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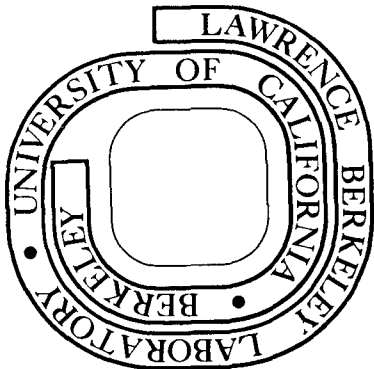
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Chapter VI

Somatic Effects - Other Than Cancer

Fertility

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IV. SOMATIC EFFECTS OTHER THAN CANCER

A. FERTILITY

The literature on radiation effects on fertility and fecundity in experimental animals is extensive, but little information on the radiation response of the testis and the ovary has become available since the publication of the 1972 BEIR report.¹ Information is now being produced on the response of human spermatogenic cells to graded doses of x irradiation.^{2,3} The application of cell population-kinetics studies to spermatogenesis and oogenesis in relation to germinal cell proliferation and differentiation has also provided a better understanding of the radiation response and tissue repair in mammalian reproductive cells.^{2,19} All this has led to further refinements of our understanding of mechanisms of impairment of fertility and of other relevance to genetic mutation frequency in experimental animals,^{2,3} and possibly in the human.

Animal Experiments

Testis

The most recent investigations on spermatogonial stem-cell renewal in the rat and mouse have provided a model (the Oakberg-Huckins model) in which the types A (stem cells), A_s (paired cells), and A_{pr} (aligned cells) are undifferentiated cells representing the sequence of development in the undifferentiated spermatogonial stem-cell compartment; differentiation probably occurs at the stem-cell level (Figure 1).^{7-10, 12-14} The types

A₁, A₂, A₃, and A₄, the intermediate, and the type B spermatogonia, are the differentiated cells that give rise to the resting primary spermatocytes and the production of mature sperm cells.

Among the undifferentiated and differentiating spermatogonia, the proliferating type A_{al}, types A₁₋₄, intermediate, and type B cells in the mouse testis appear to be most radiosensitive; the type A_{13,14,20-23} appears to be relatively resistant to x rays. Radiation doses (acute with high dose rates) of less than 15 rads of x radiation can lead to interphase cell death and prompt depletion of the differentiating-proliferating spermatogonial-cell population in the mouse; but sterility does not result, because there is immediate tissue repair and regeneration of the seminiferous epithelium, apparently from the surviving type A_s stem-cell population. Larger acute doses, 25-50 rads, can deplete the proliferating spermatogonial-cell population drastically and effectively, with a decreased production of sperm cells. However, impairment of fertility still is not immediate; existing spermatocytes and spermatids are resistant and may not be eliminated from the system for several weeks. Only temporary sterility would result with even higher doses; sufficient numbers of spermatogonial type A_s stem cells survive doses as high as 300 R, or even more, proliferate, and differentiate sequentially, regenerating and reconstituting the seminiferous epithelium with restoration of spermatogenesis. Acute wholebody exposures of young male mice up to 8 months old to doses as high as 1,000 R have failed to impair reproductive potential and fertility. _{13,16,22-23}

Fractionated or continuous whole-body x or gamma irradiation,^{22,24-27} does not necessarily impair fertility in mammals, provided that the dose rate is sufficiently low (less than 2 rads/day). Permanent sterility may ensue after higher dose rates and total doses. Male dogs exposed daily to x radiation for the duration of their life maintained sperm counts at normal values at a dose rate of 0.6 rad/week, and no evidence of deleterious changes occurred in sperm production or fertility at 0.3 and 0.6 R/week. Progressive cellular failure and sterility ultimately developed^{28,29,32-34} within months with brief daily exposures at 3 rads/week.

The proliferating and differentiating spermatogonia are extremely radiosensitive under continuous exposure; there is evidence that the testis is the mouse tissue most sensitive to^{16,20-22,32-34} continuous irradiation at very low dose rates.

At 16.5 R/day, testis weight decreased progressively with duration³² of exposure; after radiation-free intervals of up to 4 weeks, the testis weight recovered to over 90% of control weight and was restored more slowly than fertility. Dose-dependent damage to the testis has been observed at 2-20 R/day; at 10-40 R/day, permanent sterility has³³ occurred in mice. There was progressive decrease of the germinal epithelium; after 20 R/day or more for relatively long periods, complete absence of seminiferous epithelium occurred. At 2 R/day, rats and mice maintained reproduction for 10 generations or more, although the progeny showed some evidence of life-shortening. However, at slightly more than 2 R/day, there was a continuous and serious depletion of cell³⁴ population of the testis, with later sterilization.

