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Ovary Tumors in NMRI Mice Subjected to Fractionated X-irradiation During Fetal Development

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Summary. Fractionated X-irradiation of pregnant mice was performed either during late organogenesis (gestational days 11–13), during the early fetal period (g.d. 14–16), or during both periods (g. d. 11–16). The offspring were observed for 39 months. A significant increase of ovary tumor frequency was observed with 3×1.2 Gy, applied either in late organogenesis or in the early fetal period. Lower X-irradiation doses were ineffective in these periods with respect to ovary tumor development. A sharp increase in ovary tumor frequency resulted after irradiation with 6×0.8 Gy or 6×1.2 Gy. The highest incidence of ovary cysts was observed after 3×1.0 Gy or 3×1.2 Gy on g.d. 11–13, while the frequency of these cysts was lowest in the animals irradiated six times, which, however, showed a high ovary tumor frequency. Autoradiography of the fetal ovaries either 1 or 6 days after irradiation at the late organogenesis stage revealed a persistent depression of this organ's proliferation rate throughout pregnancy. This may be consistent with the low tumor inducibility after X-irradiation in this period.

Key words: Ovary Tumors – X-irradiation – In utero

Irradiation of the ovaries leads to a precocious reduction of the number of oocytes and ovarian follicles (Andersen and Simpson 1969). With the exception of these cells, practically all the other cells forming the ovary appear susceptible to neoplastic transformation by radiation (Upton 1968). Ovarian tumors are frequently inducible in the young adult mouse with doses as low as 0.5–1.0 Gy (Clapp et al. 1974). This inducibility does not occur at a uniform level at any age (Kaplan 1947); rather, there are developmental phases of maximum radiosensitivity and, accordingly, tumor inducibility (Kaplan 1948, 1950; Peters, 1966). In the rat, where both prenatal and postnatal variations in the sensitivity of female germ cells to X-rays have been studied (Beaumont 1968), two periods of enhancement have been found, one on about the 15th day of gestation coinciding with the peak mitotic activity of oogonia, and the other several days after birth, when most oocytes have entered

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the dictyate stage (Kaplan 1948; Beaumont 1968). Most investigators have been concerned mainly with the induction of ovary tumors at the postnatal stage (Kaplan 1950; Peters 1966; Pedersen et al. 1969; Anderson et al. 1972; Clapp 1978). In addition to these reports, we have now studied ovary tumor frequency when X-irradition was performed throughout fetal life.

The rationale for the following experiments arose from our former studies (Kriegel and Reinhardt 1969; Schmahl et al. 1979), when we already used the same experimental set-up, but only for prenatal examination. We were thus able to state that doses up to 3×0.8 Gy (during days 11–16 post conception) are not sufficient at the histological level to influence the development and differentiation of the embryonic tissues, although the effects of daily irradiation are regarded as very substantial in the fetus (Semagin 1961; Andersen and Simpson 1969), presumably as a result of interaction between injury and repair events (Auerbach 1956). To compare the prenatal results with long-term effects we started this study, applying the same dosages as before.

Material and Methods

Female virgin NMRI mice, 8 weeks of age, were mated between 8 a.m. and 10 a.m. and subsequently examined for vaginal plugs. The next morning was considered to be day 1 post conception (p.c.). Mother animals were divided into eight experimental groups. They received a standard diet (Altromin) and water ad libitum and were housed in cages in air-conditioned animal rooms at 23 °C with artificial light from 6 a.m. to 6 p.m. Irradiation of the pregnant mice was carried out at 9 a.m. on several days of gestation with a therapeutic X-ray unit at 180 kV and 15 mA (0.01 Gy/s). We used an 0.3-mm-thick copper plate as a filter. The focus/target distance was 40 cm. For the purpose of irradiation, five mother animals were caged together in a round, flat plastic restrainer. Registration of the radiation dose applied was performed at a central hole in this restrainer with the help of a Victoreen dosimeter.

