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Shepard Summary

Radiation

X-irradiation

Ionizing Radiation

A large body of information is available on the adverse effects of irradiation on the human and animal embryo and fetus. The effects of radiation on the human conceptus has centered on (1) damage to the fetal central nervous system, (2) early embryonic death with sex ratio changes and (3) long-term effects on carcinogenesis. The effects of accidental X-radiation on the developing fetus are well documented. Several reviews are available: Hicks and D'Amato (1966), Yamazaki (1966), Kalter (1968) and Brent (1971,1977,1980) gave general summaries, and Jacobsen (1970) reviewed data related to low dose irradiation. Sikov and Mahlum (1969) edited a large symposium on radiation biology of the fetal mammal. The main concentration was on gene mutation and development of the central nervous system. Schull et al. (1990) reviewed data on the effects on the nervous system of experimental animals and humans. They conclude that sensitivity of all mammalian species when developmental periods are compared are markedly similar. DeSantis et al. ((2005)) have reviewed the role of ionizing radiation and teratogenesis. The papers giving data on the small reduction of birth weight among the offspring of mothers with thyroid diagnostic exposure are criticlly discussed. Hawkins and Smith (1989) studied the reproductive outcome of women treated with abdominal radiation for tumors mostly Wilm's tumor. For firstborn children there was a significant (300 gm) reduction in birth weight as compared to non-radiated women with tumors. The exposed women had higher nulliparity and spontaneous abortions. Otake et al. (1990) have reanalyzed reproduction data from atomic bomb survivors and found a non-statistical increase in major malformations, stillbirths and/or dying in the first 14 days of life.

Kallen et al.l (1998) studied reproduction in 17,393 women who received radiation for hemangiomas in infancy with an average dose of 6 cGy. No adverse outcome was found except for an increase in anencephaly to 7 when 5 were expected. No increase in spina bifida or Down's syndrome was found. Brent (1999) has extensively reviewed animal work and the human risk factors that support earlier work.

Brent et al. (1987) discussed the human risk based on animal studies. At the most sensitive period (18-36 days), the minimal dose which could produce gross malformations was estimated to be 20cGy (20 rads or about 20 rem). This dose level is considerably higher than can be received during diagnostic radiation. DeSantis et al. 2007 have reviewed the effects of radiation with special emphasis on time and duration of exposure. Plummer (1952) observed that microcephaly was a common complication of intrauterine radiation after the atomic bomb explosion at Hiroshima, and that the degree of microcephaly was directly related to the distance the mother was from the epicenter. Blot and Miller (1973) found mental retardation after 50 rad doses in Hiroshima but 200 rad doses in Nagasaki and suggested the lower dose effect may have been due to a higher neutron exposure in Hiroshima. Miller (1956) and Neel and Schull (1956) did not find further health problems at that time in survivors or significant increases in defects in the subsequent offspring of parents exposed to the Japanese atomic bomb explosions. Driscoll et al. (1963) reported on histologic changes occurring in human fetuses following dosages of about 500 rads.

Otake and Schull (1984) reported the prevalence of mental retardation among 1600 offspring exposed to the Japanese atomic bombs. They found that the critical period was between 8 to 15 weeks after fertilization (six of nine children were retarded). This period corresponds to the time when major neuronal proliferation is occurring. A dose response was found. For all gestation periods the percentage of retardation was 1.4, 2.4, 17.6 and 36.8 for the 1-9, 10-49, 50-99, and over 100 absorbed fetal rads. The control was 0.8 percent. In a subsequent analysis excluding two cases of Down's syndrome from the cases exposed at 8-15 weeks Otake et al. (1996) revised their threshold dose upwards slightly giving a 95% confidence level of 0.06-0.31 Gy. Mole (1990) has raised some questions about the application of a dose response curve to the above data. Mole (1987) analyzed the findings of Otake and Schull (1984) and used the data to discuss mechanisms which could produce malformations by ionizing radiation. Yamazaki and Schull (1990) have summarized the neurological abnormalities found in the offspring of exposed mothers at Nagasaki and Hiroshima. If there is a threshold it would exist between 0.1 to 0.2 Gy of fetal dose. The few autopsies that have been performed support the hypothesis that errors in

neuronal migration are important in the mechanism of damage.

