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Review

Carcinogenic risks of prenatal ionizing radiation

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SUMMARY

The risk of cancer in offspring who have been exposed to diagnostic X-ray procedures while in utero has been debated for 55 years. High doses at high dose rates to the embryo or fetus (e.g. >0.5 Gy) increase the risk of cancer. This has been demonstrated in human epidemiology studies as well as in mammalian animal studies. Most pregnant women exposed to diagnostic X-ray procedures or the diagnostic use of radionuclides receive doses to the embryo or fetus <0.1 Gy. The risk of cancer in offspring exposed in utero at a low dose such as <0.1 Gy is controversial and has not been determined.

1. Introduction

In 1950–51, I was working in the radiation embryology section of the University of Rochester Medical Center's Atomic Energy Project. We had submitted an abstract to the Anatomy Society meetings in Detroit [1]. The completed manuscript that was submitted to *Cancer Research* was titled, 'Cancer induced in rat embryos by roentgen irradiation'. The editors rejected the manuscript and stated that if the embryos had developed cancer, there would have been a much higher mortality. So we changed the title to 'Neoplasia induced in rat embryos by roentgen irradiation' and the manuscript was accepted [2]. We examined the tumors as they first appeared and continued to grow (Fig. 1). Many of the tumors became anaplastic and contained many undifferentiated cells with a high mitotic index. At birth, most of the tumors were gone. However, there were a few pyknotic cell remnants that were still present. We followed 300 radiated survivors and controls for 4 years and these irradiated animals did not have a higher incidence of cancer than the controls.

We put this project aside with the tentative conclusion that the embryo was less vulnerable to the carcinogenic effects of low exposures of ionizing radiation than the postnatal animal.

Liane Russell [3,4] and our laboratory [5,6] had already described 'the all or none phenomenon', which indicated that the pre-somite mammalian embryo was less vulnerable to the teratogenic effects of ionizing radiation. The embryo was very vulnerable to the lethal effects of radiation; however, the surviving embryos did not have an increased risk of birth defects.

When Alice Stewart published her research results, a 60-year controversial discussion was initiated. Stewart et al. [7–10] suggested that the human embryo was more vulnerable to the leukemogenic effects of radiation and in later publications concluded that other childhood cancers also occur more frequently in persons exposed in utero to diagnostic radiologic procedures (primarily pelvimetry) (Fig. 2). These authors initially estimated that a 1–2 rad in-utero radiation exposure increases the risk of leukemia developing in the offspring by a factor of 1.5 to 2.0 over the natural incidence. This incidence is considerably greater than the increase resulting from 2 rad delivered to an adult population. In fact, an increase in the incidence of leukemia after an adult population exposure of 2 rad would be difficult to document, even for very large population groups [11,12]. Dr Stewart became a spokesperson for anti-radiation groups. She appeared as a plaintiff expert in radiation litigation and was even a plaintiff expert against her own country in a case before the World Court in which Ireland was suing the UK, claiming that a British nuclear facility (Sellafield's Fuel Handling Plant) was contaminating the Irish sea and causing increased cases of birth defects and cancer in the inhabitants on the east coast of Ireland. After more than a decade of litigation the World Court decided in favor of the UK [13]. Dr Stewart claimed that the embryo was many times more vulnerable to the carcinogenic effects of radiation than children and she was critical of scientists who disagreed with her [8,14].

As a medical and graduate student and part-time instructor, I did not have time to further pursue the question of the resistance of the embryo to the carcinogenic effects of radiation. However, there were many publications exposing animals to carcinogenic agents. In particular, urethan (urethane; ethyl carbamate) was used by Klein [15] and Vesselinovitch et al. [16] to produce neoplasia in rodents. Only a few of the investigators utilizing urethan exposed pregnant animals to this carcinogenic agent. Klein [15] reported

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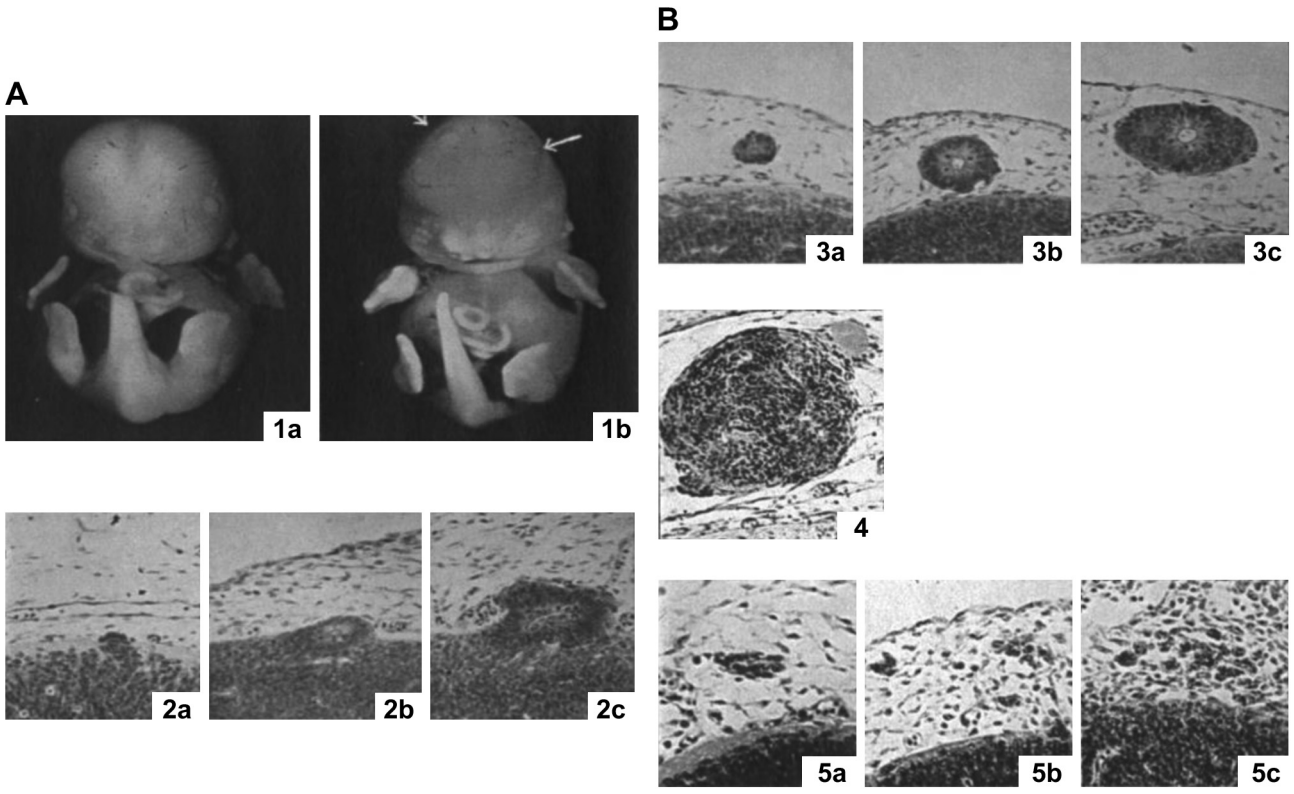

