removes a factor essential for growth and maintenance of these cells. The deficiency syndrome in cultures with dialyzed serum can be corrected by chicken serum dialysate, but not by inositol, cholesterol, vit. B_{12}, spleen nucleoprotein fraction, or by a more complex synthetic nutrient, NCTC 109. Proteose-peptone at 0.1% may be substituted for serum dialysate to restore full activity of whole serum.

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Influence of Dose Rate on Radiation Effect on Fertility of Female Mice. (25288)

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Studies of the variables that affect the action of radiation on cell populations may be expected to yield answers concerning both the nature of the radiation effect and the properties of cell population concerned. An understanding of these factors is of special importance in gametogenic cells, for proper interpretation of results of genetic experiments is not possible. It has long been known that, following irradiation with even a relatively low acute dose, female rodents produce only one or a limited number of litters before permanent sterility sets in, a response entirely different from that of males, which regain fertility even after high doses. The basis radiation-induction of permanent sterility in the female is the extremely rapid destruction of immature primordial oocytes, shown for the mouse by Brambell and Parkes(1) and by Murray(2), whose findings were, in general, confirmed recently by Oakberg(3). The careful quantitative studies of Mandl(4) in the rat lead to similar conclusions. (Her paper gives a review of some of the voluminous literature on radiation effects on the ovary.) It has been found that new formation of oocytes does not occur following irradiation(1,3, etc.), supporting the view that oogonia do not persist in the adult. Since the first meiotic division is not completed until shortly before ovulation which, in any case, involves only very few cells at each estrus, practically the entire gametogenic cell population of adult mouse ovary consists of primary oocytes. Diplotene is

* Operated by Union Carbide Nuclear Co. for U.S. Atomic Energy Comm.

completed by 72 or 96 hours after birth(5). The oocyte nucleus then enters into a modified resting stage, named "dictyate"(6), that lasts throughout the subsequent life of the oocyte, until diakinesis occurs only a few hours prior to ovulation. Extreme radiosensitivity is usually associated with obvious activity, mitotic or otherwise, of cells. Therefore, in view of histological and cytological facts outlined, it seems, *a priori*, puzzling that the adult ovary should be so radiosensitive. Its gametogenic cell population consists of non-dividing cells, and the nuclei are in apparently uniform resting stage. It was in an attempt to contribute to an understanding of this rather unusual type of radiosensitivity exhibited by the mammalian oocyte that the present experiments were undertaken. Preliminary reports of some of the results have been published(7, 8). Various factors which might be expected to influence response to dose-rate changes could very well work in opposite directions to each other. On the one hand, lowering dose rate might, in some respects, tend to increase the sterilizing effect. Thus, for matings made at a given interval following accumulation of total dose, the lower the dose rate, the earlier and, therefore, the more sensitive the oocyte stage at which radiation was begun. Similarly, existence of some cycle of sensitivity, might result in more damage from radiation distributed in time than from a single acute dose. On the other hand, if repair of damage can occur in oocytes, lowering of dose rate should, in this respect, tend to decrease the effect of a given dose. Past fractionation and dose-rate experiments on female mice have yielded apparently conflicting results. While some investigators indicated that fractionation of dose lessens the sterilizing action of radiation(9,10), others noticed only a limited effect of changes in dose rate(11), or no effect(12). Still others claim to have found an *inverse* relation between dose rate and sterilizing action(13), *i.e.*, the lower the rate of administration of a given dose of chronic radiation, the greater the damage. It will be shown that these apparent conflicts can be explained in the light of present findings.