The irradiation scheme, the numbers of mother animals, stillbirths, and mean litter sizes are listed in Table 1.

The animals were observed until the end of the experiment at an age of 39 months. All animals were autopsied after their spontaneous death or killed. Pathologic abnormalities were registered and a histological observation was also performed with the exception of the animals with a severe autolysis.

In addition, sex dams received ^{3}H-thymidine (5 μ Ci/g body weight; specific activity 5 Ci/mmol) i.p. immediately after a single X-irradiation exposure of 2.0 Gy on day 12 p.c. Three dams were autopsied on day 13 p.c., the other 3 on day 18 p.c. Whole body sections of their fetuses (day 13 p.c.) or of the gonadal region of the abdomen (day 18 p.c.) were processed for histoautoradiography by dipping them in Kodak NTB 2 emulsion, developing them in D 19, and subsequently staining them with H. E.

Statistical Methods

The distribution of ages at death differed considerably among the experimental groups. For this reason, the observed incidences of ovary tumors and lymphoproliferative diseases do not accurately reflect the tumorigenic effectiveness of the radiation exposures. To reflect this effectiveness more accurately, we decided to adjust the incidence values to those that presumably would have been observed had all the groups shown the same distribution of ages at death, as in the case of a standard population. We determined the age-adjusted incidences according to Ullrich et al. (1976) and, in further analogy, used Abbott's formula to evaluate the corrected tumor incidences.

We also tested goodness of fit by using standard 4 square X^2-tables after applying Yates correction values.

Results

The fetal, as well as the postnatal mortality rates show considerable differences between the experimental groups (Tables 1 and 2, Fig. 1). An outstanding high post-

Table 1. Treatment schedule and mortality rates of mouse offspring after fractionated X-irradiation in utero

Group No.	1	2	3	4	5	6	7	8
Fractionation scheme		3 × 0.8 Gy on days 11–13 p.c.	3 × 0.8 Gy on days 14–16 p.c.	3 × 1.0 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 14–16 p.c.	6 × 0.8 Gy on days 11–16 p.c.	6 × 1.2 Gy on days 11–16 p.c.
Whole X-irrad. dose (Gy)	0	2.4	2.4	3.0	3.6	3.6	4.8	7.2
Number of mother animals	11	15	13	38	37	16	25	52
Number of live offspring	145	150	133	307	245	174	294	351
(% of litter)	(99.1)	(92.1)	(98.5)	(72.9)	(57.0)	(94.4)	(97.4)	(63.1)
Stillbirth	2	13	2	107	184	10	8	205
(% of litter)	(0.9)	(7.9)	(1.5)	(27.1)	(43.0)	(5.6)	(2.6)	(36.9)
Mean litter size	13.4	10.9	10.4	11.1	11.6	11.5	12.1	10.7

Table 2. Early and long-term mortality rates of mouse offspring after fractionated X-irradiation in utero

Group No.	1	2	3	4	5	6	7	8
Fractionation scheme		3 × 0.8 Gy on days 11–13 p.c.	3 × 0.8 Gy on days 14–16 p.c.	3 × 1.0 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 14–16 p.c.	6 × 0.8 Gy on days 11–16 p.c.	6 × 1.2 Gy on days 11–16 p.c.
Whole X-irrad. dose (Gy)	0	2.4	2.4	3.0	3.6	3.6	4.8	7.2
Immediate postnatal mortality (%)								
within 1st day	4.7	11.9	1.5	32.0	24.5	8.5	3.8	18.6
within 1st week	5.7	12.6	3.0	39.2	43.4	10.5	9.2	53.8
within 1st month	8.5	12.6	5.2	45.1	52.8	15.2	17.7	62.9
Number of offspring for long-term observation								
a) total	132	137	125	169	116	150	239	131
b) females	63	74	52	68	59	71	112	64
Mortality rate at 24 months								
a) total	48%	63%	58%	62%	79%	82%	56%	92%
b) females	49%	59%	58%	63%	77%	83%	52%	86%

