ABNORMALITIES IN CHILDREN EXPOSED TO X-RADIATION DURING VARIOUS STAGES OF GESTATION: TENTATIVE TIMETABLE OF RADIATION INJURY TO THE HUMAN FETUS, PART I

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During the 1920's and early 1930's ionizing radiation was widely used to treat many diverse diseases. On occasions the pelvic region was heavily irradiated in women in whom pregnancy was not suspected or irradiation was carried out with the express purpose of causing sterility or therapeutic abortion (frequently unsuccessful). It was soon learned that irradiation leads to severe damage of the fetus and that most, although not all, surviving children showed marked abnormalities and malformations. Reports of Stettner (*1*), Zappert (*2*), Murphy (*3*), Goldstein (*4*) and others brought to light the most common sequelae in the surviving children: microcephaly, mental retardation, microphthalmus and cataracts. Since the 1940's, publications on irradiation injury to the human fetus have become less frequent with the exception of reports on casualties of the atomic bomb explosions in Hiroshima and Nagasaki (*5–7*).

We have had an opportunity to study in detail a child whose mother received a large dose of irradiation to the sacroiliac joints when pregnancy was not suspected. While appraising this case and surveying the literature, it became apparent that so far no systematic correlation has been made in man between the type of abnormality encountered in infants and the stage of gestation when irradiation took place. Because it is important to know the time of greatest susceptibility of developing organs to ionizing radiation in man, we decided to review all known reports on radiation damage occurring during prenatal life and to prepare a tentative timetable of organ sensitivity to ionizing radiation during various stages of gestation. Because of a particular difficulty in assessing the radiation dose when radium treatment was used, only reports on x-radiation were considered.

MATERIALS AND METHODS

Out of over 200 cases of pelvic x-ray radiation in pregnant women listed in the literature only 26 including the present patient were accepted as having sufficient information for our purpose. Because the importance of recording the parameters of radiation was not always appreciated, determining the actual number of roentgens delivered to the pelvic region presented a considerable problem in several case reports. Many authors, however, gave information regarding HVL, KV, distance, size of portals, duration of irradiation or a total air dose in addition to stating that this was a "castration" dose, "malignant neoplasm dose" or "myoma" dose. Using all this information as well as the irradiation tables (*8–10*) which have recently become available, it was possible to estimate the range of irradiation that each of the 26 women received. My sincere thanks are due to NIH physicists C. Robbins and J. R. Howley for their help in estimating the irradiation dose to the pelvic region at a depth of 4 cm below the skin.

The experimental studies indicate that a dose of 200–300 R measured in air consistently causes fetal damage (*11–14*).

In one of the case reports surveyed (*15*) our estimate of irradiation delivered to the midpelvic region was at variance with the estimate of the author; taking all available information into account, three physicists independent of each other estimated the midpelvic irradiation range as being between 250 and 300 R. The next smallest irradiation dose was 320 R as stated by the author himself (*16*). The calculated average dose in 10 mothers who received lowest irradiation was 560 R at the midpelvic region; the remaining 16 received doses which ranged from one to many thousands of roentgens. Since the estimated doses refer to the midpelvic region of the mother, the amount of irradiation received by the fetus will be closely related to this dose although not necessarily identical. From the above data it