Material and methods. The following procedures apply to both experiments (fractionation and continuous exposure). Females used were genetically uniform (101 x C3H) F_1 hybrid mice and were at least 6 weeks old when treatment was begun. In the 2 experiments, females were distributed randomly among various component groups. Each group was comprised of 12 females, with exception of the control group for the continuous exposure experiment, in which there were 18. The course of exposures was arranged in such a way that the various groups, within each of the 2 experiments, completed accumulation of their respective total doses on approximately the same date. Six females of each group were mated immediately following total dose accumulation, while the other 6 were mated 10 days later (corresponding control groups being mated concurrently). This was done to provide information for the intervals where there would otherwise be gaps, *i.e.*, when females would not be available for mating as a result of being pregnant. Age at time of mating ranged from 3-5 months. Each female was caged separately with a (101 x C3H) F_1 male for the rest of her life. Litters were recorded and killed on day of birth. In the fractionation experiment, females were exposed to either a single or to fractionated doses of acute X rays (dose rate about 80 r/min; 250 Kvp; 15 ma; inherent filtration 3 mm Al; H.V.L. 0.4 mm Cu; target-object distance 84 cm; exposure in individual lucite tubes on rotating 10.8-cm-high masonite scatter block; heads of animals shielded). Total doses and ways in which they were fractionated are shown in Tables I and II. There are 2 groups of controls: one "exposed" to one sham-irradiation; and one "exposed" to 30 sham-irradiations (5/week), *i.e.*, receiving as much handling as the most frequently handled irradiated group. The experiment, with controls, thus comprised 12 groups. The 144 females produced 5,810 young in 958 litters. In the continuous exposure experiment, females were exposed to radiation from a 5 curie Cs^{137} source. Exposure was continuous except for about 1-2 hours each week. Total doses† and

† In a preliminary abstract of this experiment(8), the total accumulated doses were reported about 16-17% higher than here. The revision was made following an accurate recheck of dosimetry.

dose rates, which were regulated by distance, are shown in Tables III and IV. The experiment comprised 14 groups. The 174 females produced 12,494 young in 1,970 litters.

Results. Total performance of various groups is summarized in Tables I and II for the fractionation experiment and in Tables III and IV for the continuous exposure experiment. Tables I and II also include, in addition to results of the present experiment, some unpublished data of W. L. Russell and J. S. Gower for performance of (101 x C3H) F_1 females following single acute doses of 300, 400, or 500 r (based on 59, 130, and 26 females, respectively.

Analysis of the data in terms of time elapsed following irradiation is presented in Figs. 1 and 2 for fractionation and continuous exposure experiments, respectively. In these figures, 2 parameters are plotted for

TABLE I. Litters Produced by Females Irradiated with Acute X-rays in Single or Fractionated Exposures. Mean number of litters/female and stand. errors.

Total dose (r)	Single exposure (unpublished data of W. L. Russell and J. S. Gower)	Single exposure	25-r fractions (2/wk)*	10-r fractions (5/wk)†
0		14.67 ± .56		15.17 ± .64‡
50		4.00 ± .21	9.00 ± .33	12.82 ± .69
100		2.08 ± .08	3.33 ± .25	9.67 ± .98
200		1.75 ± .13		4.17 ± .32
300	1.36 ± .06	1.42 ± .15		2.00 ± .0
400	1.14 ± .04			
500	.69 ± .12			

* Irradiated Mondays and Fridays. † Irradiated daily, Mondays through Fridays. ‡ This group of controls underwent 30 sham-irradiations. Mean No. of litters for the 2 control groups combined is 14.92 ± .42.

TABLE II. Offspring Produced by Females Irradiated with Acute X-rays in Single or Fractionated Exposures. Mean number of offspring/female and stand. errors.

Total dose (r)	Single exposure (unpublished data of W. L. Russell and J. S. Gower)	Single exposure	25-r fractions (2/wk)*	10-r fractions (5/wk)†
0		91.17 ± 2.71		91.67 ± 5.97‡
50		23.17 ± 1.48	52.25 ± 3.39	79.82 ± 5.40
100		14.08 ± .58	17.75 ± 1.74	61.83 ± 1.84
200		10.00 ± 1.02		21.00 ± 1.46
300	8.44 ± .36	7.58 ± .94		13.67 ± .70
400	5.84 ± .26			
500	1.85 ± .41			

* Irradiated Mondays and Fridays. † Irradiated daily, Mondays through Fridays. ‡ This group of controls underwent 30 sham-irradiations. Mean No. of young for the 2 control groups combined is 91.42 ± 3.20.

