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RADIATION INDUCED CONGENITAL MALFORMATIONS (AN EXPERIMENTAL STUDY)

A Thesis Submitted for Fulfillment of Ph.D. Degree
in Childhood Studies (Medical Studies Department)

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وإنْ تعدوا نعمةَ اللّهِ لا تُحصُوها

(٣٤ إبراهيم)

Praise be to Allah, who guided me to His path and to the light of Faith through His Messenger Mohammad "prayers and peace be upon him".

To my better half, my dear loving wife
MONA
you stood by me, encouraged me
and enlightened my life
words will never
say how
grateful
I am

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ABSTRACT

Title of thesis : Radiation Induced Congenital Malformations (An Experimental Study).

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Aim

This study was performed to relate the radiation dose, time of gestation at which irradiation occurred and the radiation effects induced.

Experimental Methods

Seventy Five pregnant albino rats were divided into three groups according to day of gestation. First group was irradiated on 9^{th} day of gestation, corresponding to period of early organogenesis. Second group was irradiated on 12^{th}day of gestation corresponding to period of major organogenesis. Third group was irradiated on 15^{th}day of gestation corresponding to period of fetal growth. Each group was subdivided into control and four subgroups irradiated with doses of 0.5, 1, 2 and 3 Gy of Cobalt-60 gamma rays.

Results

Morphological studies on number of absorption sites, number of litters and measurements of size, weight, body and tail lengths, umbilical girth, antro-posterior and biparietal dimensions of skull. These studies revealed signs of intrauterine growth retardation evidenced at 2 Gy on the 12^{th} day of gestation. The dose of 3 Gy on 9^{th} day of gestation was lethal to all embryos. Observations on congenital malformations revealed penguin shaped litters, absence of eyes and tails, small limbs and low set ears. These

malformations appeared mostly in animals irradiated during major organogenesis, with doses of 1 and 2 Gy. Histopathological studies on thirteen tissues taken from litters revealed that large intestine, bone, pancreas and meninges were not affected. Thymus, lungs and heart were least affected. Brain, spleen and suprarenal were moderately affected. Liver, ileum and kidney were severely affected. The dominant pathological feature observed was cellular degeneration. All data recorded were statistically evaluated.

Conclusions Results indicated that the whole period of gestation is vulnerable to the hazards of ionizing radiation. The cellular activities and biological processes of proliferation, differentiation and growth are the major causes of radiation induced injury to the developing embryo and fetus. Doses of 0.5 Gy were incapable of inducing deterministic radiation injury during the whole period of gestation; however, it may induce probabilistic effects. The results obtained from the studies performed support the basic scientific premise that pregnant women should not be exposed to ionizing radiation during the whole period of pregnancy.

Key words :

radiation, congenital, morphological, histopathological.

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Mean
AP	Antro-posterior
BP	biparietal
c	Centigrade
C	Velocity of light
Circum.	Circumference
CM	Congenital Malformation
CNS	Central Nervous System
Co	Cobalt
DNA	Deoxyribonucleic Acid
EMH	ExtraMedullary Hemopoiesis
Gy	Gray (new unit of radiation absorbed dose)
h	Height
Hg	Mercury
Hx & E	Hematoxylin and Eosin stain.
ICD	International Classification of Diseases
ICRP	International Commission on Radiological Protection .
ID	Ionization Density
IQ	Intelligent Quotient
IUFD	Intrauterine Fetal Death
IUGDR	Intrauterine Growth and Developmental Retardation
kg	Kilogram
km	Kilometer
l	Length
Lat.	Lateral
LET	Linear Energy Transfer
LMP	Last Menstrual Period
m	Mass
MeV	Million electron Volt

