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Genetic radiosensitivity of specific post-dictyate stages in mouse oöcytes

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1. INTRODUCTION

The irradiation of germ cells in meiotic and post-meiotic stages induces a relatively high incidence of dominant lethals, which cause early death of affected embryos. The radiosensitivity of particular stages of meiosis is known to vary, but investigation of this phenomenon in female mammals has been hampered by the difficulty of knowing what stage or stages are being irradiated. In adult mice, the interval between the dictyate (resting) stage and metaphase of the second meiotic division (which occurs just before ovulation) is approximately 12 hr., but the time of resumption of meiosis varies greatly even in females entering oestrus on the same day. Nevertheless, Russell & Russell (1956, 1959) have shown that irradiation at or near metaphase of the first meiotic division induces a higher incidence of dominant lethals than irradiation at the dictyate stage.

The aim of the present investigation was to measure the radiosensitivity of various stages of meiosis by using the technique of induced ovulation. Mature female mice, injected with pregnant mares' serum (PMS) and with human chorionic gonadotrophin (HCG) 40 hr. later, ovulate approximately 12 hr. after the injection of HCG (Fowler & Edwards, 1957). Most of the treated mice mate just before ovulation, and more than 90% of eggs are fertilized. The oöcytes in all treated females develop synchronously, so the exact stage of meiosis at a particular time can be forecast with accuracy (Edwards & Gates, 1959). Thus, by using this technique, it is possible to irradiate oöcytes at specific stages of meiosis with greater precision than was previously possible. If the females are mated after irradiation, the relative sensitivity of different stages in the oöcyte for the induction of dominant lethals can be calculated. In the present experiment we compare the relative sensitivity of dictyate, late prophase I, metaphase I, and anaphsae I (i.e. of the first meiotic division), metaphase II (i.e. of the second meiotic division), and the post-fertilization pronuclear stage.

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2. MATERIALS AND METHODS

The female mice were F_1 hybrids between the inbred strains C3H/He/H and 101/H. At the age of about 10 weeks each was given an intraperitoneal injection of 1·5 i.u. PMS followed by 2·0 i.u. HCG 40 hr. later. Groups were picked at random, and the following treatments given:

Time of irradiation	Meiotic stage irradiated	Time of pairing with males
None (controls)	—	7 hr. after HCG
½ hr. before HCG	Dictyate	,,
2¼–2½ hr. after HCG	Late prophase I	,,
5–5½ hr. after HCG	Metaphase I	,,
9½–9¾ hr. after HCG	Anaphase I	10 hr. after HCG
11½–11¾ hr. after HCG	Metaphase II	12 hr. after HCG
24 hr. after HCG	Pronuclear stage before or during DNA synthesis (Sirlin & Edwards, 1959)	7–11 hr. after HCG

Groups 1–4 were mated 7 hours after HCG to obtain maximum mating performance; groups 5 and 6 were mated immediately after irradiation. The females were paired with males of outbred strain *TO*, and examined several times between 3 and 18 hours after irradiation for evidence of mating (judged by the presence of a vaginal plug). Females that mated were killed 13 days later, and the numbers of corpora lutea, live and dead foetuses were counted. The incidence of foetal mortality during the first 13 days of gestation was estimated from these counts.

The experiment involved three series of injections and irradiations (120 kV, dose rate 48 r./min., HVL 1 mm. Al), each with its own control group. Mice were given 100 r. in the first series, 200 r. in the second series, and 100 or 200 r. in the third series, the irradiation being given to the whole body from beneath. A preliminary experiment showed that with a dose of 400 r. too few mice became pregnant for the results to be useful. Another preliminary experiment showed the time of ovulation in the hybrid strain used was similar to that found in other strains by Edwards & Gates (1959).

3. RESULTS

The main results are given in Tables 1 and 2. The experimental data are given in Table 1, and analysed in Table 2, to give estimates of the rate of induction of lethals.