De Santis et al. ((2005)) reviewed records of 236 women who had thyroid radiation in the first part of pregnancy and found a small but significant drop in birth weight after doses of over .040 mGy.

Schull et al. (1990) summarized the literature on the animal and human findings of central nervous system function after radiation. For animals, in general, positive findings were found at doses of 0.25 to .75 Gy (25 to 75R) but the time of exposure and type of test were important variables. For humans, exposed between 8-15 weeks a dose of 1.0 Gy was estimated to reduce IQ by 21-33 points. Schull and Otake (1999) have summarized the data on cognitive function and ionizing radiation and suggest that with the limited samples it is still not possible to establish a threshold dose for an effect.

Miller (1956) did find a subsequent leukemia incidence of 1 in 1,000 in children who were under 10 years of age and were within 1500 meters of the epicenter of the atomic bomb explosion. Yoshimoto et al. (1988) found that among 1630 individuals exposed in utero to the atomic bombs, there were two cases of childhood cancer in the first 14 years of follow-up. The relative risk for adult type cancer 40 years after exposure was 3.9 in the 0.30+ Gy exposure group. The crude cancer rate per 100,000 was 23, 32, 72 and 91 for the uterus organ doses of 0, 0.01-0.29, 0.30-0.59 and 0.60+ Gy, respectively. There were no differences in risks that could be associated with exposure in different gestational periods. The risk of cancers other than leukemia is less convincing and the fact that the relative risk for virtually all other forms is 1.5 suggests an underlying bias (Boice and Miller, 1999).

Long term effect of maternal radiation on the incidence of malignancies in the offspring was reported by MacMahon (1962). The extensive data of the Oxford Survey of Childhood Cancers (Bithell and Stewart, 1975) indicated a relative risk estimate of 1.47 for mothers with prenatal radiation exposure. Translated into numbers of childhood cancers per 10,000, the increase would be from 10 to 15 cases. The risk was dependent on the number of films taken and could be described as a linear relationship. Exposure in the earlier months of pregnancy appeared to carry a much higher risk. Other factors leading to maternal radiation are hard to separate from the radiation effect. A special committee of the United Nations (1972) carefully assessed the reports dealing with this subject. Diamond et al. (1973) studied 20,000 children exposed to radiation during gestation and found a tripling of the leukemia death rate in the treated white group but none was observed in an equal-sized group of Black children similarly exposed.

Sever et al. (1988) studied malformations among 672 malformed offspring of workers around the Hanford plant in the state of Washington. The cumulative whole-body radiation dose of each of the 195 workers was known. Some increase in congenital dislocation of the hip and tracheoesophageal fistula was found among the twelve malformation types studied but no association with dose was found. Given the number of statistical tests, the authors felt some or all of these correlations could represent false findings. Macht and Lawrence (1955) surveyed the offspring of radiologists and could detect no increase in congenital defects. Wagner and Hayman (1982) summarized the relative safety of pregnancy in female radiologists. Robert et al. (1999) studied the offspring of mothers living within 5 or 10 kilometers of four French nuclear plants and found no increase in malformations among 23,074 newborns.

Schull et al. (1981) compared gonadal doses from atomic bomb exposed parents with life expectancy, chromosomal aneuploidy, and electrophoretic mutants of their offspring. Their pregnancy outcomes were also studied. Although all four indicators were found to be changed as expected, there was no statistical significance. The average genetic doubling dose for the four indicators was 156 rems.