TABLE III. Litters Produced by Females Irradiated with Various Dose Rates of Continuous Gamma Radiation from Cs^{137}. Mean number of litters/female and stand. errors.

Total dose accumulated (r)	Dose rate (r/wk)				
	—	10.1	23.1	47.2	88.2
0	13.88 ± .37				
86		13.33 ± .73	12.08 ± .68	13.25 ± .45	13.33 ± .45
171			13.00 ± .50	11.33 ± .70	11.00 ± .37
256			11.83 ± .27	11.25 ± .51	8.42 ± .34 9.00* ± .64
345				9.25 ± .22	7.75 ± .46

* Results of pilot experiment, which preceded the experiment proper by a few months. All other groups concurrent.

TABLE IV. Offspring Produced by Females Irradiated with Various Dose Rates of Continuous Gamma Radiation from Cs^{137}. Mean number of offspring/female and stand. errors.

Total dose accumulated (r)	Dose rate (r/wk)				
	—	10.1	23.1	47.2	88.2
0	84.76 ± 3.08				
86		86.67 ± 7.15	78.08 ± 3.56	83.00 ± 3.11	86.33 ± 1.72
171			86.00 ± 3.80	73.67 ± 5.48	62.17 ± 2.73
256			72.67 ± 2.19	72.67 ± 4.32	51.75 ± 3.46 59.00* ± 6.09
345				59.08 ± 1.94	47.83 ± 2.65

* Results of pilot experiment, which preceded the experiment proper by a few months. All other groups concurrent.

each group. The top graph shows, for each time interval, percentage of females that had at least one litter in that time interval. (For the sake of brevity this parameter will be referred to, subsequently, as percentage of "productive" females.) The bottom graph represents mean size of litters born. Most females regularly mater postpartum during major portion of their reproductive life. When young are killed at birth, litters from such matings are spaced approximately 3 weeks apart, and the results have consequently been tabulated for 3-week intervals, such that, during the height of reproductive activity, almost every female had one litter in each interval. (Occasionally, synchrony broke down leading to 2 litters in one interval and none in the next. When this happened with several females in a group, the top graph takes an artificial dip not indicative of lowered performance; see, *e.g.*, 64-84 day intervals in Fig. 2B, C, D). The first interval, which starts at 19 days (*i.e.*, length of gestation period) is 24 instead of 21 days long. This has been done to include the first surviving litter from those females whose first conceived litter died as a result of the high dominant lethal incidence from matings made in the night following irradiation(14). Since, handling had apparently no effect on performance of nonirradiated animals, (Tables I and II) the 2 control groups used in the fractionation experiment have been combined for Fig. 1. The few females that died before the end of their reproductive period (one in the group that received 50 r in 10-r fractions, one in controls of continuous ex-