(i) *Numbers of corpora lutea*

The three series of mice showed some differences in the numbers of eggs shed, as judged by the numbers of corpora lutea. For example, control mice in series II average fewer corpora lutea than controls in series I and III (14·0 against 19·8 and 19·6). This was probably due to different samples of gonadotrophins used: a preparation similar to the International Standard in series II, and 'Gestyl' (PMS) and 'Pregnyl' (HCG) of Messrs Organon in series I and III. Numbers of implanted embryos were therefore higher in series I and III.

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Table 1. *Reproductive data from three series of female mice irradiated after PMS and HCG injection and autopsied at 13½ days' gestation. PF indicates irradiation shortly after fertilization*

Series	Dose (r.)	Hours post-HCG	Number mated	Number with implanted embryos	Numbers of corpora lutea		Implanted embryos		Live embryos at 13½ days		Live embryos: Corpora lutea	Live embryos: Total implants	Total implants: Corpora lutea
					Total	Mean	Total	Mean	Total	Mean			
I	0	(Control)	8	8	158	19·8 ± 1·7	99	12·4 ± 2·1	81	10·1 ± 1·4	0·51	0·82	0·63
	100	0	13	13	250	19·2 ± 1·1	128	9·8 ± 1·0	103	7·9 ± 1·1	0·41	0·81	0·51
	100	2¼	15	14	217	15·5 ± 1·1	133	9·5 ± 1·0	119	8·5 ± 0·9	0·55	0·90	0·61
	100	5	10	6	73	12·2 ± 1·1	48	8·0 ± 0·8	25	4·2 ± 1·0	0·34	0·52	0·66
	100	9½	13	12	184	15·3 ± 1·4	90	7·5 ± 0·6	59	4·9 ± 0·6	0·32	0·66	0·49
	100	11½	8	8	118	14·8 ± 1·3	66	8·3 ± 1·0	48	6·0 ± 0·7	0·41	0·73	0·56
II	0	(Control)	17	14	196	14·0 ± 1·2	90	6·4 ± 0·7	80	5·7 ± 0·9	0·41	0·89	0·46
	200	0	10	8	111	13·9 ± 1·5	53	6·6 ± 0·8	42	5·3 ± 0·8	0·38	0·79	0·48
	200	2¼	13	12	152	12·7 ± 0·9	71	5·9 ± 0·8	53	4·4 ± 0·8	0·35	0·75	0·47
	200	5	13	8 (2)*	56	9·3 ± 1·6	42	5·3 ± 0·7	9	1·1 ± 0·4	0·12†	0·21	0·56†
	200	9½	6	4 (2)	20	10·0 ± 1·0	25	6·3 ± 1·0	5	1·3 ± 0·6	0·13†	0·20	0·63†
	200	11½	5	4 (1)	24	8·0 ± 0·6	17	4·3 ± 1·0	9	2·3 ± 1·3	0·28†	0·53	0·53†
	200	PF	9	8	91	11·4 ± 1·1	46	5·8 ± 0·7	33	4·1 ± 0·8	0·33	0·72	0·51
III	0	(Control)	18	16	314	19·6 ± 1·3	150	9·4 ± 1·0	142	8·8 ± 1·0	0·45	0·95	0·48
	100	5	15	11	193	17·5 ± 1·3	72	6·5 ± 0·8	45	4·1 ± 0·8	0·23	0·63	0·37
	100	11½	9	7	109	15·6 ± 1·2	49	7·0 ± 0·7	30	4·3 ± 0·7	0·28	0·61	0·45
	100	PF	9	9	149	16·6 ± 1·2	83	9·2 ± 1·3	75	8·3 ± 1·4	0·50	0·90	0·56
	200	0	11	10	168	16·8 ± 1·7	82	8·2 ± 1·3	65	6·5 ± 1·2	0·38	0·79	0·49
	200	2¼	9	9 (1)	157	19·6 ± 1·6	68	7·6 ± 0·8	22	2·4 ± 0·4	0·14†	0·35	0·39†
	200	5	18	15 (4)	129	11·7 ± 1·3	78	5·2 ± 0·5	19	1·3 ± 0·4	0·11†	0·24	0·44†
	200	9½	16	14 (2)	173	14·4 ± 1·3	85	6·1 ± 0·7	28	2·0 ± 0·4	0·14†	0·33	0·42†
	200	11½	15	14	250	17·9 ± 0·9	107	7·6 ± 0·8	41	2·9 ± 0·5	0·16	0·38	0·43
	200	PF	5	3	39	13·0 ± 2·5	18	6·0 ± 2·6	13	4·3 ± 2·4	0·33	0·72	0·46

* Figures in brackets (included in totals) are the number of pregnant mice in which luteal counts could not be made, usually because no embryos survived beyond early implantation and corpora lutea atrophied.

