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Congenital Malformations in Neonates after Irradiation of Rats During Pregnancy

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ABSTRACT

Radiation is considered a teratogen during the whole period of embryonic development and fetal growth. However, the time of gestation at which irradiation takes place will affect the type of congenital malformation Induced. A study was carried out to observe various forms of congenital malformations induced after irradiation of pregnant rats to 1, 2 and 3 Gy on the 9th, 12th and 15th days of gestation. Various types of congenital malformations were observed in the neonates of irradiated animals as compared to controls. Most of the malformations were observed in neonates of animals irradiated with 2 and 3 Gy on the 12th and 15th days of gestation. This confirms that developmental anomalies occur mostly during the period of organ development. Other periods of gestation are less vulnerable to, induction of malformation after irradiation. Some representative photographs of the malformations induced such as penguin shape, absence of tail, low set ears, growth retardation and others are illustrated in the text.

Key word: Radiation /Congenital /Malformation.

INTRODUCTION

The whole period of gestation from conception to delivery of the newborn litters is a very sensitive period and highly vulnerable to disorganization from extrinsic and intrinsic factors. Exposure to ionizing radiation induces several different effects to the embryo and fetus during the period of intrauterine life. Variations of these effects are mainly dependent on radiation dose and specific stage of gestation at which irradiation took place. Developmental abnormalities occur particularly during the stage of organogenesis. This is because of the high proportion of radiosensitive culls and the criticality of cellular activities during organ development. From pastreports, radiation exposure during early organogenesis results in high incidence of prenatal deaths. Irradiation during late organogenesis results in a high incidence of abnormalities at birth with lower incidence of mortality[1] The main malformations that commonly appear are retardation of growth, skeletal deformities and CNS changes[2,3].

EXPERIMENTAL MEIHODS

This study included sixty pregnant female rats after verification of successful mating by microscopical vaginal smear. The animals were divided into three groups according to day of gestation 9th, 12th and 15th days. Each group comprised 20 animals and subdivided into 4 subgroups of them comprised 5 animals. The first subgroup did not irradiated and considered as control subgroup. The second to fourth subgroups irradiated with I, 2 and 3 Gy of gamma rays from cobalt-6o respectively.

Al animals were sacrificed on day 21 of gestation. The uteri were opened. The number of litters was recorded. Congenital malformations were observed on live litters, recorded and photographed.

RESULTS

- **Animals irradiated on 9th day of gestation:**

The malformations observed include, decrease in length, absence of tail and eye fissures in some litters. Most malformations were observed in litters of I and 2 Gy irradiated subgroups.

- **Animals irradiated on I2th day of gestation:**

The malformations observed include, non viable very small litters, haemencephalocele, penguin shaped abnormal litters, small limbs and tails, no ears and cranial haemorrahage.

- **Animals irradiated on 15th day of gestation:**

The congenital malformations observed included no eye fissures and congested litters.

Plate (1) shows viable litters from an unirradiated control mother. The average length of a control litter is 35 mm (at birth). (Magnification of 1:1).