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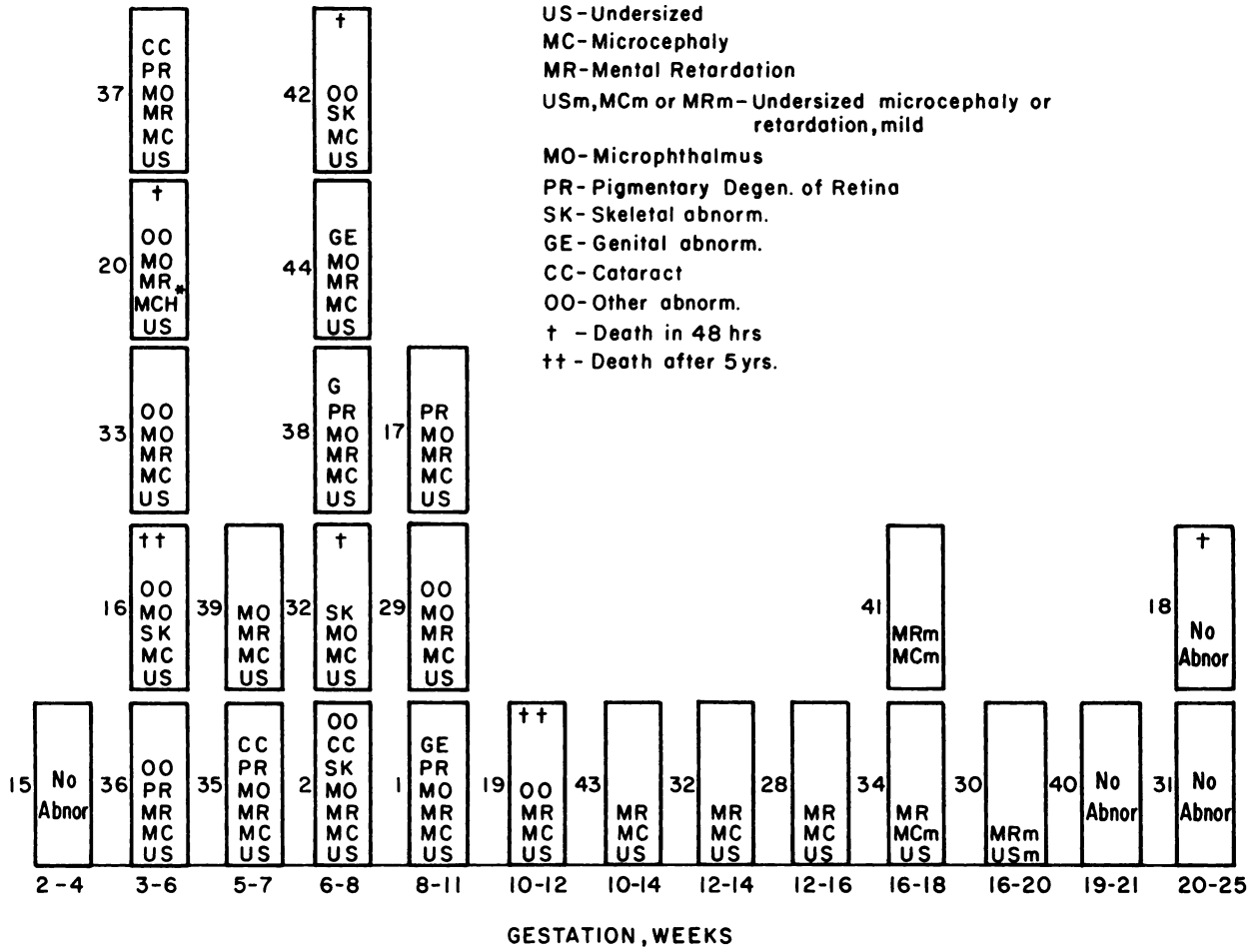

FIG. 1. Graphic summary of findings in each of 26 children who received irradiation during various stages of gestation. Number on left of each rectangle gives reference number of case report.

appears that the pelvic region of all the 26 women must have received a sufficiently high dose to cause irradiation injury to the fetus during the sensitive stage. The variable which we set out to evaluate in this study is the effect of x-radiation (when moderate or high dose was used) during different stages of gestation in producing specific types of abnormalities in children. The selected 26 case reports provided sufficient information on gestational stage at the time of irradiation and on major abnormalities present in these children to permit individual tabulation of the data (Fig. 1).

RESULTS

Present case report (*17*). The family history is negative for mental deficiency, malformation or hereditary disorders. The mother was in good health until her early thirties when she developed a painful back condition. This was diagnosed as rheumatoid spondylitis, and she received deep x-ray therapy of 1,200 R to the thoracolumbar segment of the spine. Her menstruations were somewhat irregular before and after treatment. In February of the next year an additional deep irradiation of 1,200 R was given to the sacroiliac joints and ischiac tuberosities because of severe pain. Two months later she was found to be in the fifth month of pregnancy. The estimated dose to the midpelvic region was about 900 R. From then on she had good obstetrical care, and her pregnancy continued normally. On August 21 (at the age of 41) she gave spontaneous birth to a female infant whose birth weight was 1,370 gm. The age of the fetus at the time of irradiation was estimated between 10 and 12 weeks. The child was microcephalic with all fontanels closed and the head circumference was 25.5 cm. The infant's development was slow; she began to crawl at 2 and to walk at 3 years of age.