† These estimates are made on the assumption that the average number of corpora lutea was the same in the mice in which they could not be counted as in the others in the group.

Table 2 shows that the mean numbers of corpora lutea in irradiated mice were lower than the numbers in controls, the decrease being greatest in the 5 hr. and 9½ hr. groups with 200 r. irradiation. In the preliminary experiments with 400 r., mentioned above, no reduction in the numbers of eggs shed could be found after irradiation, hence there was little if any killing of oöcytes before ovulation. Mice with few corpora lutea had few foetuses. The reduced numbers of corpora lutea could be due to the increased mortality of embryos after irradiation or to the somatic effects of irradiation. The total implant/corpora lutea ratio showed no marked decline after irradiation (Table 1), due to the decline in both the numbers of corpora lutea and of implanted embryos.

Table 2. *Analysis of Table* 1 *data, giving estimates of induced dominant lethality, etc Weighted means have been calculated where two estimates are available*

Dose (r.)	Hours post-HCG	% of mice with implanted embryos	Corpora lutea: % of control	Implanted embryos: % of control	% induced overall death (0–13½ days)†	% induced death after implantation
100	0	100	97	80	19·7	1·6
100	2¼	93	79	77	−6·8	−9·4
100	5	68	79	68	43·1	34·8
100	9½	92	77	61	37·4	19·8
100	11½	88	77	70	29·3	22·4
100	PF	100	85	98	11·3	4·5
200	0	86	92	94	11·3	13·9
200	2¼	95	95*	87	38·2	36·1
200	5	74	62*	65	74·1	74·8
200	9½	82	73*	72	69·2	68·0
200	11½	90	85*	78	56·5	55·4
200	PF	79	77	83	15·1	20·5

* Estimates excluding those females in which full luteal counts could not be made.
† Calculated from formula of Russell & Russell (1956).

Fifty-eight pronucleate eggs taken from mice irradiated 2¼, 5 or 9½ hr. after HCG were examined under the phase-contrast microscope. All of them possessed two pronuclei and appeared to be morphologically normal.

(ii) *Foetal mortality*

Foetal mortality before implantation can be detected by a decrease in the proportion of mice with implanted embryos and by a reduction in the numbers of embryos that implant. The proportion of mice with implanted embryos was lowest with 200 r. irradiation 5 hr. after HCG (Table 2). The mean number of implanted embryos was also lowest at 5 hr. post-HCG. These figures suggest that for the induction of pre-implantation mortality metaphase I is the most sensitive stage, followed by anaphase I and metaphase II.

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Irradiation of these stages also caused the highest incidence of foetal death after implantation, the proportion of living foetuses at 13 days being lowest after irradiation at 5 and 9½ hr. with both 100 r. and 200 r. (Table 1). Only after 200 r. were females found in which every embryo was dead. This occurred in 1/21 mice (5%) irradiated 2¼ hr. after HCG, 8/23 (35%) at 5 hr., 3/18 (17%) at 9½ hr., and 1/18 (6%) at 11½ hr. Implanted foetuses which died could be divided into two major classes: those dying before 9 days were recognizable as small moles (deciduomata), while those dying between 9 and 13 days were recognizable as placentae with or without the remains of dead foetuses. Death after 8 days occurred in 2·6% of foetuses in controls, 1·9% in females given 100 r., and 2·6% in females given 200 r. Induced dominant lethals thus acted before or shortly after implantation.