natal mortality can be seen especially in the groups 4, 5, and 8. As a function of the irradiation dose and the subsequent perinatal mortality, there are different age peaks of the mortality incidences. There is, however, no prevalence for any disease in the experimental groups, with the exception of ovary disorders (Table 2). Even one of the most outstanding diagnoses, prominent in all radiobiological long-term studies with mice, viz. leukemias, was only observed at a lower rate in all experimental groups (22.0% in the control groups, 13.3–17.5% in the experimental groups). There are also no marked age peaks, nor is there any sex prevalence in leukemia incidence.

The pathologic findings of the ovaries are listed in Table 3.

Ovary Tumors

Most of the ovary neoplasms were of the tubular adenoma type (about 80%), while the rest consisted of equal amounts of luteomas and granulosa cell type tumors.

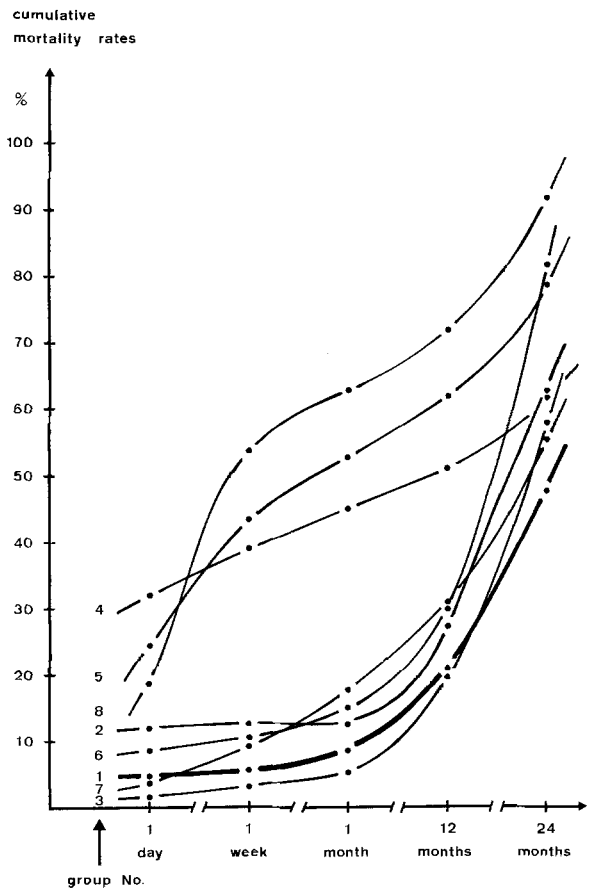


Fig. 1. Cumulative mortality rates of the controls and the different experimental groups after in utero X-irradiation

Ovary tumors were found in all groups, starting at 11 months of age and a continuously increasing frequency with age. However, there was in all groups a peak incidence for ovarian tumors between 21 and 24 months of age.

In the controls their incidence rate was 14.2%, in the experimental groups it ranged between 13.5% and 27.6% of all the female offspring. The age-adjusted incidences were in the range between 0.03% and 12.4%. We also determined the incidence rates in relation to all embryos irradiated, respectively to the live neonates (Fig. 2). These incidences are completely distinct from the above ones, due to the great differences in fetal and postnatal mortality.

After application of 2.4 Gy in fractionated doses either in the late organogenesis (group 2) or in the early fetal period (group 3), no increase in ovary tumor frequency was observed. The same is true for 3×1.0 Gy within days 11–13 p.c. (group 4). Due to a marked frequency in stillbirths and in postnatal deaths the ovary tumor incidence rate per irradiated embryos is severely decreased (2.4%) in relation to the controls (6.1%).