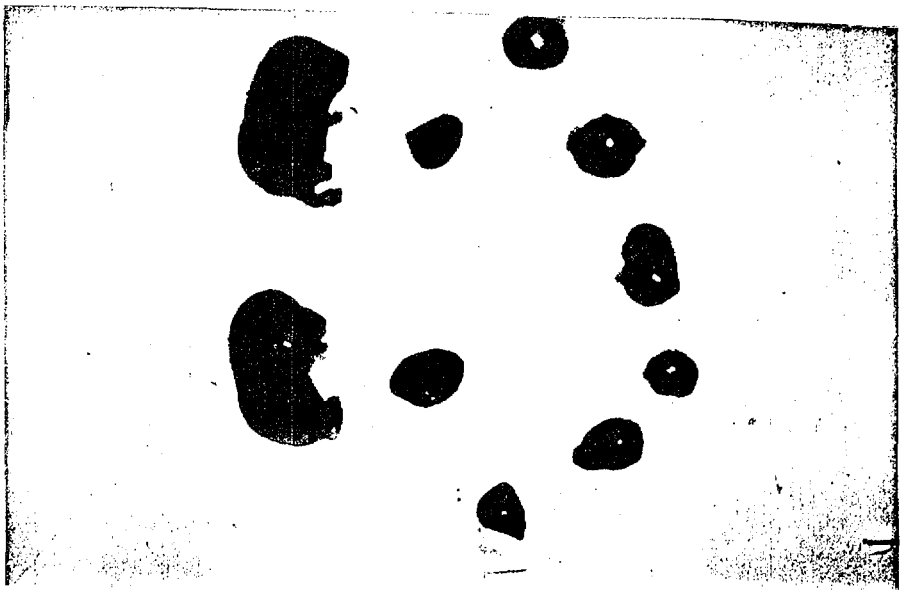


Plate (2) shows two small viable litters, (20 mm length) (at birth) from a mother exposed to 2 Gy on 9th day of gestation. The litters shown have no tail. The uterus included several absorption sites. (Magnification of 1:1).

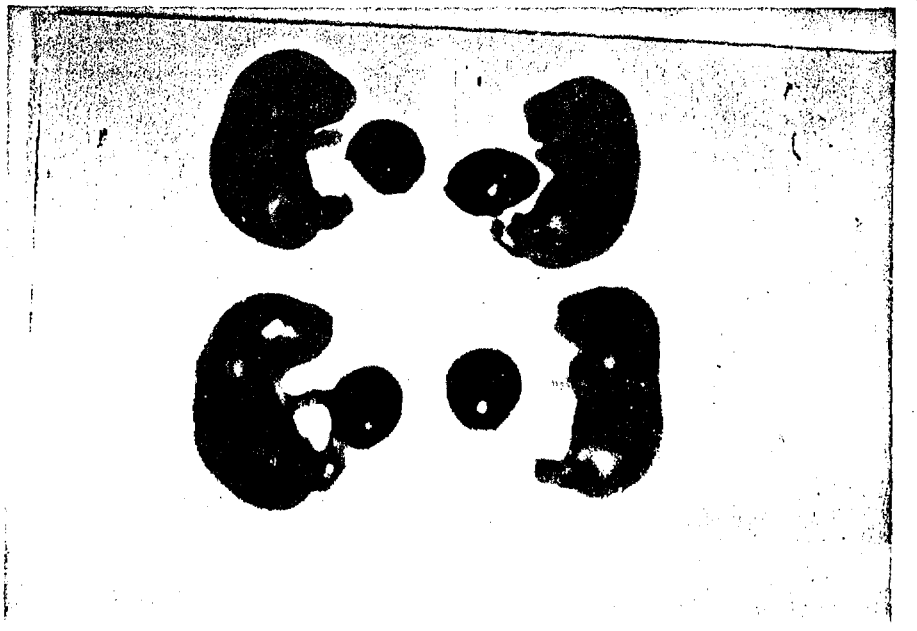


Plate (3) shows four small viable litters (23 mm at birth) from a mother exposed to 2 Gy on 9th day of gestation. The litters have no eye fissures. (Magnification of 1.3:1).