mGy	MilliGray = 10^{-3} Gray
ml	Milliliter = 10^{-3} liter
mm	Millimeter
mSv	MilliSievert = 10^{-3} Sievert
n	Number of population
NCRP	National Council on Radiation Protection and Measurement.
P	Probability value
PDGF	Platelet-derived growth factor
PGF	Polypeptide Growth Factor
Rad	Radiation absorbed dose (old unit)
RBE	Relative Biological Effectiveness
SE	Standard Error
SI units	International System of units
Sv.	Sievert (unit of effective dose)
TBq	Tera Becqurel = 10^{12} Becqurel
TLD	Thermoluminescense Dosimetry.
UNSCEAR	United Nations Scientific Committee on Effects of Atomic Radiation.
w	Width
WHO	World Health Organization
W_R	Radiation Weighting Factor
W_T	Tissue weighting factor
$\bar{X}$	Mean
x_i	All individual values
Z	Atomic number (number of protons)
Σ	Sigma = summation
μm	Micrometer

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INTRODUCTION

1. INTRODUCTION.

The effects of ionizing radiation on the embryo/fetus during the various developmental stages were studied since the early fifties. The experiments in this field indicated that the embryo and fetus are very radiosensitive during the total prenatal period of intrauterine life. The type and severity of radiation effects depend strongly on the developmental stage at which the radiation exposure occurs, the total exposure dose and other radiation related factors such as dose rate, fractionation and linear energy transfer (LET) **(NCRP, 1985).**

It is customary to consider the period of intrauterine life into three main stages or phases depending on the bioembryological processes that take place and the related cellular mechanisms and activities that dominate during each phase. The main developmental features of each stage are specific in type and time of occurrence. These are considered by general consensus of embryologists to be well established. The stage of fertilization constitutes intermingling of male and female pronuclei to form a zygote. The stage of preimplantation constitutes formation of a morula (12–16 blastomeres), then changed into a blastocyst. The stage of organogenesis constitutes formation of the organs primordia. The stage of fetal growth which is the longest stage comprising final organ development and growth mechanisms.

The basic developmental features that take place during intrauterine life of humans are very much similar to those that occur in rats (the experimental animals used in this thesis). The main difference is in the timing since the intrauterine life in humans is 265 days, compared to 21 days in rats. In spite of this fact, the staging and sequence of intrauterine development is fundamentally similar.

From past reports and publications on the subject, radiation exposure during the preimplantation period results in high incidence of prenatal deaths. Irradiation during the period of major organogenesis results in a high incidence of abnormalities at birth with lower incidence of mortality. Irradiation during the fetal growth period usually results in brain and CNS abnormalities.

The main malformations that commonly appear are retardation of growth, skeletal deformities, CNS changes and behavioral alterations **(Russell and Russell, 1954; Jensh and Brent, 1988 and Devi et al., 1994).**

In spite of the extensive experimental studies performed and data obtained from epidemiological studies on mankind, this subject remains lacking precise information on establishing a dose-effect relationship and the involvement of the time of gestation in the type and severity of effect produced. The general pattern of results reported in the studies performed points essentially toward the fact that the whole period of embryonic development and fetal growth from a time of fertilization until delivery is highly radiosensitive.

The aim of this thesis is to assess radiation induced effects on embryo/fetus and identify the relationship between time of gestation, dose of radiation and type of radiation induced effect. For this purpose, the experiments performed have been constructed to include three major studies, namely, morphological, congenital malformations and histopathological. The periods of gestation chosen as time of irradiation were 9^{th}, 12^{th} and 15^{th} days of gestation to correspond to early organogenesis, major organogenesis and fetal growth respectively. These periods have variable radiosensitivies of the embryonic tissues and organs. The radiation doses used were 0.5, 1, 2 and 3 Gy as single acute exposure to pregnant rats. These include the higher levels of low doses

(0.5 Gy) and the low levels of high doses (2 and 3 Gy). this distribution, established a spectrum of doses that included a wide bracket.

The construction of the experimental aspect of the thesis as described appears to cover the subject collectively both from its medical biology and radiation points of view.