At the next higher radiation dose (3×1.2 Gy) applied during late organogenesis (group 5), a significant increase in the incidence of ovary tumors was found

Table 3. Age-adjusted incidences of pathological findings in the offspring up to 39 months after in utero X-irradiation

Group No.	1	2	3	4	5	6	7	8
Fractionation scheme		3 × 0.8 Gy on days 11–13 p.c.	3 × 0.8 Gy on days 14–16 p.c.	3 × 1.0 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 11–13 p.c.	3 × 1.2 Gy on days 14–16 p.c.	6 × 0.8 Gy on days 11–16 p.c.	6 × 1.2 Gy on days 11–16 p.c.
Whole X-irrad. dose (Gy)	0	2.4	2.4	3.0	3.6	3.6	4.8	7.2
Ovary tumors								
% of females	14.2 (0)[c]	13.5 (− 0.04)	15.3 (1.08)	14.7 (− 0.03)	16.9 (2.2)	19.7[a] (4.6)	27.6[b] (12.4)	25.0[b] (10.8)
% of irradiated embryos	6.1	6.1	5.9	2.4	2.3	7.6	10.2	2.8
% of living offspring	6.1	6.6	5.9	3.2	4.0	8.0	10.5	4.5
Ovary Cysts								
% of females	3.1 (0)	6.7[a] (2.6)	3.8 (0.04)	10.2[b] (6.8)	10.1[b] (6.5)	2.8 (− 0.08)	3.5 (0.01)	3.1 (0)
Lymphoproliferative diseases (%)	22.3 (0)	16.8 (− 5.1)	15.2[a] (− 5.9)	14.8[a] (− 7.4)	14.4[a] (− 7.6)	13.3[a] (− 7.8)	14.6[a] (− 7.6)	17.5 (− 6.2)

[a] $= p < 0.05$

[b] $= p < 0.001$ (Significances as evaluated with the X^2-test after Yates correction)

[c] Numbers in parentheses represent corrected incidences using Abbott's formula

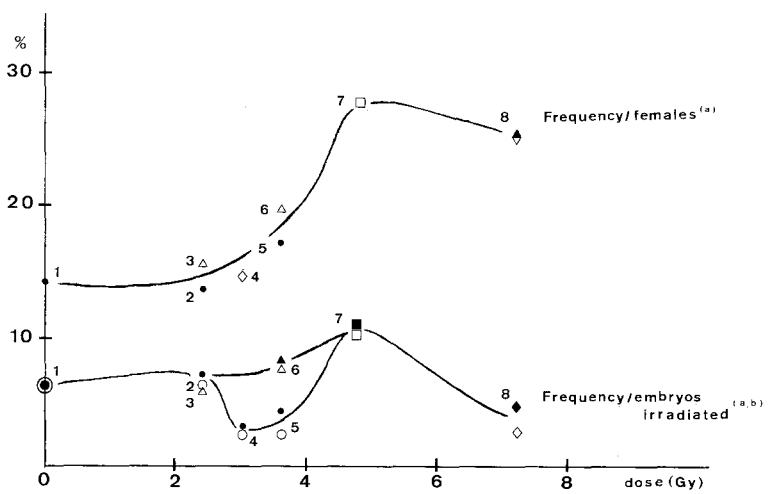


Fig. 2. a, b. Percent incidence of ovary tumors after in utero X-irradiation. **a** Round symbols: irradiation during days 11–13 p.c. Angular symbols: irradiation during days 14–16 p.c. **b** Dark symbols: frequency per live offspring. Light symbols: frequency per total number of fetuses (live fetuses and stillbirth)

(17.7% and 2.2% age-adjusted respectively). This frequency was much higher if the same dose was applied at a later developmental stage (group 6: 19.3% and 4.6% respectively). However, a main difference could be seen, when comparing the frequencies per irradiated embryos. This value is very low in group 5 animals (2.3%, see Fig. 2), while markedly higher in group 6 (7.6%) which is also significantly increased against the control value (6.1%).