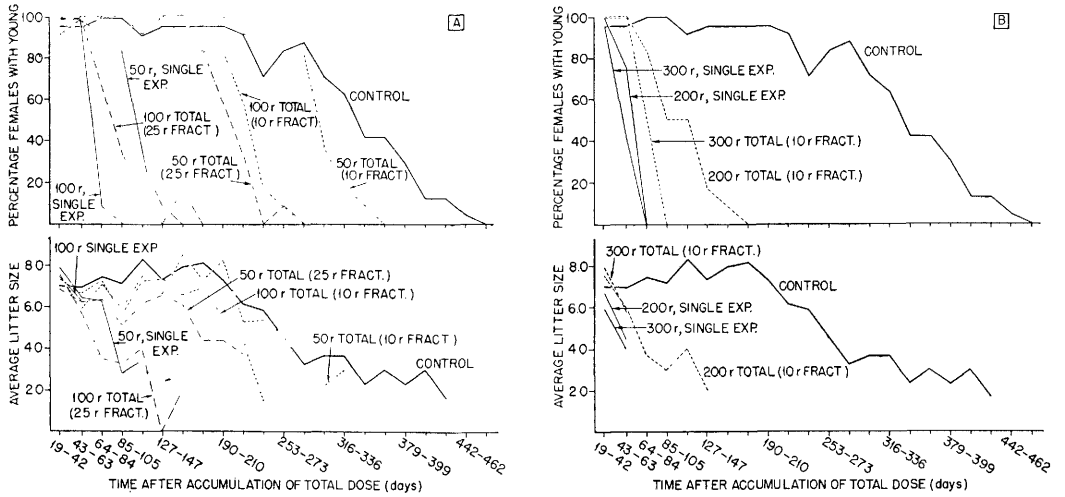

FIG. 1. Percentage of females that had at least one litter (upper graphs) and mean littersize (lower graphs) in various intervals (of 3-wk duration each) following accumulation of various total doses of X-rays, administered either in a single exposure or in fractions of 25 r or 10 r. (A) Total doses of 50 r and 100 r. (B) Total doses of 200 r and 300 r. Note: mean littersize is plotted only for intervals in which at least 10% of females had litters.