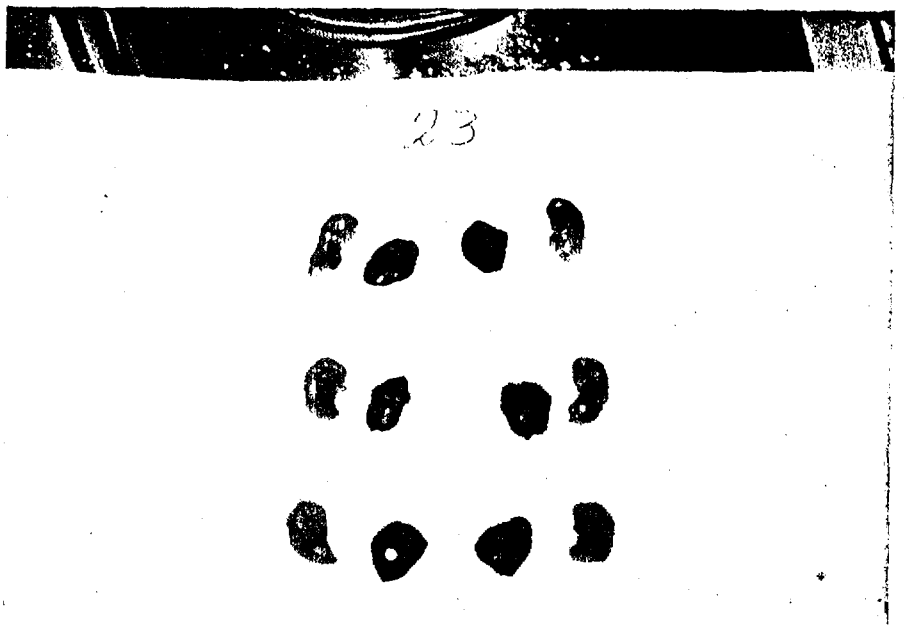


Plate (4) shows six nonviable litters from a mother exposed to 2 Gy on 12th day of gestation. They are nonviable very small litters (about 13 mm length). The litters present no features. (Magnification of 1:1).

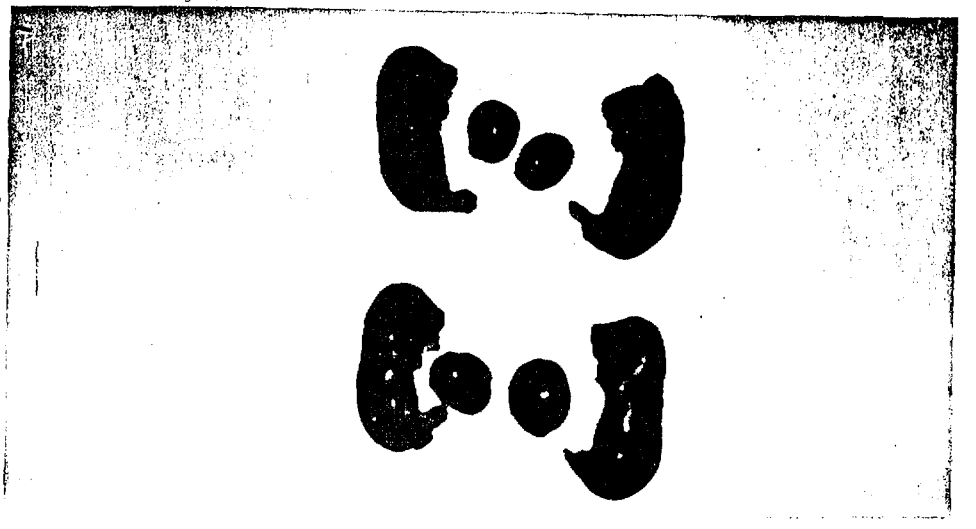


Plate (5) shows four viable litters from a mother exposed to 2 Gy on 12th day of gestation. They are 3 viable litters and one litter shows haemencephalocele(?). (Magnification of 1:1.2).

Plate (6) shows three litters (two viable and one small non-viable) from a mother exposed to 3 Gy on 12th day of gestation. They are penguin shaped abnormal litters. Small limbs and tails, with no ears. The occipital region of the skull shows dark blood coloration which appears as blood collection inside the skull.
(Magnification of 1.2:1).