A sharp increase in ovary tumor frequency resulted after 6-times irradiation throughout days 11–16 p.c. in both dosage groups 7 (3 × 0.8 Gy: 27.6% and 12.4% respectively) and 8 (3 × 1.2 Gy: 25.0% and 10.8% respectively). Irrespective of the dose applied, this increase was nearly twice the frequencies observed in groups 2–6. The difference is statistically significant ($p < 0.001$). However, the frequency per irradiated embryos is rather high in group 7 (10.2%), whereas in group 8 animals this value is as low as in groups 4 or 5 (2.8%).

Ovary Cysts

Ovary cysts were observed in all animals, but in most cases (groups 1, 3, 6, 7, 8) they occurred at a low degree and at an equal rate to the controls. The frequency rate was higher in groups 4 and 5 ($p < 0.05$), but the reliability of these data is diminished by the fact that some bloodfilled cysts of the ovaries, which were registered under this heading, may have turned out to be preneoplastic (hemangiomatous) lesions, but it had been impossible to observe them histologically. This can also be confirmed by the observation that experimental groups with a pronounced ovary tumor incidence developed only a low ovary cyst incidence (see groups 7 and 8).

The histoautoradiograms revealed a markedly diminished number of labelled fetal ovary cells 24 h (Fig. 3) and 6 days (Fig. 5) after X-irradiation, as compared to the untreated controls (Figs. 4 and 6).

Discussion

Our findings indicate a remarkable degree of ovary tumor inducibility by prenatal X-irradiation during the fetal period, while irradiation in the organogenesis period is of low efficacy with respect to this disease. This response to fetal X-irradiation was indeed expected on the basis of reports indicating a high radiosensitivity of the fetal ovaries (Beaumont 1966; Haas et al. 1973; Dobson and Cooper 1974; Nash 1969, 1976) and the correlation between radiosensitivity in young animals and tumor induction in the ovaries (Kaplan 1950; Pedersen et al. 1969). Our incidence rates are remarkably lower than those reported after irradiation of young adult RF/Un-mice with 0.5–1.0 Gy (Clapp et al. 1974: 45–55%; Clapp 1978: 50–60%; Ullrich et al. 1976: 35%), but are roughly equal to those reported in strain A mice (Kaplan 1947: 20% after 6 Gy; Furth and Butterworth 1936: 27.9% after 4 Gy).