The thesis comprises 5 chapters including the chapter of introduction. Every chapter constitutes a detailed monograph of its purpose. The chapter on review comprises extensive comprehensive statements on several aspects that are intimately relevant to the subject. The third chapter provides complete information and description of the experiments performed. The chapter on results is divided into the three studies performed and fully supplemented with tables, curves, photographs and microphotographs. The chapter on discussion provides concise synopsis of basic informations on the radiobiology of mammalian cells and tissues, main features of cellular functional mechanisms during embryonic development and fetal growth and interpretation of results obtained with concluding remarks.

The thesis is supplemented with 28 tables, 24 figures (each one comprises curve and table), 47 plates, 101 references, an appendix, English and Arabic summaries.

It is believed that the systemic studies carried out in this thesis contribute an extra dimension to the subject of radiation effects on embryonic development and fetal growth.

Review of Literature

2.REVIEW OF LITERATURE

2.1.CONSIDERATIONS OF MAMMALIAN DEVELOPMENT

2.1.1.Fundamentals of Embryonic Development in Humans.

Fertilization (The First Week).

Human development begins at fertilization. Oocytes are produced by the ovary (oogenesis) and are expelled during ovulation. The oocyte is swept into the uterine tube where it may be fertilized. Sperms are produced by the seminiferous tubules in the testes (spermatogenesis) and are stored in the epididymis. Ejaculation during sexual intercourse results in the deposition of millions of sperms in the vagina. When a sperm contracts an oocyte, the oocyte completes the second meiotic division, to give a mature ovum and a second polar body. The nucleus of the mature ovum constitutes the female pronucleus. After the sperm enters the ovum's cytoplasm, fertilization is complete when the maternal and paternal chromosomes intermingle during metaphase of the first mitotic division of the zygote, the cell that gives rise to a human being. Division of the zygote into two daughter cells called blastomeres begins about 30 hours after fertilization. Three days after fertilization, a solid ball of several blastomeres, called a morula, enters the uterus. About four days after fertilization, spaces appear between the central cells of morula, converting it into a blastocyst About eight days after fertilization, the blastocyst attaches itself to the endometrial epithelium and starts proliferating rapidly and gradually differentiates **(Beck, et al., 1985).**

Implantation (The Second Week).

Implantation of the blastocyst begins at the end of the first week and continues to be completed during the second week. The ten days conceptus becomes completely embedded in the uterine endometrium. The end of the second week is characterized by the appearance of the

chorionic villi. The extraembryonic somatic mesoderm and the two layers of trophoblast constitute the chorion **(Moore, 1988).**

Gastrulation (The Third week).

The process by which the inner cell mass is converted into trilaminar embryonic disc is called gastrulation. This occurs during the third week with the formation of the three primary germ layers namely, ecto, meso and endoderm. Formation of the primitive streak and notochord are important processes that occur during gastrulation. The allantois appears on about day 16. Neurulation is the process of formation of the neural tube. About the eighteenth day, the neural plate invaginates along its central axis to form neural groove that has neural folds on each side. By the end of the third week, the neural folds move together and fuse, converting the neural plate into a neural tube. As the neural tube separates from the surface ectoderm, some neighboring (neuroectodermal) cells called neural crest cells migrate to form sensory ganglia of the spinal and cranial nerves, sheathes of nerves (Schwann cells), meningeal covering of the brain and spinal cord and other parts.

Towards the end of the third week, the paraxial mesoderm begins to divide into paired cuboidal bodies called somites. The somites give rise to most of the axial skeleton (head and trunk) and associated musculature, as well as to the adjacent dermis (skin). About 38 pairs of somites form during the so called somite period of development (days 20 to 30). Eventually 42 to 44 pairs of somites develop. The intraembryonic coelom (cavity) appears during the third week **(Moore, 1988).**

During this period also, blood vessel formation begins in the extraembryonic mesoderm of the yolk sac, connecting stalk and chorion. The primitive heart is formed from mesenchymal cells in the cardiogenic area. By the end of the third week, the heart tubes fuse to form a primitive cardiovascular system. The blood circulates by the end of the third week and the heart begun to beat. The cardiovascular system is the first organ system to reach a functional state **(Nishimura et al., 1974).**

Placentation (The fourth week).