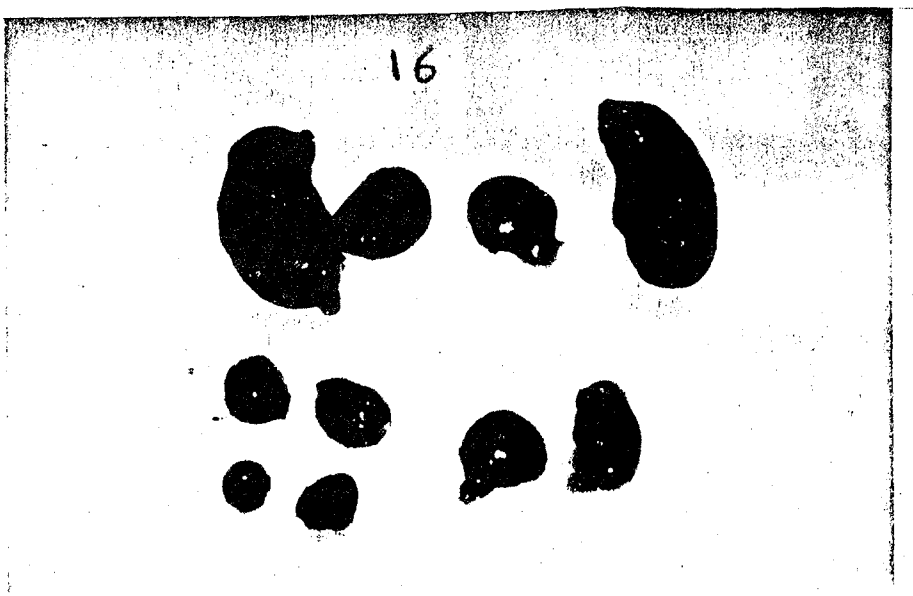


Plate (7) shows three viable litters from a mother exposed to 3 Gy on 12th day of gestation. They are penguin shaped abnormal viable litters. They have very small limbs and tails, low set ears. The occipital region of the skull shows dark blood coloration that appears as blood collection inside the skull.
(Magnification of 1:1).

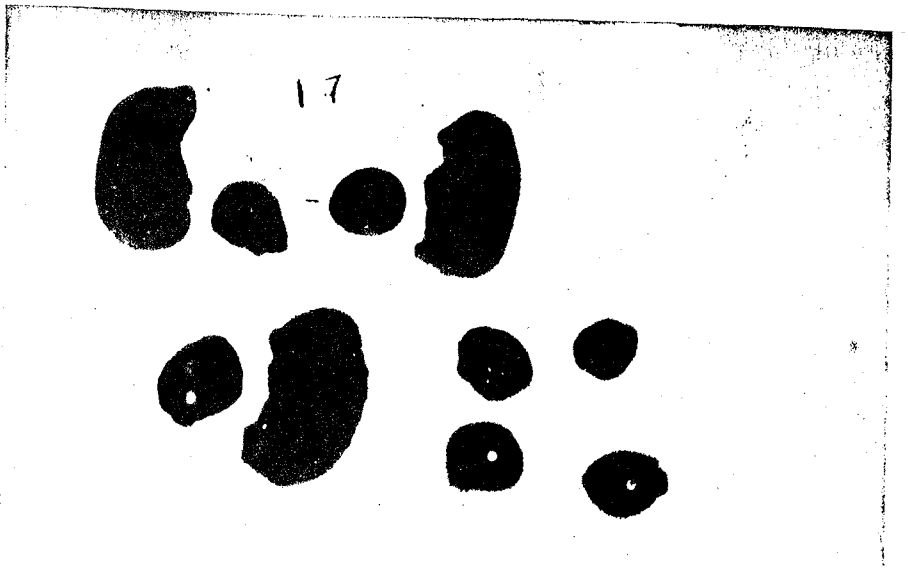
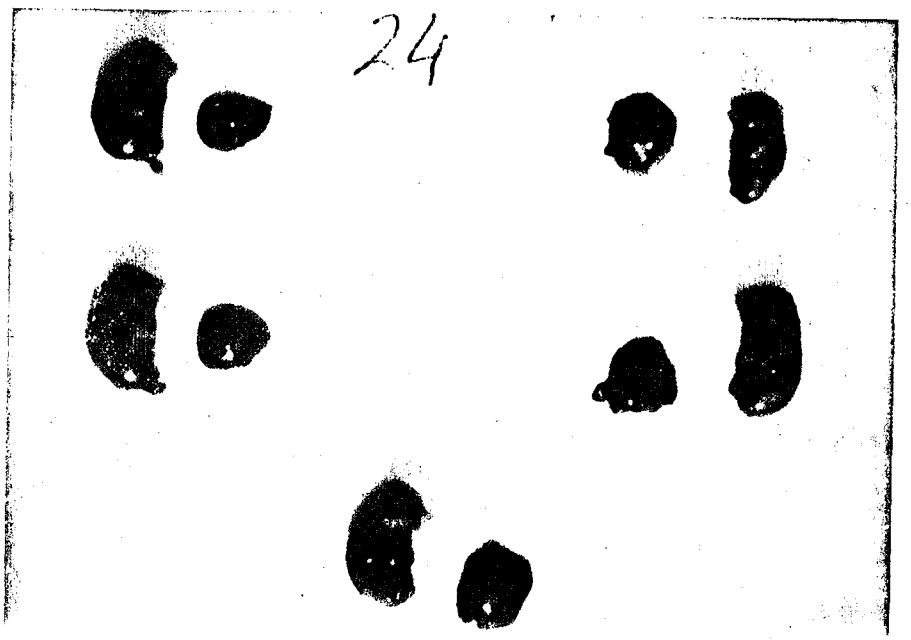