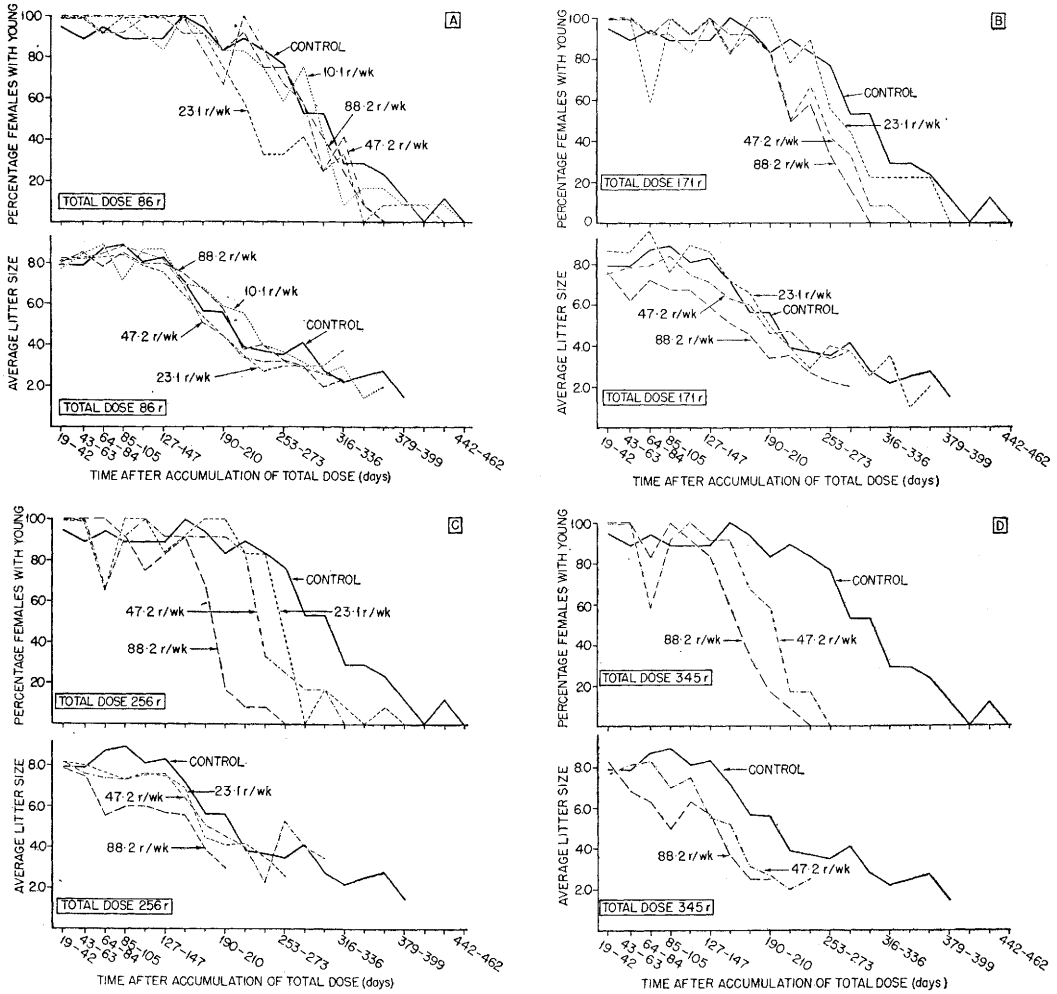

FIG. 2. Percentage of females that had at least one litter (upper graphs) and mean littersize (lower graphs) in various intervals (of 3-wk duration each) following accumulation of various total doses of continuous gamma rays, administered at dose rates of 88.2, 47.2, 23.1, or 10.1 r/wk. (A) Total accumulated dose, 86 r. (B) Total accumulated dose, 171 r. (C) Total accumulated dose, 256 r. (D) Total accumulated dose, 345 r. Note: mean littersize is plotted only for intervals in which at least 10% of females had litters.

posure experiment, and 3 in group that received 171 r at 23.1 r/wk) do not contribute to the Tables or to Fig. 3, but are included in Fig. 1 and 2 until the time of their death.

The results for both fractionation and continuous exposure experiments are summarized in Fig. 3.

A. Single, acute exposure. Even a dose as low as 50 r, when given in a single exposure, reduces performance of females drastically, *i.e.*, to one-fourth of normal (Table I and II). This is all the more striking since higher doses do not greatly increase the effect (Fig. 3). This is, of course, due to the very high sensitivity of early oocytes and relatively high radiation resistance of oocytes contained in mature follicles, as demonstrated by histological studies of the ovary (see above), and by studies of ovulated eggs during dominant lethal experiments(14). As a result of radiation resistance of mature oocytes, even females exposed to high doses usually produce one or 2 litters before becoming sterile. Thus, in the group exposed to 400 r, 98% produced at least one litter; and, even after 500 r, 62% had one or more litters.

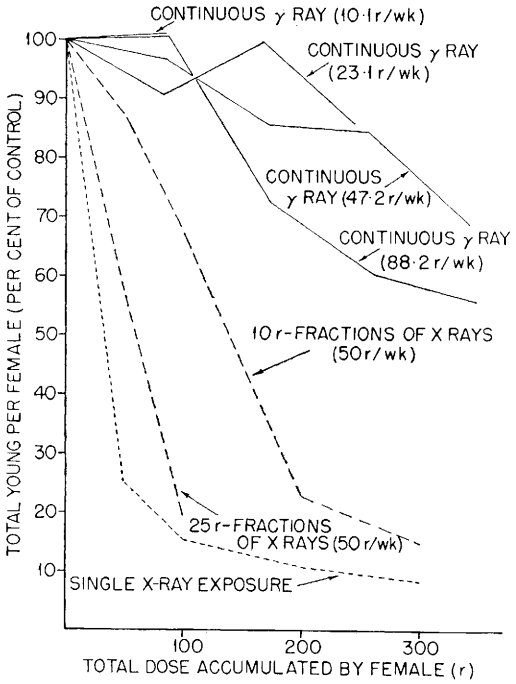

FIG. 3. Total No. of offspring produced by females following irradiation with various doses, administered in single, acute exposure, in fractionated acute, exposures, or, in continuous exposure at various dose rates; expressed as % of controls.

