 3. It appears that the ovary of 5-day-old mice is more sensitive to ionizing radiations from radioiodine than is the ovary of the 15-day-old mouse. 4. Even though exposure of the ovary of the young mouse to ionizing radiations was relatively brief, sterility was not evident for at least 4 months. Not only was the overall fertility of the female reduced, but so also was the length of the reproductive life span.

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