Plate (8) shows five viable litter from a mother exposed to 3 Gy on 12th day of gestation. they are penguin shaped abnormal litters. They have very small limbs, tails and ears. The occipital region of the skull of these litters present dark blood coloration which appears as a blood collection inside the skull.
(Magnification of 1:1).



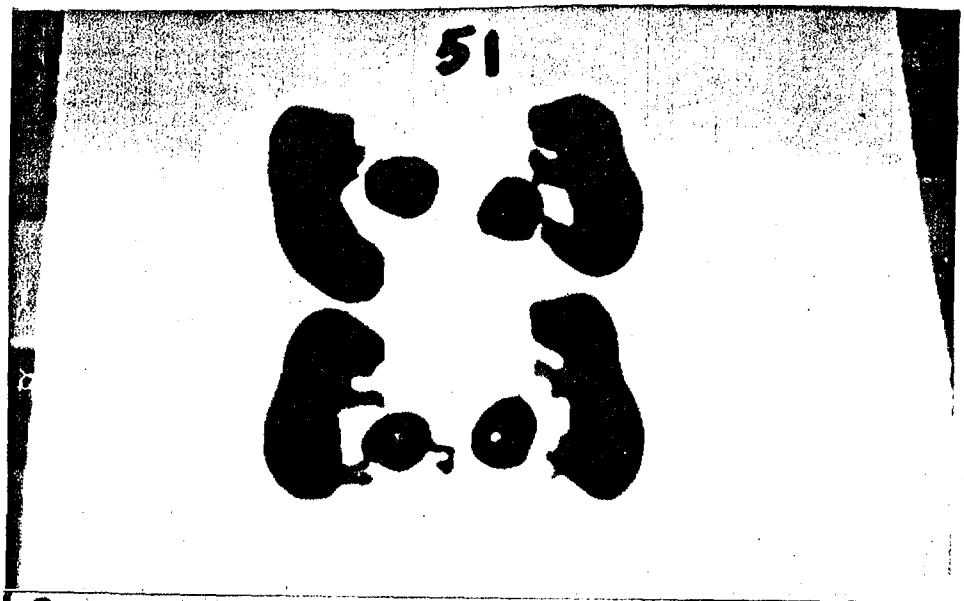


Plate (9) shows 4 of 9 viable litters from a mother exposed to 1 Gy on 15th day of gestation. All the litters have no eye fissures.
(Magnification of 1:1.2).