The dose curve for total number of young produced following a single, acute X-ray exposure (Fig. 3, lowest curve) is, thus, obviously a compound curve. The relatively level portion at higher doses represents radiation effects on resistant mature oocytes, which give rise to progeny even after doses that have killed the less mature, more sensitive cells. (It should be pointed out that most, if not all, of the slope in that portion of the curve is probably due to dominant lethals, *i.e.*, induced genetic changes leading to death of embryos(14,15) rather than to killing of oocytes.) The initial steep slope of the curve is presumably compounded of various slopes for the more sensitive stages. Thus, the dose-effect curve for most immature oocytes alone (*i.e.*, those found by Oakberg to be most quickly killed by radiation) is presumably considerably steeper even than the steepest portion of the compound curve. It might be possible, with more extensive data, to analyze the curve into its component parts, thereby determining percentage contribution to total progeny made by each oocyte stage, as well as slope of killing curve characterizing each of these stages.

The histological finding(3) of marked correlation between degree of immaturity and radiosensitivity of oocytes is well borne out by breeding data. When performance is examined in terms of time elapsed after irradiation (Fig. 1) it becomes obvious that number of litters cast does not decrease until just prior to complete sterility. On the simplest assumption, this result would indicate that increase in sensitivity with immaturity is a rather steep one.

B. Effect of fractionation. Fractionation of dose markedly reduced the damage to fertility, and that division of dose into 10-r fractions was more effective in this respect than division into 25-r fractions. At each total dose, the differences between exposure groups (single exposure *vs.* 25-r fractions, 25-r fractions *vs.* 10-r fractions) are highly significant (in all comparisons, $P << 0.0001$) for mean number of litters cast (Table I). The same is true for mean total number of young (Table II) except for one difference (namely, that between single exposure and the 25-r fraction group at 100 r total dose), which is significant only at a lower level ($P = 0.047$).

The results for total young/female may be compared in the summarizing Fig. 3. For initial steep portions of curves, the ratio of slopes is about 4 in comparison between single exposure and 10-r fractions, and about 2 for comparison between single exposure and 25-r fractions. (Note that these ratios may be underestimates, since initial portion of the curve for single, acute exposure may very well prove even steeper when dose points intermediate to 0 and 50 r are filled in.) This indicates that the sensitive, immature oocytes are capable of considerable recovery from radiation damage. As the curves flatten out at higher doses, the ratio of slopes decreases. It seems probable that the curves would approach each other even more at higher doses, since one would deal there only with the most mature oocytes, the viability of which is essentially unaffected by radiation. Whether or not some differences remain due to genetic changes (dominant lethals) induced in these

cells is problematic.

When the results are examined in detail, in relation to time elapsed after irradiation (Fig. 1), it appears, for number of productive females ("percentage females with young"), that fractionation of dose is roughly equivalent to giving a lower dose in single exposure. Similarly, 10-r fractions at one dose are roughly equivalent to 25-r fractions at a lower total dose. Thus, the extra young obtained when doses are fractionated, are not the result of prolongation of a period of low-level fecundity. Instead, the period of full-scale production is extended and, as in single exposures, number of productive females does not decrease appreciably until shortly before sterility sets in. Time relations for littersize will be discussed below.

C. Effect of lowering dose rate. It may be seen, by comparing the results in Tables III and IV with those in Tables I and II, that continuously exposed females were considerably less affected in breeding performance than those which received fractionated irradiation. This is true even of the comparison between highest dose rate of continuous irradiation (88.2 r/wk) and smallest fractions of acute irradiation (5 10-r fractions/week) (Fig. 3). Groups that received a total accumulated dose of 86 r were not significantly different from controls in their performance. This is in contrast to animals receiving only 50 r in 10-r fractions which differed significantly in mean number of litters from combined controls of the fractionation experiment.