An association between Down's syndrome and maternal X-ray exposure was suggested by three retrospective studies (Uchida and Curtis, 1961; Sigler et al., 1965; Alberman et al., 1972A), but Carter et al. (1961) could not show a connection. Uchida (1977) recently summarized 11 studies of which 9 showed an increase in radiation exposure of the mothers giving birth to Down's infants. Although Neel and Schull (1956) did not report significant sex ratio changes in the offspring of irradiated parents, Scholte and Sobels (1964) offered some evidence for a change in sex ratio after parents were given radiation therapy. Boue et al. (1975) reported an increase in chromosomally abnormal abortuses from fathers who were occupationally exposed to X-rays,

An increase in spontaneous abortion has been associated with gonadal radiation (Alberman et al., 1972B). They reported that matched controls received 180 mR while all forms of spontaneously aborting women received 245 mR. Among the group with abnormal karyotype, the average exposure was 331. Mothers of triploid embryos averaged 735 mR and these authors point out that most of the increased risk is expressed by non-viable conceptuses. Strobino et al. (1978) have reviewed the effect of radiation on human reproduction.

Among commonly used animal models the mouse was studied extensively by Russell (1950). She reported that preimplantation irradiation tended to be lethal or to have no effect. Exposure on days 6.5 through 13.5 produced little or no prenatal death but a high incidence of growth retardation and abnormalities which in general were related to dose and time

of administration. Eye defects (microophthalmia and coloboma) were most common after treatment on days 7.5 through 9.5, while renal changes were associated with treatment at day 9.5 and skeletal changes appeared after exposure during days 9.5 to 12.5. After treatment on day 14.5 abnormalities were uncommon, but cataracts, hydrocephalus and skin defects did develop in later life. Dr. Lillian Russell used radiation doses of 100 to 400 rads. Kuno et al. (1994) confirmed Russell's studies of eye defects in mice and detailed the type of eye defect seen in mice exposed on days 8 or 9 to 4.6 Gy. Devi et al. (1994) treated mice at 11.5 days postcoitus and found a concentration response decrease in brain growth starting at 0.05 Gy and extending through 0.5 Gy. Devi et al. (1999) also reported dose response decreases in the function of mice treated on day 17 even down to 0.3 Gy. At 1.0 Gy impaired function occurred without notable changes in brain morphology. Devi and Hossain 2001 found that 0.5 Gy or above give on day 14 to the mouse relayed postnatal development and growth without producing congenital defects.

Hicks and D'Amato (1966) concentrated their studies in rats and mice on the central nervous system effects occurring when treatment is given in the late embryonic and fetal periods. Jensh et al. (1987) radiated mice with 0.4 or 0.6 Gy on day 9 or 17. Most postnatal studies were not different from the sham controls but those exposed to the highest dose on day 17 exhibited higher conditioned avoidance. Norton and Kimler (1987) administered 1.0 Gy on day 11 or day 178. The behavioral effects were correlated with the thickness of 5 cortical layers. Significant association of behavior was found with layers 5 and 6. Jensh and Brent (1988A) gave 0.75 or 1.5 Gy to rats from the 14th to the 18th day. Weight reduction at birth and delay in acquisition of several reflexes was found. After weaning, the body weight to organ weight ratios were reduced for the brain, kidneys, testes, ovary but not liver. Jensh and Brent (1988B) radiated day 18 rats with 1.5 Gy and found testicular hypoplasia and some decreased mating performance and positive inseminations.

Sun (1999) studied the effect of beta-irradiation on the offspring of mice injected with tritiated water on day 13 of gestation. At 0.4 Gy a significant reduction in brain weight was found at 8 weeks of age. A dose-related reduction in pyramidal cell densities was found.

Wilson et al. (1953) reported the effect of timed radiation on type of defect including those of the cardiovascular system. The effect of radiation on the skeletal system of mouse fetuses was detailed by Degenhardt and Franz (1969) and Murakami and Kameyama (1964). Rugh et al. (1964A,B) carried out studies of the association of X-rays with cataract formation and skeletal retardation. The cataracts developing in mice were most common after exposure immediately after fertilization and were interpreted as overall damage rather than direct effects on the organ primordia. Okamoto et al. (1968) studied the effect of fast neutron irradiation on the 7th through the 11th days in the rat fetus and found a dose-related increase in congenital malformations. Cardiovascular anomalies were the most frequent and an increased mortality of female fetuses was observed.

Kalter (1968) reviewed the work that was done in the rabbit and hamster. The teratogenic action of different isotopes such as tritium, strontium, and 131I are listed under their separate headings.

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