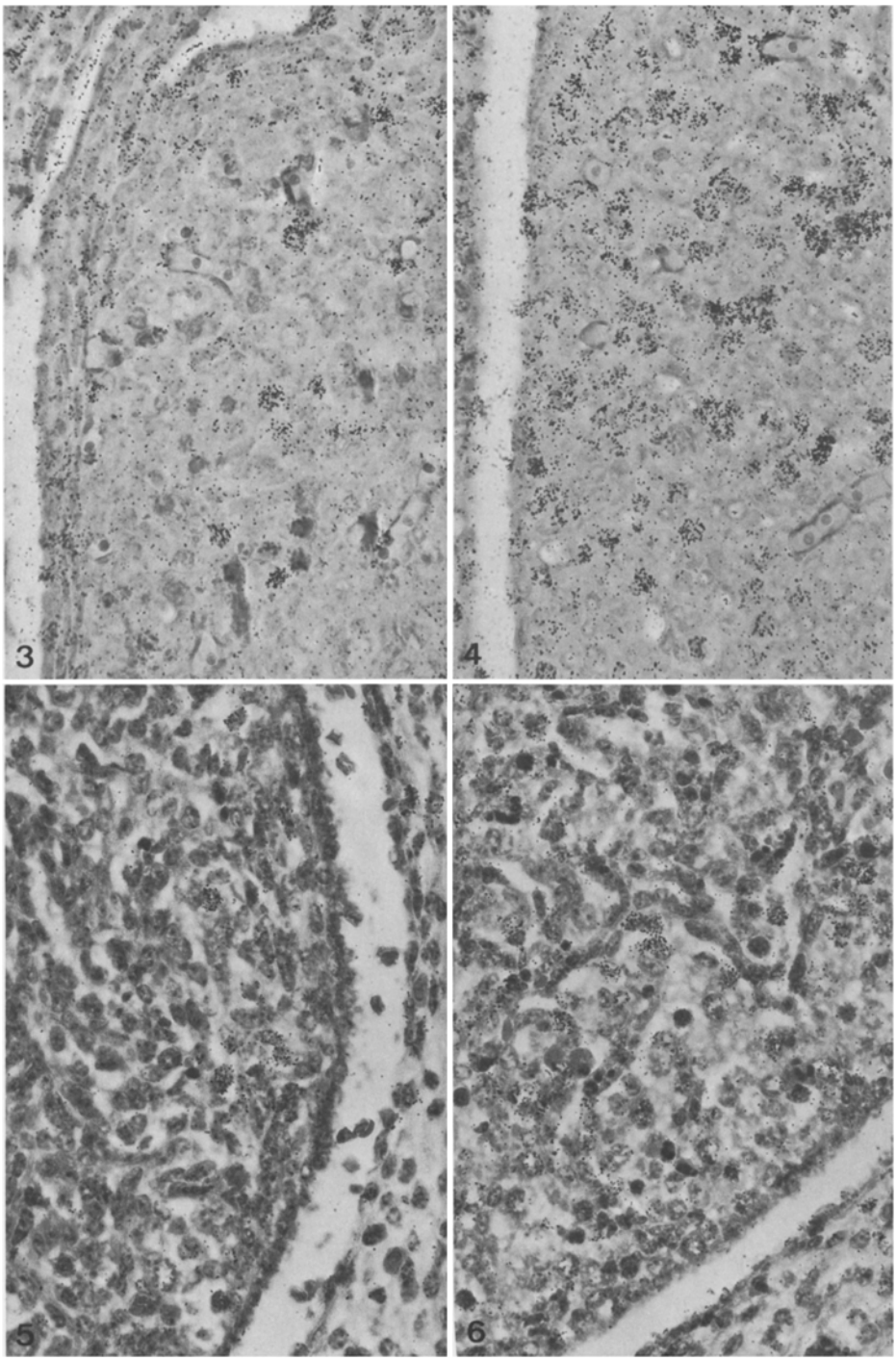
►

Fig. 3. Fetal ovary 24 h after a single X-irradiation with 2.0 Gay at gestational day 12 and subsequent injection of ^{3}H-thymidine. Note the markedly diminished number of labelled cells of the ovary anlage. H & E, × 370

Fig. 4. Fetal ovary 24 h after application of ^{3}H-thymidine to the dam at gestational day 12. Frequent and intensely labelled cells of the ovary anlage. H & E, × 370

Fig. 5. Fetal ovary at gestational day 18, 6 days after X-irradiation with 2.0 Gy and subsequent application of ^{3}H-thymidine. Only a few primordial cells are poorly labelled. H & E, × 370

Fig. 6. Fetal ovary at gestational day 18, 6 days after application of ^{3}H-thymidine to the dam. Frequent and intensely labelled primordial cells. H & E, × 370


3
4
5
6

However, X-irradiation with 7 Gy in Charles River mice (Anderson et al. 1972) and with 8 Gy (Brambell et al. 1927) induced ovary tumors at an incidence of only 10%.

These discrepancies may be partly due to strain differences. Dose-effect relationships must, however, also be considered, and attention should also be given to recent results (Clapp 1978) on a maximum inducibility of ovarian tumors in young adult mice in the 0.5–1.0 Gy dose range and a gradual decline in incidence from 1 Gy to 4 Gy.