Further, in comparing different dose-rate groups within the continuous exposure experiment, it is obvious, at least at total doses above 86 r, that the lower the dose rate the smaller is the deleterious effect on fertility. Both for mean number of litters (Table III) and mean number of young (Table IV), the difference between 88.2 r/wk and 23.1 r/wk is clearly significant at total doses of 171 r and 256 r ($P = 0.001$ and $P << 0.0001$, respectively, for litters; $P << 0.0001$, at each total dose, for offspring); and the difference between 88.2 r/wk and 47.2 r/wk is clearly significant at total doses of 256 r and 345 r ($P << 0.0001$ and $P = 0.003$, respectively, for litters; $P = 0.0002$ and $P = 0.0006$, respectively, for offspring). Of the 3 remaining dose-rate comparisons at total doses above 86 r, 2 are on the borderline of significance for at least one parameter (23.1 r/wk *vs.* 47.2 r/wk at 171 r, both for number of litters, $P = 0.05$, and number of young, $P = 0.06$; 47.2 r/wk *vs.* 88.2 r/wk at 171 r for number of young, $P = 0.06$); and one (23.1 *vs.* 47.2 at 256 r), though not significant, at least goes in the expected direction.

Analysis of results of continuous exposure experiment in relation to time elapsed after irradiation (Fig. 2), presents an even clearer picture of direct correlation between dose-rate and sterilizing effect. At each total accumulated dose, above 86 r, the decline in percentage of productive females (top portions of Fig. 2B, C, D) occurs earlier the higher the dose rate. This correlation is apparent even in the few cases where totals (Tables III and IV) failed to give clearly significant differences. Even at lowest accumulated dose, 86 r (Fig. 2A), where none of the totals differed significantly from controls, there is a faint suggestion of effect, at least for the 2 highest dose rates, 88.2 r/wk and 47.2 r/wk, which slightly curtail length of reproductive period. (Note: 23.1 r/wk results at 86 r were, for some unknown reason, temporarily out of line with all others; but the group rallied and went on breeding almost as long as controls.) In all groups, production, in terms of number of litters cast, was at maximum level until the time of decline that ends in sterility. This decline is in all cases somewhat steeper than the decline due to normal ageing (controls).

Analysis with respect to littersize (bottom portions of Figs. 1A, B; 2A, B, C, D) is not nearly as clear as that with respect to percentage of productive females. It appears, at first glance, that a great many irradiated groups are characterized by depressed littersizes through the major part of their breeding period. However, the following considerations make it questionable that this is an effect additional to the one already discussed. Thus, when decline in littersize is regarded in relation to decline in productive females (in controls the former precedes the latter), the littersize depression in each case is to be ex-

pected in terms of impending sterility. However, the total situation is undoubtedly considerably more complex. Thus, littersize is affected not only by number of oocytes ovulated, and this, under certain circumstances, may actually be *in*creased by radiation(15), but also by genetic changes induced in these oocytes that lead to death of embryos (dominant lethals)(14,15).

Discussion. That a lowering of dose rate decreases sterilizing action of a given dose of radiation has been clearly demonstrated both within the fractionation experiment and within the continuous exposure experiment. Comparison *between* experiments shows that continuous exposure at the rate of about 50 r wk (47.2 r wk) of gamma rays is several times less sterilizing than exposure to five 10-r fractions of X rays week (Fig. 3). This difference is very much greater than might be explained on the basis of radiation quality alone (gamma *vs.* X rays). Thus, comparison between experiments strengthens the conclusion reached on the basis of each experiment alone.

In view of this very clear-cut dose-rate effect, it is necessary to re-examine reports in the opposite direction from that found here. It can be shown that past experiments which are in apparent disagreement with the present results, used methods of testing which were not suitable for revealing what is really the characteristic effect of radiation on female fertility, namely, shortening of breeding period.