It has been demonstrated that 0.009 R/min or less is near the threshold for recovery processes, permitting maintenance of the mouse spermatogonial population. ³⁵⁻³⁹ However, with total doses greater than 300 R, a dose rate of 0.001 R/min resulted in the spermatogonial-cell population's reaching an equilibrium ³⁵⁻³⁷ at 80% control. Studies in the mouse testis exposed to continuous gamma irradiation at 1.8 rads/day (0.00125 rad/min) and at 45 rads/day (0.03125 rad/min) to accumulated doses of up to 630 rads demonstrated that, at extremely low dose rates, the spermatogonia are sensitive to radiation death and cellular depletion. However, even after 15 weeks of continuous exposure at 1.8 rads/day, the type A stem-cell population could be maintained at control values, and the temporal sequence of cellular recovery to regenerate the seminiferous epithelium begins with the ^{16,20-24} type A stem cells.

Ovary

In the mammal, susceptibility to radiation-induced cell death in the ovary depends on a number of factors, including the developmental stage of the germ cell, the age of the animal, and the mitotic activity of the oogonia. In the rat, the oogonia appear most sensitive to radiation in the fetal ovary at about 15.5 days of gestation; this would correspond in the human to ⁴⁰⁻⁴³ approximately the fifth month of gestation. Thereafter, radiosensitivity, in the rat, appears to be relatively low during the leptotene, zygotene, and pachytene stages of meiotic

prophase; it increases with the diplotene stage of prophase when the oocyte becomes surrounded by a single layer of granulosa cells to form the primary follicle. In the rat, mouse, and rabbit, the primary follicles are quite sensitive to acute exposure, but sensitivity appears to decrease as development of the follicle proceeds. ⁴¹⁻⁴⁵

This response appears species-specific; in the guinea pig and monkey, the earlier stages of prophase in the primary follicle are relatively radioresistant, and sensitivity increases with follicular development.

In addition, the radiation doses required to kill a given fraction of primary follicles are also species-dependent: ^{36,40,49} in the mouse, a single acute dose of 10 R of x rays reduced the number of primary oocytes to half; in the rat, the comparable dose was 100 R; and in ⁴⁸ the monkey, perhaps as high as 900 R.

Oocytes in the mouse change in sensitivity to radiation between ^{40,45-47,49-50} the period of birth and sexual maturity; ^{40,45-47,49-50} sensitivity appears to be low at birth and increases until 7 weeks of age.

Differences in radiosensitivity of oocytes to cell-killing form the basis for the apparent age variation in sensitivity to radiation-induced sterility. Relatively low radiation doses (such as an acute dose of 25 R of x rays) given during the second and third weeks after birth impair fertility, owing to marked depletion of the oocyte cell population resulting from radiation-induced cell-killing. ^{40,45-47,49-50}

In mammals, there is no repopulation of cells after loss from existing oocyte pool, because the maximal numbers are established in the fetus. Thus, infertility and sterility result when the supply of functioning oocytes, which

survive radiation injury, is exhausted. Furthermore, the radiation-induced reduction in fertility is much less than the reduction in oocytes; the younger the female, the more efficiently she may use the limited oocyte supply.

Irradiation of the mouse and rat ovary results in early and progressive decline in the numbers of oocytes and ovarian follicles. ⁴⁷⁻⁵⁰ In the female mouse fetus, doses of 60-80 R/day for 5 days (to total doses of 300-400 R), given during the late development of the ovarian tissue, result in permanent sterility. Continuous irradiation of female mice with gamma rays (12.4 R/day) or with fission neutrons has shown that the interval between irradiation and conception has a striking effect on the mutation frequency in the offspring. ⁵¹ Continuous gamma irradiation in mice (12.4 R/day, up to approximately 175 R) from conception to day 14 caused a significant shortening of the reproductive period. When female mice were irradiated with fission neutrons (approximately 63 rads), the mutation frequency was high in the first 7 ⁵¹ weeks after exposure; after that, no mutations were found. This appears to be due, in part, to the low mutational sensitivity of oocytes in immature follicle stages. ⁴⁸⁻⁵⁴ Exposure early in the postnatal period has marked effects on fertility in females. The LD ⁵⁰ of stage I oocytes in 10-day-old female mice is approximately 8.4 R; it is about 5 R in slightly younger mice. Continuous gamma-ray exposure at 8.4 R/day from birth to weaning sterilized female mice. It may be that in the monkey, and possibly the human, the stage of development of the ovary

equivalent to the early postnatal stage in the mouse occurs late during intrauterine fetal development. At the lower doses, impaired fertility and fecundity were manifested as high litter mortality, decreased litter size, and diminished litter frequency. Impairment of the ovulation rate in rats appears to depend on radiation dose. Female fetuses exposed in utero to doses as high as 220 rads and then mated to unirradiated males showed no significant effect on fertility or fecundity. 50-55

Human Studies

The reproductive cells of the human testis constitute the seminiferous epithelium and are subject to a proliferating-cell renewal system consisting of four compartments: a self-maintaining stem-cell compartment, a proliferating progenitor compartment [types A_d (A-dark), A_p (A-pale), and B spermatogonia], a differentiating-maturing compartment [spermatocytes, types R (resting, preleptotene), L (leptotene), Z (zygotene), and P (pachytene) spermatocytes], and a functional end-cell compartment types [Sa, Sb, Sc, and Sd spermatids]²⁻⁴. The seminiferous epithelium is in a steady state of cell renewal; new cells are formed throughout reproductive life, replacing functional end cells that leave the system. In man, the type B spermatogonia are the most radiosensitive, and doses of only a few rads will deplete this proliferating population.^{3,30,31} The spermatogonia preceding type B (types A_d and A_p) are also radiosensitive; spermatocytes are less radiosensitive, and spermatids are the most radio-resistant of all.