(iii) *Indices of dominant lethal induction*

Russell & Russell (1956, 1959) compared the ratio of living embryos to corpora lutea in irradiated mice with that in controls as a measure of the rate of induction of dominant lethals. With their method, estimates obtained from our data for the percentage of lethals obtained after radiation at different stages of meiosis are shown in Table 2 and Fig. 1. An alternative estimate, based on the ratio of living

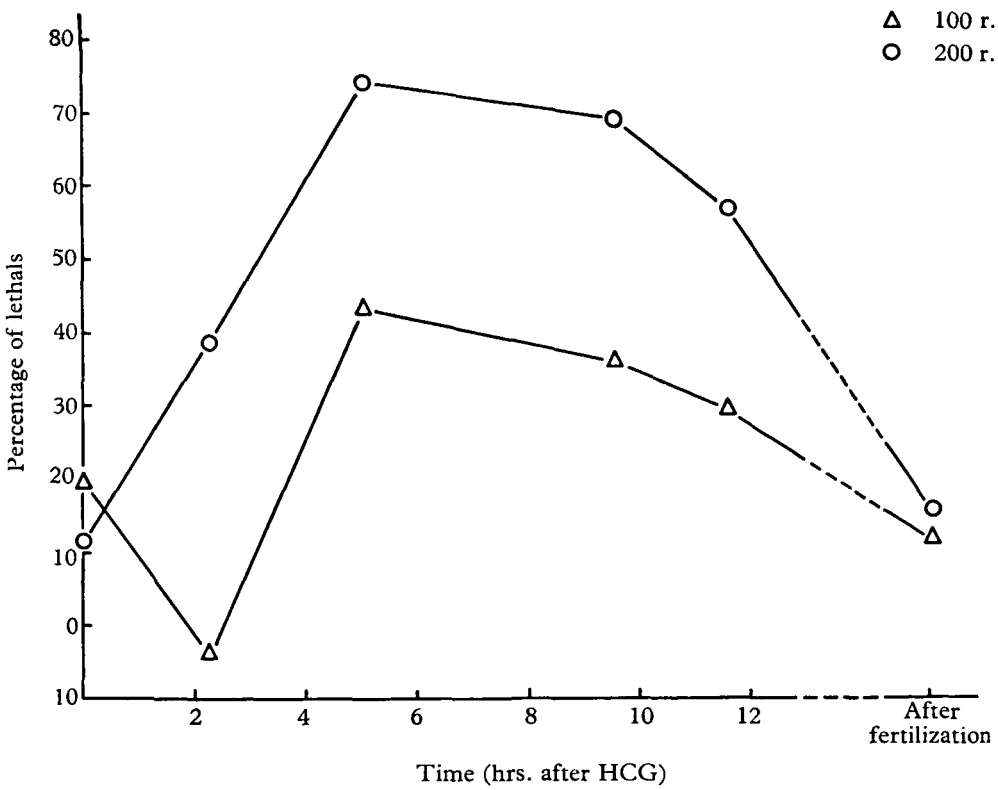

Fig. 1. The overall percentage of dominant lethals (derived from living embryo/corpus luteum ratio) induced in mouse oöcytes by X-irradiation at various times after HCG injection.

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foetuses to total implants in irradiated and control mice is also given in Table 2. This method measures only post-implantation mortality, but avoids any masking through 'embryonic compensation' (see Discussion) and the somatic effects of irradiation on corpora lutea. Both estimates show that the incidence of dominant lethals rises sharply in late prophase I or early metaphase I, reaching a peak at mid-metaphase I. After metaphase, the rate begins to decline; it is still high in anaphase-telephase and in metaphase II, but then declines after fertilization to the