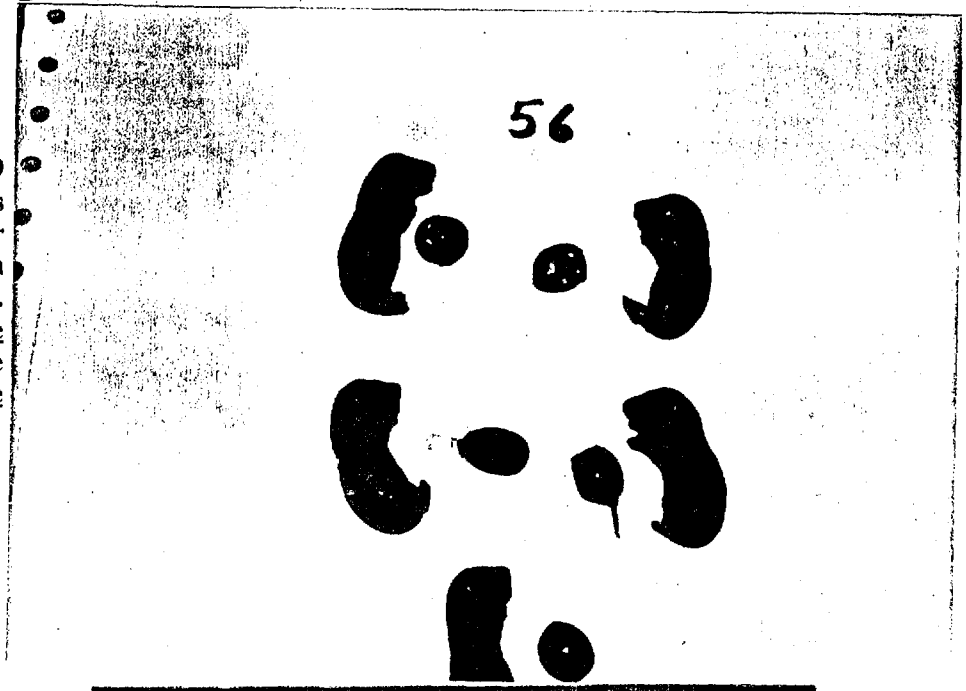


Plate (10) shows 5 of 9 normal viable litters from a mother exposed to 1 Gy on 15th day of gestation. They have no eye fissures. One of the litters has only one eye.
(Magnification of 1:1.5).

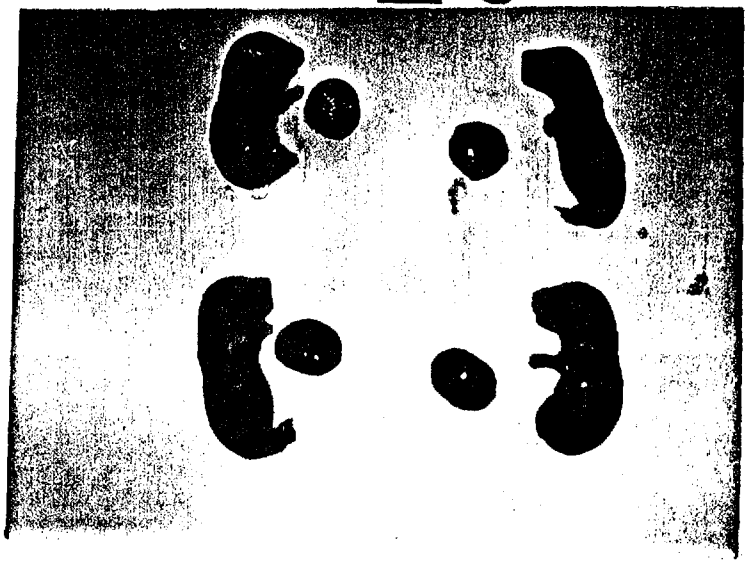


Plate (11) shows 4 of 7 litters from a mother exposed to 1 Gy on 15th day of gestation. They are viable litters have no eye fissures. Three of the litters are congested.
(Magnification of 1:1.4).

Plate (12) shows 4 of 8 *litters from a mother* exposed to 1 Gy on 15^{th} day of gestation. They are viable litters have no eye fissures. (Magnification of (1:1.4).