Our results are contrary to a study conducted by Upton et al. (1960) also on the subject of prenatal X-irradiation. Prenatal irradiation was regarded as having a low tumor induction effect. The lowest incidence rates were found after X-irradiation throughout days 17–19 p.c., while neonatal irradiation caused an ovary tumor frequency of nearly 66% (Upton et al. 1960). However, this discrepancy can be explained by the well-documented decrease in radiosensitivity of the ovaries at the later stages of fetal development (Mintz 1959; Beaumont 1962; Langendorff and Neumann 1972), at which time Upton et al. (1960) irradiated (days 17–19 p.c.). This explanation is reasonable, as another study on late effects after earlier prenatal irradiation – within days 16–18 p.c. – at 3×2.0 Gy (Sasaki et al. 1978) reports a significant increase in the ovary tumor frequency of offspring. This same study further states that a single X-irradiation of 2.0 Gy on day 12 p.c. did not result in any ovary tumor outcome. This we can confirm in principle, as we, too, did not observe an increase in ovary tumor frequency after fractionated X-irradiation at similar doses (2.4–3.0 Gy) in the same developmental period (organogenesis). Further, these results are consistent with our earlier observations (Schmahl and Kriegel 1978) on a decrease of the prenatal chemical inducibility of tumors after antecedent X-irradiation at midgestation times. One possible explanation for this would be an increased embryonic death in these animals leading to the elimination of a great proportion of animals carrying transformed ovaries. This does not mean that we suggest a direct link between malignant transformation and embryonal death. However, it seems possible that potentially transformed tissues are unequally distributed within the whole fetal population in utero, occurring with a higher probability in those offspring which exhibit severe embryotoxic effects, than in apparently less affected individuals. This point of view is demonstrated by correlating the tumor frequencies to the number of irradiated embryos, as is shown in Fig. 2. Very low frequencies are present in group 4 and 5 animals. The higher frequencies observed in group 6 animals after irradiation in a late fetal stage, can also be explained in this context: In this group the survival of the irradiated embryos is greater, i.e., a higher proportion of animals carrying transformed ovaries have died in group 5 than in group 6.

Another possibility of explaining the low efficacy of irradiation during organogenesis for ovary tumor induction would be, apart from altered mortality rates, the decreased cell proliferation in some or all organs due to X-irradiation (Kauffman 1976), which is also consistent with the observations of a low tumor iducibility in rat brains with postirradiational hypoplasia (Warkany et al. 1976). Indeed, we also observed by autoradiograhy a decreased incorporation of ^{3}H-thymidine in the fetal ovaries both 24 h and 6 days after irradiation. Therefore, a compensation of the initial proliferation decrease by an onset of increased proliferation a few days later

does apparently not occur in the ovaries as it does in the biphasic regeneration of the fetal liver, as described by Konermann (1976).

If X-irradiation in the organogenesis stage is combined with further X-irradiation in the fetal period, a markedly increased ovary tumor yield results, although comparability is difficult to establish because of the greater total X-irradiation dose applied simultaneously. This effect can be seen best in group 7 (6×0.8 Gy), whereas the application of higher doses (group 8: 6×1.2 Gy) leads to a decrease in tumor frequency. This is presumably due to a high mortality and is also caused by a decreased proliferation rate of the ovaries.

Hypoplasia is induced in the ovary only by irradiation in late organogenesis (Beaumont 1966) and not after irradiation in the early fetal period. Cystic degeneration is only increased after irradiation in the early fetal period, while this premitotic degeneration does not appear to increase at the doses we have used in cells capable of hypoplasia.

The study conducted by Sasaki et al. (1978) also reports a decreased occurrence of lymphoreticular tissue tumors after 2.0 Gy X-irradiation on day 12 p.c. This finding can be confirmed by us, too, and may be explained by a similar growth depression effect of the irradiation, as in the ovaries. This effect presumably also causes the high mortality of the offspring within the first 24 months of life, mostly due to pyogenic infections and amyloidosis, which appear as secondary occurrences to a very marked dysplastic skin syndrome (Schmahl et al. 1980) with severe skin ulcerations.

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