Fig. 1. (A, B) Fifteen-day-old rat fetuses exposed to 1.5 Gy at day 9 post conception. The arrows in 1b are pointing to tumors under the scalp that can be seen in histological sections in 3a, 3b, and 3c. The tumor growths are derived from outgrowths of the radiated neural tube as seen in 2a, 2b and 2c. Some of the growths dedifferentiated into more aggressive-appearing tissues (4). At the time of the birth of the fetuses almost all the growths had regressed except for a few remnants of pyknotic cells located between the brain and the scalp (5a, 5b, and 5c). All photographs are reproduced with permission from Wilson et al. [2].

that cesarean-delivered mice exposed in utero had significantly fewer lung tumors than animals treated postnatally. Significantly more tumors per lung were observed in mice injected with urethan at 47 days of age than at birth, suggesting an increased susceptibility with age. Vesselinovitch et al. [16] exposed pregnant mice on multiple days in mid pregnancy (days 12–18). The incidence of liver and lung tumors was significantly higher in mice exposed to this carcinogen at the end of gestation. Neonatally treated animals developed all of the tumor types more readily than those exposed to the carcinogen in utero and also developed leukemia which did not occur in the in-utero-exposed population. The urethan animal studies reinforced the animal studies from our laboratory, which indicated that the fetus had lower carcinogenic risks from mutagenic or carcinogenic agents when compared to the postnatal animal's vulnerability.

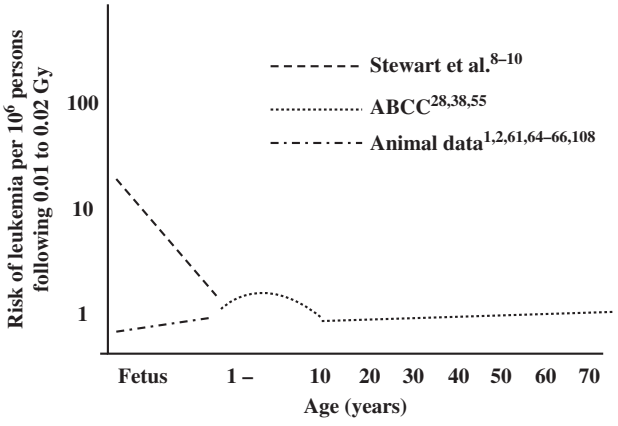

Fig. 2. Risk of cancer from in-utero radiation. When Stewart first reported the risks of cancer in the offspring of pregnancies in which the mother had been exposed to diagnostic radiological studies in the 1950s, the risk of leukemia was stated as one to two orders of magnitude greater than the risk of cancer following similar exposures in childhood. Children were believed to be slightly more vulnerable than adults. Animal studies were inconsistent, but many of the animal studies were negative and many of the studies did not expose the pregnant animals to doses of <0.10 Gy. ABCC, Atomic Bomb Casualty Commission.

2. Human studies concerning the vulnerability of the embryo to the carcinogenic risks of ionizing radiation

Lilienfeld [17] reviewed the epidemiologic considerations with respect to leukemogenesis. His results, confirmed by others [18–21] support the thesis that diagnostic radiation absorbed in utero was associated with an increased risk of leukemia. Six of nine studies reported in Lilienfeld's paper indicate a 1.3–1.8-fold increase in the risk of leukemia after diagnostic radiation exposure in utero. Lilienfeld states: 'When one considers the variety of control groups used and the sampling variability, the results are remarkably consistent in showing an excess frequency of leukemia among children of radiation-exposed pregnant mothers [17].' Diamond et al. [22] confirmed and extended the observation of a three-fold increased incidence of leukemia in children exposed to diagnostic radiation in utero. Interestingly, this effect did not occur in the African-American population. When MacMahon [23] extended his studies, the 1.5-fold excess leukemia incidence remained, but the excess in other childhood cancers was no longer present (Table 1).