DISSCUSION

The stage of organogenesis is characterized by certain biological mechanisms, which are very specific and critical of this stage of embryonic development. These biological mechanisms are cellular proliferation, cellular and tissue differentiation, cleavage, migration, rotation and growth. These critical biological mechanisms render this stage of organogenesis highly vulnerable to ionizing radiation. Exposure to ionizing radiation may result into disturbance of the normal hierarchy of the biological mechanisms during the critical phase of tissue organization, organ formation, cellular and tissue processes required for the final stage of organ and species formation. Disturbance of such intricate processes has a probability of resulting in tissue and organ malformation or disturbed development. These may include disturbances in fetal weight and alteration in the normal growth mechanisms. Other abnormalities during this stage may appear as congenital malformations.

The fetal growth period has the maximum rate of increase in size and weight of the fetus. Differentiation is also completed at this stage. The embryo remains relatively small through fertilization, cleavage and gastrulation phases and begins to increase in size during organogenesis. When the organ systems are established there is marked increase in growth. Absolute growth increases throughout pregnancy, but relative growth begins to decrease about the middle pregnancy. This period takes from the beginning of fetal period and a rapid increase in linear dimension and weight of the fetus begins at that time and ends at birth[4].

The studies of the appearance of congenital malformation after in utero irradiation during pregnancy in mammals have been the most important aspect concerning investigators. Since the early studies on this subject, up to now, the most important biological end point has been the various congenital malformations produced after irradiation with different doses during the various stages of gestation. The salient features produced by these studies reveal that the major incidence at congenital malformations were obtained after irradiation during the stage or organogenesis, during which tissue organization and organ development is maximum. This particular stage is different from the early phase of gestation (preimplantation and early organogenesis); by the fact that during the stage of major organogenesis, the mechanisms and biological processes of tissue organization, differentiation and cellular kinetics are most prevalent Consequently, any sustainable radiation injury during that phase has a high probability inducing some type of congenital malformations.

The induction of these types depends mostly on the tissue receiving radiation insult, the status of cellular organization, the degree of differentiation of cellular population and other major cellular biological processes. The repair mechanisms and the compensatory processes of the tissue cellular populations will finally manifest in the congenital deformity and abnormality that will eventually establish the type of congenital malformations manifested at birth. The induction of congenital malformations depends on a lesser extent on radiation dose. Although it is conceivable that higher doses will result in more biological injury than lower doses, however, it is basically the type of tissue affected, the degree of injury the sequential development of the injury and the final biological end point attained that will demark the type and extent of the congenital malformation.

Following this important introductory notation, the congenital malformations recorded in the present study are very consisting with radiobiological rationality. The overall features of the results obtained in this study indicate that the congenital malformations produced are growth retardation, absence of tail, absence or eye fissures, penguin shaped litters, very small ear, haemencephalocele and other types. These congenital malformations were observed in live litters removed from uteri or irradiated animals after animal sacrifice and abdominal dissection at full term on the 21st day of gestation. The congenital malformations were observed in litters of irradiated animals as compared to litters of control unirradiated animals.

The features of the results of congenital malformations, in spite of few exceptions, show that most of the malformations occurred in litters whose mothers were irradiated on the 12th day of gestation to a dose of 2 Gy. These findings conform with the fact that the 12th day of gestation (in rats) is the peak of tissue organization during the period of major organogenesis.

On the other hand, viable penguin shaped litters were essentially observed among litters whose mothers were exposed to 3 Gy at 12th day of gestation. Also, penguin shaped litters showed other congenital malformations in the form of very small limbs, small tails, low set cars or no ears. These various malformations were observed in litters from mothers irradiated on 12th day of gestation with 2 or 3 Gy.

It must be mentioned in this respect that congenital malformations after in utero irradiation are irreproducible. This fact is also true for all types of radiation induced injuries to the developing embryo and fetus. The only effect that is reproducible to a very great extent is intrauterine embryonic death resulting in absorption sites or complete resorption of embryonic remnants. Tissue effects are observed at relatively high doses (2.5 Gy or above) amid '4,en irradiation takes place at early periods of gestation.

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