The human ovary contains the full complement of approximately 7 million oocytes at a fetal age of approximately 5 months; later, the oocyte population undergoes physiologic attrition until menopause in the adult. ^{22,56} The female is born with only 2 million, and ovulation provides only some 360-400 mature oocytes throughout her reproductive life. ^{22,56} There is no oocyte renewal after the degenerative sequence progresses, and the ovary therefore lacks the capacity to replace damaged or lost reproductive cells after this time. The oocytes arrest in a preovulatory meiotic diplotene prophase stage, which is relatively radiosensitive in the mouse, but radioresistant in the human. Selection processes for cells damaged by radiation or other mutagens may not be operative until ^{22,56} the cell is ovulated and later fertilized.

Testis

^{2,3} Rowley and colleagues have reported the results of their 10-yr study on the effects of acute doses of x rays on the normal human testis. Sixty-seven men, aged 25-52 yr, received acute testicular x irradiation in doses of 8-600 rads. Most received single exposures; one subject was given weekly irradiations of 5 rads for 11 weeks. The conclusions on the endocrinologic and cellular response include the following: there was an initial rise in urinary gonadotropins. There was a decrease in urinary testosterone coupled with a rise in plasma luteinizing hormone; this suggested radiation interference with Leydig-cell function. Spermatogonia are the most radiosensitive and spermatids the most

radioresistant cells of the germinal-cell line. Type B spermatogonia are the most radiosensitive, followed by types A^d and A^p, whereas the differentiated preliptotene spermatocyte is relatively radio-resistant, in comparison with its progenitor cells. Single acute doses of 600 rads or less cause significant cellular damage in the testis; these changes are dose-dependent, with complete recovery after doses of 600 rads or less, and with the time until recovery also dose-dependent, extending up to 5 yr.

Atomic-Bomb Survivors

Information on impairment of fertility in man is available from the study of atomic-bomb survivors and from Marshallese and Japanese who were inadvertently exposed to fallout during atomic-bomb testing in the Pacific. The data lack precision, but demonstrate the following: Relatively low doses can decrease production of sperm cells, but effects on spermatogenesis are transient; The sterilizing dose in the male is probably much greater than about 400-500 rads, i.e., it probably exceeds the mean lethal dose to the whole body. Fertility is impaired in the oocyte population only after moderately high doses--200-400 rads. Little is known regarding the delayed effects of radiation on fertility in these exposed populations, nor is there information on the extent of impairment, if any, in the male and female populations exposed in utero and in the F₁ populations of exposed parents. Followup studies of the Japanese atomic-bomb survivors and the Marshallese women exposed to fallout have failed to demonstrate any long-term effect on fecundity.

58-60

Radiotherapy Patients and Victims of Nuclear-Reactor Accidents

Clinical data are available on male radiotherapy patients and men exposed during criticality accidents at nuclear-reactor installations. ^{30,57} Careful sperm-count studies after limited partial-body radiation exposure have indicated that, if sterility occurs, normal sperm counts can return in about 1 yr after doses of 100 rads and even in 3 yr after exposures in the near-lethal range. ^{30,57} Acute whole-body exposure has not been shown to cause permanent sterility in males. ⁵⁷ The sterilizing dose therefore exceeds the lethal whole-body dose for acute radiation. Similarly, sterilization of the human testes have never been shown to result from continuous or fractionated (protracted) low-dose exposure. ^{29,30,53,58}

In women, radiotherapy experience has suggested that acute doses of 300-400 rads or slightly higher doses given in two or three fractions result in permanent sterility. ^{22,52,56,57,59} If fractionation is protracted over a 2-week period, much larger doses (possibly 1,000-2,000 rads) are required for sterilization, ^{52,56,57,59} depending on the age of the woman. The ovaries of younger women are much less radiosensitive; permanent sterility is more likely as the menopause is approached.

Conclusions

In the human testis, populations of mature spermatozoa are maintained by proliferating spermatogonial stem cells. Provided that the dose remains below 400 rad (low-LET radiation, acute exposure), radiation depletion of the spermatogonial cell population

is only temporary, and the seminiferous epithelium is repopulated and regenerates from surviving and proliferating spermatogonial cells in the damaged tissue. Exposure much greater than this (perhaps by an order of magnitude), directed only at the testis, could probably result in permanent sterility.

In the human ovary, impairment of fertility can result from absorbed doses in the range of 300-400 rads (low-LET radiation, acute exposure), but this depends, in part, on age. Radiotherapeutic experience has shown that women approaching the menopause may have long-term impairment of fertility or permanent sterility, whereas in younger women only transient infertility associated with amenorrhea may result. This may be associated, in part, with oocyte populations, which decrease primarily by physiologic atresia (and to a much lesser extent by ovulation) with age.

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