Thus, size of first litter born following accumulation of total dose, was used as the basis for the conclusion reached by H. and M. Langendorff(12) that there is no effect of fractionation. It was used as 1 of 2 criteria of effect by Neary, Munson, and Mole(13), who report an inverse relation between dose rate and damage. Similarly, most results of Deringer, Heston, and Lorenz(11) are based on first litters; and although their comparison between acute and chronic exposure is in agreement with the present results, the authors "failed to demonstrate any effect of dose administration" when comparing their various chronic-irradiation series with each other. As is obvious from the present paper, differences in effects of various dose rates are not apparent from the first litter following irradiation. Decrease in size of first litter is probably primarily due to dominant lethals and not to decreased number of ovulations(14).

Another complication that may obscure true dose-rate effect is age of females. Unless adequate controls are used, or unless special precautions are taken to terminate radiation exposures at the same age in groups being compared, it is obvious that the lower the dose rate, the more advanced in age, and thus the less productive from natural causes, are the females when tested for fertility. This consideration must be applied to results of Deringer *et al.* and may even explain the inverse relation between dose rate and damage reported by Neary *et al.*, some of whose females were irradiated for almost 9 months. As a matter of fact, among experiments of the latter authors, there is one, for which controls were available, which seems to support this view.

Neary *et al.* suggested as possible explanation for their results that radiation sensitivity of females may increase with age. Their small, supplementary experiment on this point cannot be considered conclusive because of inadequate controls. Indeed, it seems more likely that their results are a consequence of unsatisfactory methods of testing discussed above. Another factor may also have added confusion: after long-continued irradiation, already the first mating (as well as all subsequent ones) must utilize oocytes that had received some of their dose in the highly sensitive early stages; after a shorter-term exposure, such oocytes would not be used until later matings. By either criteria used by Neary *et al.*, this would result in apparently greater damage from lower dose rates. Whether or not such a factor has played a role in results of Neary *et al.*, it must have been of minor importance in the present data, since it was obviously outweighed by factors that decrease oocyte damage as dose rate is decreased.

In the light of preceding discussion, it is clear that results of other workers are not in major conflict with the present data. Because of measures of effect chosen, the 3 experiments discussed(11-13) failed to reveal what the present data show clearly, namely, that the characteristic effect of radiation on female fertility is a shortening of the breeding period,

and that this effect is very strongly dependent on dose rate.

The most plausible explanation of direct relation between dose rate and damage to oocytes is that some repair is occurring. The mechanism by which radiation kills oocytes is not known. Since the cells do not divide, chromosome imbalance cannot be the cause of death. Oakberg(3) finds the early oocytes to be killed very rapidly. Our experiments, reported elsewhere(16), indicate that the sensitive system, whatever its nature, is not markedly protected by hypoxic conditions during irradiation.

Summary. 1) In an attempt to contribute to an understanding of unusual radiation sensitivity exhibited by the mammalian oocyte, a non-dividing cell, fertility experiments were carried out to determine the effect of dose rate (fractionation, different intensities of continuous radiation). 2) Fractionation markedly reduced damage to fertility; and division of dose into 10-r fractions was more effective in this respect than division into 25-r fractions. Continuously exposed females were even less affected in breeding performance than females which had received fractionated irradiation, and the lower the dose rate the smaller was the deleterious effect on fertility. In all groups, production, in terms of number of females casting litters, remained at maximum level until beginning of a sudden steep decline that ended in sterility. It is for this reason that some experiments of other investigators, who have measured performance only in terms of the first postirradiation litter, have failed to show similar dose-rate effects. 3) The results indicate that some repair of radiation damage to oocytes can occur, and that repair is greater at lower dose rates.

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Comparison of Physostigmine and Amphetamine in Antagonizing the EEG Effects of CNS Depressants.* (25289)

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Many investigators have shown in animals that cholinergic drugs activate EEG by exciting subcortical centers(1-3). Other experiments reveal that adrenergic drugs also induce EEG activation by acting on the same areas of the brain(2-5). This indicates that the

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