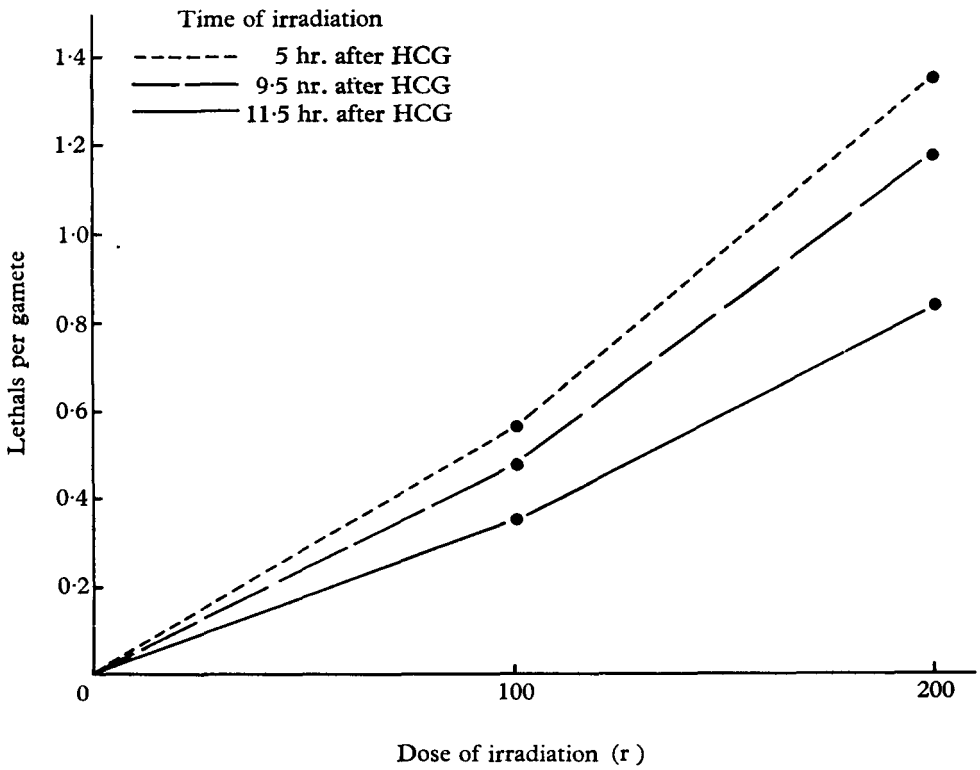

Fig. 2. Mutation rates to dominant lethals induced in mouse oöcytes by 100 r. and 200 r. X-irradiation at various times after HCG injection.

levels found in the dictyate stage. The only serious discrepancy between replicate experiments was in mice irradiated 2¼ hr. after HCG, when oöcytes were in diplotene or diakinesis (compare series II and III, 200 r., Table 1). Since this stage shows the most rapid change in radiosensitivity, the difference found is not altogether surprising.

Figure 2 shows the relation between dose and mutation rate to dominant lethals for the three most sensitive stages, on the assumption that the numbers of irradiated gametes carrying 0, 1, 2, ... induced dominant lethal mutations form a Poisson series. Thus, if m is the mutation rate to these lethals, $e^{-m} = 1-p$, where p is the proportion of gametes carrying at least one lethal, taken as equivalent to the

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estimated overall incidence of induced dominant lethality. With all three oöcyte stages the dose-mutation relationship shows a similar departure from linearity. Assuming that $m = kx^n$ (where x is the dose of X-rays), n has a similar value for the three sensitive stages, being 1·26 for metaphase I and II, and 1·33 for anaphase I. The following LD_{50} values can be derived ($m = 0{\cdot}693$): metaphase I, 118 r.; anaphase I, 134 r.; metaphase II, 173 r. During late prophase I the LD_{50} probably falls rapidly, but the exact situation cannot be revealed without further experiments. The LD_{50}'s for the dictyate stage of prophase and for irradiation shortly after fertilization cannot be accurately estimated from our data, but are both probably of the order of 500 r., i.e. similar to that obtained with irradiation of mouse spermatozoa.