Physical examination at 3½ years of age showed an undersized girl with normal respiratory and circulatory systems. The liver and spleen were not enlarged, and there was no external evidence of malformation. Her head circumference was only 38.7 cm (normal 51 cm), she had no speech and

her mental performance was at the 12–16 month level (imbecile range). Neurological examination was negative but her skill of movements was deficient. Her eyes were small, and she had bilateral esotropia. Funduscopic examination showed pigmentary degeneration of the retina and pallor of disks. Routine laboratory analyses and tests for toxoplasmosis, torulosis and syphilis were negative. The EEG was normal but pneumoencephalogram revealed a large fourth ventricle and hypoplasia of the vermis of the cerebellum. Diagnosis was microcephaly, severe mental retardation, mild microphthalmus, pigmentary degeneration of the retina and hypoplasia of the cerebellum.

Of the 25 case reports accepted for this study, 17 were published between 1921 and 1935 and eight between 1936 and 1956. The present report adds the 26th case. The age range of mothers at the time of birth of the irradiated child was between 23 and 42 years with an average of 36 years and 7 months.

The reasons for pelvic irradiation were as follows: (1) dysmenorrhea or metrorrhagia in 16 women; this was associated with uterine myoma or fibroma in nine; (2) multiple myomata near the cervix without excessive bleedings in two mothers; (3) pregnancy mistaken for myoma without bleedings in two mothers; (4) primary or secondary malignant neoplasm involving uterus, ovary or pelvic bones in four mothers; (5) tuberculous osteomyelitis of sacroiliac joints, and rheumatoid arthritis involving lumbar spine and sacroiliac joints in one woman each. Existence of pregnancy at the time of irradiation was not known in 20 women; four mothers refused interruption of pregnancy and because of pain or rapidly growing malignant tumor, irradiation had to be administered. In the remaining two mothers the known pregnancy was complicated by myomata in the region of the cervix. In the 1920's such myomata were thought to be amenable to cure by irradiation which then would permit normal course of pregnancy and spontaneous delivery. In these two women, myomata did not recede sufficiently to permit natural birth.

Estimation of the age of the fetus during irradiation could not be very precise; however, by using the range rather than specific age, the error was considerably reduced. In one female (*15*), irradiation of the pelvis occurred 2–4 weeks after conception; in the remaining 25 mothers the gestational age of the fetus during irradiation was spread between 4 and 25 weeks. The numbers of children irradiated at various gestational ages is given in Fig. 1.

Twenty children were alive when last examined at 3 months to 16 years of age. Out of the remaining six, one died during delivery, three within 4 days from birth, one at 7 months and one at 13 years. An autopsy was performed in three children: the mother of the first (*18*) received enormous irradiation (over 20,000 R) for uterine sarcoma at 6 months of gestation. The infant died 24 hr after birth; the main findings were anemia, generalized hemorrhages and atrophy of the lymphoid tissue. The mother of the second child (*19*) received about 1,100 R at 10–12 weeks of gestation. The child died at 13 years of age of septicemia. The autopsy findings included atrophy of kidneys, hypoplasia of the brain and genital organs, partial fibrosis of the bone marrow and hyperplasia of parathyroids. The mother of the third child (*20*) received over 600 R at 5–7 weeks of gestation; the child died at 7 months of age of septic meningitis following ventriculography (his head transilluminated). The main findings at autopsy consisted of marked hypoplasia of the brain associated with hydrocephalus and microphthalmus.

The following were most frequent abnormalities in children who were irradiated during intrauterine life: (1) small size at birth and markedly stunted growth, (2) microcephaly, (3) mental retardation, (4) microphthalmus, (5) pigmentary degeneration of the retina, (6) genital and skeletal malformations and (7) cataracts. Certain of these abnormalities are easily detectable while the others require careful examination by a specialist; here would belong conditions such as incipient cataracts and retinal lesions. Also, it may take months or years for cataracts to develop following irradiation injury (*21,22*). Likewise, presence of mental retardation could not be recorded in the infant who died 4 days after birth even though his retardation could be presumed if he had lived longer because of severe microcephaly or grossly hypoplastic brain. These aspects have to be kept in mind when assessing listed abnormalities in each child as outlined in Fig. 1.

Similarly, as in experimental animals (*14,23*), it appears that the presence or absence of the abnormality and the type of lesions depended largely on the gestational stage when the fetus received heavy irradiation (Fig. 1). The gestational stages in this series at the time of irradiation ranged from 2 to 4 weeks up to about 25 weeks. It appears that if moderate or large doses of deep therapeutic irradiation to the maternal pelvis are used, the pregnancy may proceed to fruition and the infant frequently will be born alive. The majority of these children have a variety of serious abnormalities and a small proportion of them may die during neonatal stage or shortly thereafter; certain of the children who were irradiated during fetal life were apparently normal.