4. DISCUSSION

Two factors could complicate the interpretation of the results of the present experiment. Firstly, somatic effects caused by whole-body irradiation could possibly lead to embryonic mortality independently of genetic effects on the embryos. The period of oöcyte maturation and pronuclear growth covered by the irradiation schedules coincides with the rapid formation of the corpora lutea, and damage to corpora lutea could suppress normal foetal development. But this seems an unlikely interpretation of our results. Corner (1928) found that the complete set of foetuses persisted in rabbits when almost all corpora lutea were surgically removed. Chang & Hunt (1960) transferred irradiated rabbit ova to non-irradiated females and *vice versa*, and showed that with irradiation shortly after fertilization most of the foetal mortality was due to embryonic lethals. Mandl (1962) has reported that high doses of X-rays, probably higher than used in the present experiment, do not inhibit ovulation but might impair the ability of the granulosa cells to become fully luteinized. Nevertheless, the fact that many foetuses died after implantation shows that the corpora lutea were sufficiently active to permit implantation during early pregnancy. Reduction in numbers of corpora lutea might therefore have occurred after the death of many implanted foetuses.

The second factor lies in the technique of induced ovulation. Variability between mice in the numbers of eggs shed is much greater than normal (Falconer *et al.*, 1961), and this could lead to increased preimplantation mortality when large numbers of eggs are present in a uterus (Bowman & Roberts, 1958). The histogram in Fig. 3 shows that increased mortality occurred in our control mice, preimplantation death being proportionally greater with increasing numbers of corpora lutea (Edwards *et al.*, 1963). Increased mortality before implantation could lead to *embryonic compensation* (Carter & Lyon, 1961), i.e. a greater proportion of normal embryos implant in irradiated than in control mice, since the death of embryos with lethals reduces competition for available uterine sites. The full effects of induced lethality before implantation could thus be masked by embryonic compensation. This phenomenon would affect our estimates for the most sensitive stages of meiosis more than those for the least sensitive stages. For example, Bateman (1958) showed that

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mortality before implantation is high only with extreme radiation damage. Also, irradiation of mouse spermatozoa with between 0 r. and 500 r. X-rays did not alter the proportion of mouse embryos that reached the blastocyst stage or the mean number of nuclei in $3\frac{1}{2}$-day-old embryos, but greater amounts of irradiation curtailed embryonic development (Edwards, 1957). There was no masking of lethals after implantation in the present experiment, for the proportion of dead implants did not rise with increasing numbers of implantations in control mice.

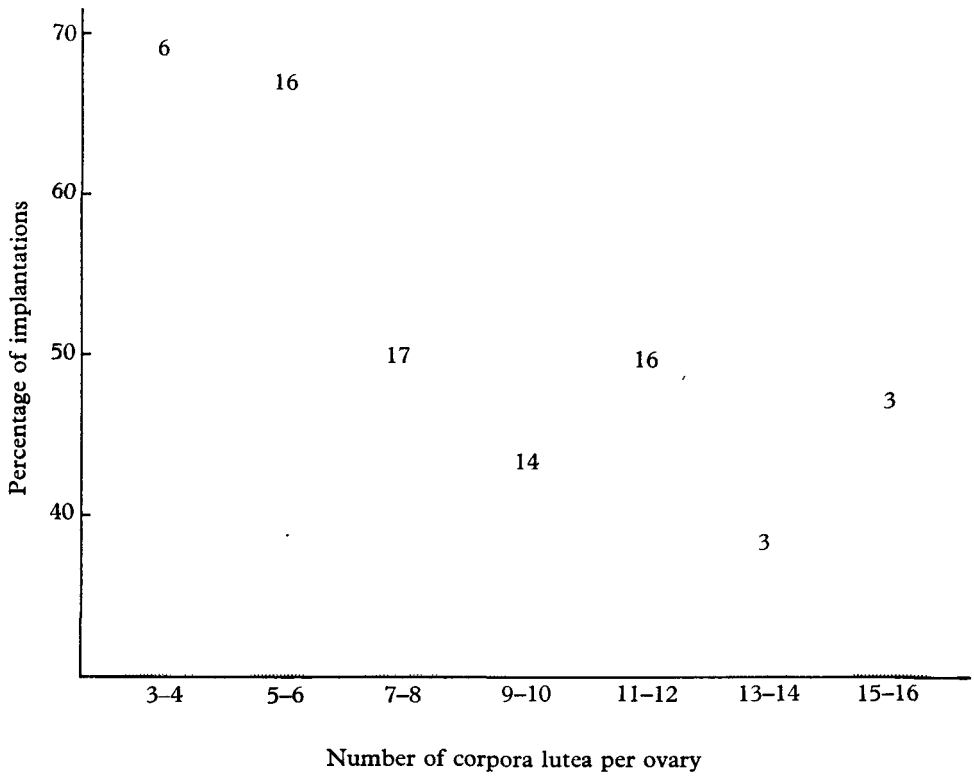

Fig. 3. Histogram showing the relationship between the percentage implantation per uterine horn and the number of corpora lutea in the corresponding ovary. The numbers above each column show the numbers of ovaries in the group.