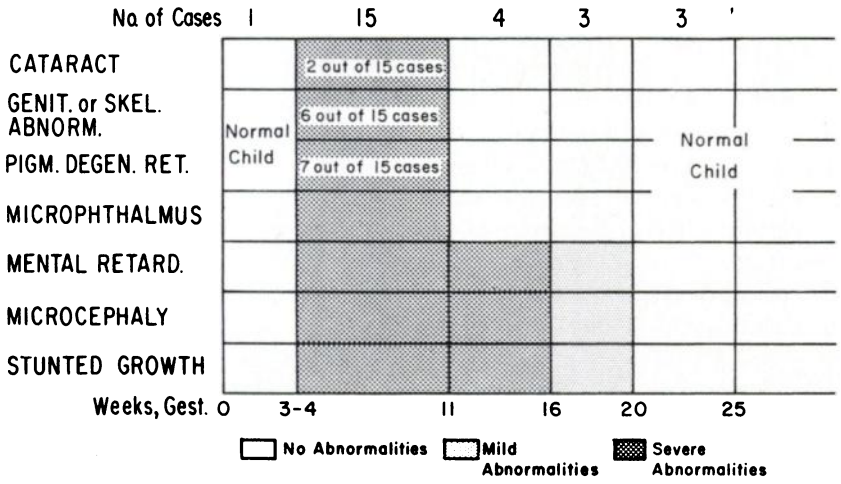

FIG. 2. Tentative timetable of abnormalities in man induced by irradiation of fetus during various stages of gestation.

Figure 2 gives a tentative timetable of various abnormalities in children who were exposed to ionizing radiation during different stages of pregnancy. Data in this figure and in Fig. 1 can be summarized as follows: A human embryo irradiated at 2–4 weeks of gestation continues to develop and will be a normal child. Experimental data indicate that irradiation of mammals during preimplantation and early implantation stages leads to a high incidence of embryo deaths but those that survive continue to develop and are generally normal (*23,24*). Between about 4 and 11 weeks of gestation many organs and systems were very sensitive to irradiation and the surviving children have marked abnormalities involving the brain (as shown by microcephaly and mental retardation), eyes, genital, skeletal and other systems as well as stunting of growth. Three out of 15 patients in this age group had recurrent epileptic attacks.

Irradiation between about 12 and 16 weeks of gestation was associated in this series largely with stunted growth and mental retardation usually related to abnormality of the brain (microcephaly is generally the expression for the undersized or malformed brain). There were no obvious abnormalities of eyes, skeletal or genital system; however, the occurrence of late cataracts could not be assessed in this material. One out of four children in this age group had epileptic attacks.

The gestational stage between about 16 and 19 weeks appears to be transitional in regard to the sensitivity to irradiation. Here, the abnormalities listed for the stage of 12–16 weeks of gestation, namely microcephaly, mental retardation and stunted growth were also present but in a much milder form.

When irradiation took place between about 20 and 25 weeks of gestation, no organ or system abnormalities occurred and the children were apparently normal during the last examination (minor deficits in mature age cannot be excluded). However, certain of these children had epilation, deficient hematopoietic system or healed skin lesions. The last conditions are known to occur following heavy ionizing radiation given at any time during postnatal life. Naturally, an excessively large dose of irradiation at this gestational stage or at any other period of prenatal or postnatal life would be lethal within a short time.

COMMENT

The causal relationship between ionizing radiation of the fetus at specific stages of gestation and the specific organ damage are well established in experimental animals (*23,25–27*). In the human material the evidence is less direct but nevertheless convincing. High incidence of microcephaly and eye abnormalities in children following therapeutic application of radium and x-rays during pregnancy has been recorded in several hundreds of cases (*3,4*). Casualties of the atomic bomb explosion in Hiroshima and Nagasaki bring additional evidence. Plummer (*5*) found that 11 children were born to pregnant mothers who were within 1,200 meters of the bomb hypocenter in Hiroshima. These children were examined at 4½ years of age and seven of them had microcephaly and mental retardation, while none of the 194 children born to pregnant mothers who were at greater distance from the exploded bomb had this abnormality. Similar, although less striking, observations were made by Yamazaki *et al* (*6*) following explosion of the atomic bomb at Nagasaki.

The present series adds to the evidence. Although many of the irradiated pregnant women had pathological conditions involving pelvic organs, a few of

the others were healthy and their pregnancy was mistaken for myoma. Also, one can argue with considerable success that such a specific set of abnormalities and in particular microcephaly and microphthalmus could not have occurred by chance in these many children who had a rare, common factor: heavy exposure to ionizing radiation during fetal life. If all the evidence now available is considered we can safely assume that in man, too, there is causal relationship between fetal irradiation and the specific abnormalities present in children.

Microcephaly in children, which was invariably associated with permanent mental retardation, presents a most serious problem and warrants further consideration. If one excludes craniostenosis (none was present in this series and only one in other reports), the microcephaly reflects abnormal smallness of the brain. The natural impulse for expansion of the skull during fetal life and during childhood is the growing brain since the sutures are not firmly united until about 12 years of age. From the embryological studies of the human brain (*45,46*) it is known that the brain undergoes rapid growth and marked structural changes between 4 and 20 weeks of gestation. Thus certain cerebral structures would be formed by 9–11 weeks of gestation and from then on they will grow in size while the others will be at their height of differentiation (as for example cerebral cortex) during subsequent months of intrauterine life. Therefore the smallness of brain which underlies microcephaly in children irradiated at various times between 4 weeks (single cerebral vesicle) and 20 weeks of gestation (greatly expanded and differentiated cerebral cortex) would be expected to have different pathological lesions. The types of these various lesions are little known in man since the necessary pathological material for appropriate study is rarely available. We therefore decided to conduct a separate experimental investigation especially designed to obtain the information needed here. The detailed results of this study are published separately (*23*) but the pertinent data are summarized here. In the irradiated mouse fetuses at consecutive stages of gestation, the cerebral findings at the time of birth can be divided into four groups: (1) Irradiation prior to 7 days of gestation leads to death and absorption of the majority of fetuses but those who survive appear normal and their brain is free of structural abnormality. This stage of development in the mouse would correspond to less than 3 weeks of gestation in man. Primitive streak stage in the mouse embryo occurs at 6½ g.d. and neural tube begins to form at 7½ g.d. (*47*), while in man the primitive streak stage is around 16 g.d. (*48,49*) and the neural tube begins to form at about 22 ± 1 g.d. (*50*) or 5–8 somites (*46*). (2) Irradiation of the mouse fetus with comparable doses on the eighth and ninth days of gestation leads to the abnormality of early organogenesis. Here exencephaly, dysraphism, single cerebral ventricle, hydrocephalus and generally hypoplastic and small brain may occur but focal lesions are very rare. This stage in man would correspond to about 3–7 weeks of gestation. (3) Irradiation of mice on 10 through 13 days of gestation produces marked brain damage, cellular deficit, heterotopias, deformities of various structures and secondary dilatation of ventricles; thus the brain itself is small. Using great approximation this stage in the development of the mouse brain would correspond to 8–16 weeks of gestation in man. (4) Irradiation of mice on 14–16 days of gestation produces mild cortical abnormality of a diminishing degree to almost normal as seen at birth. The size of the brain is only slightly reduced or normal. This stage of development in mouse brain approximates roughly 17–24 weeks of gestation in man.

SUMMARY

Severe and obvious abnormalities encountered in 26 children who received heavy x-radiation during various stages of gestation were compiled and evaluated. The following conditions occurred most frequently: stunted growth, microcephaly, mental retardation, microphthalmus, pigmentary degeneration of the retina, cataracts, genital and skeletal anomalies. A tentative timetable for man is presented which correlates specific types of abnormalities with irradiation during particular stages of gestation when the dose is in the range of therapeutic irradiation. On the basis of the patient material presently available and with some support of experimental data the following generalizations are made: (1) Moderately large dose of ionizing radiation (over 250 R but the upper limit cannot be stated) delivered to the human embryo before 2–3 weeks of gestation is not very likely to produce severe abnormality in most of the children born although experimental data indicate that considerable numbers of these embryos are resorbed or aborted (*23,24*). (2) Irradiation of the fetus with doses used in medical therapeutics between 4 and 11 weeks of gestation would lead to severe abnormalities (predominantly malformation) of many organs in most or all of the children. (3) Irradiation in a similar dose range between 11 and 16 weeks of gestation may produce little or no eye (late cataracts not considered), skeletal and genital organ abnormalities but stunted growth, microcephaly and mental retardation is frequently present. (4)

Irradiation of the fetus between 16 and 20 weeks of gestation with a similar dose range may lead only to mild degrees of microcephaly, mental retardation and stunting of growth. (5) Irradiation of the fetus with a similar dose range after 20 weeks of gestation is not likely to produce overt abnormalities leading to a serious handicap in early life. However, a proportion of the infants may show evidence of irradiation exposure such as skin erythema, abnormal pigmentation, epilation, or deficiencies in the hematopoietic system.

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