Our observations in the mouse confirm those of L. B. Russell (1956) and Russell & Russell (1956, 1959) that metaphase of the first meiotic division is highly radiosensitive, and provide estimates of the radiosensitivity of other meiotic stages. Since meiotic events were not synchronized in the experiments of Russell and Russell, stages adjacent to metaphase I may also have been irradiated. Their estimates of the LD_{50}'s were 700 r. for dictyate and 70 r. at or near metaphase I. Russell & Russell (1956) assumed that females irradiated at metaphase I had an equal number of corpora lutea as controls, because of the unreliability of luteal counts when few or no embryos were implanted. If we make the same assumption for our data,

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induced lethality at metaphase I rises to 80·4%, and the LD_{50} falls to 95 r. In the rat, Mandl (1963) has shown that there is a progressive increase of genetic radiosensitivity as the oöcyte passes from late dictyate through successive stages, at least up to metaphase I. Mandl judged the stage of maturation of the irradiated oöcytes by excising one ovary and classifying the oöcytes in it.

Our findings of increased radiosensitivity during meiotic metaphase and anaphase also agree well with results of other studies on a wide variety of organisms. For example, Whiting (1945*a* and *b*) found that in *Habrobracon* metaphase I was 32 times as sensitive as prophase I (diplotene) with respect to induced dominant lethal damage, as measured by egg hatchability. La Chance & Leverich (1962) found in the screw worm *Cochliomyia* that the LD_{50} radiation dose with respect to egg hatchability was 1309 r. for metaphase I, 1639 r. for anaphase I, but 7939 r. for prophase I. Studies of chromosome aberrations in F_1 *Sciara* larvae by Bozeman & Metz (1949) showed anaphase I of meiosis to be the most radiosensitive stage, with prophase I comparatively insensitive. In all these studies, as in our own, oöcytes could be treated in known stages of development. Where this has not been possible so far, as in *Drosophila*, fully comparable results are not yet available, but Sävhagen's (1960) findings suggest metaphase I and anaphase I of male meiosis are the most sensitive with respect to the induction of XO males. In plants, work by Sparrow and others on *Trillium*, reviewed by Evans (1962), showed that the rate of induction of chromosome aberrations was highest following irradiation of cells between diplotene and metaphase I. Evans discusses the reasons for the great increase in radiosensitivity during the division stages. It could obviously be a result of the contracted state of the chromosomes, but Evans suggests that much of it may be due to an increase in intracellular oxygen tension in dividing cells relative to interphase cells.

5. SUMMARY

The induction of dominant lethals after X-irradiation of dictyate, later meiotic stages, and the pronuclear stage after fertilization have been compared using the technique of induced ovulation in mice. The injection of gonadotrophins ensures that the time at which the synchronously dividing oöcytes reach any particular meiotic stage is accurately known. Embryonic lethality up to 13½ days was studied after 0 r., 100 r. and 200 r. acute X-irradiation. Metaphase I, anaphase I and metaphase II were the most sensitive stages, with LD_{50}'s of about 120 r., 130 r. and 170 r. respectively. The dictyate and pronuclear stages were much less sensitive, with LD_{50}'s in the region of 500 r., and sensitivity rose steeply during prophase I. Numbers of corpora lutea decreased with irradiation, the decrease being greatest with irradiation at metaphase I and anaphase I. The ovulation of large numbers of eggs, which increased the preimplantation loss of embryos above normal, and the low luteal counts probably masked lethality to some extent. Results generally agree well with those reported in a number of plant and animal species.

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