By the beginning of the fourth week, the anatomical arrangements necessary for physiological exchanges between the mother and the embryo are established. The placenta consists of two parts, a fetal portion derived from the villous chorion and a maternal portion formed by the decidua basalis. The two parts are held together by anchoring villi and the cytotrophoblastic shell. The fetal circulation is separated from the maternal circulation by a thin layer of fetal tissues known as the placental membrane (placental barrier). It is a permeable membrane that allows water, oxygen, nutritive substances and hormones to pass from the mother to the embryo or fetus. Excretory products and noxious agents pass through the placental membrane from the embryo or fetus to the mother. The principal activities of the placenta are metabolism, transfer channels between mother and embryo and endocrine secretion **(Behrman and Vaughan, 1987).**

Organogenesis (The Fourth to Eleventh Week).

These eight weeks are called the embryonic period, because it is the time of rapid development of the embryo. All the major organs and systems of the body are formed during this period. At the beginning of the fourth week, a cylindrical shaped embryo is formed after a folding process. The formation of head, tail and lateral folds is a continuous sequence of events that result in a constriction between the embryo and the yolk sac. During folding, the dorsal part of the yolk sac is incorporated into the embryo and gives rise to the primitive gut.

As the head region "swings" or folds ventrally, part of the yolk sac is incorporated into the developing embryonic head as the foregut. Folding of the head region also results in the oropharyngeal membrane and the heart is carried ventrally and the developing brain becomes the most cranial part of the embryo.

As the tail region "swings" or folds ventrally, part of the yolk sac is incorporated into the caudal end of the embryo as the hindgut. The terminal part of the hindgut expands to form the cloaca. Folding of the tail region also results in the cloacal membrane, allantois and connecting stalk being carried to the ventral surface of the embryo. Folding of the embryo in the horizontal plane incorporates part of the yolk sac into the embryo as the midgut. The yolk sac remains attached to the midgut by a narrow yolk stalk. During folding in the horizontal plane, the lateral and ventral body walls are formed. As the amnion expands, it envelops the connecting stalk, yolk stalk and allantois, thereby forming an epithelial covering for the new structure called the umbilical cord **(Wessels, 1977).**

The three germ layers derived from the inner cell mass during the third week, differentiate into various tissues and organs, so that by the end of the embryonic period, the beginning of all the main organ systems become established. The external appearance of the embryo is greatly affected by the formation of the brain, heart, liver, somites, limbs, ears, nose and eyes. As these structures develop, the appearance of the embryo changes and these characteristics mark the embryo as unquestionably human.

At the nine week, primary ossification centers appear in the skeleton, especially in the skull and long bones. The external genitalia of males and females appear somewhat similar until the end of ninth week. The liver is the major site of erythropoiesis, however, by the end of the twelfth week this activity decreases in the liver and begins in the spleen. Urine starts to form between the ninth and twelfth weeks and excreted in the amniotic fluid **(Thompson, 1986).**

The period from fourth to eleventh weeks constitute the most critical period of human development. Developmental disturbances during this period induced by intrinsic or extrinsic factors may give rise to major congenital malformations of the embryo **(Moore, 1988).**

The Fetal Period (The Twelfth Week to Birth).

The fetal period begins twelve weeks after fertilization and ends at birth. Rapid body growth and differentiation of organ systems characterize this period. An obvious change is the relative slowing of the head growth compared with that of the rest of the body.

Thirteen to sixteen weeks: Growth is very rapid and ossification of the skeleton begins. Scalp hair patterning is determined and gives a clue to early fetal brain development **(Smith and Gong, 1973).**

Seventeen to twenty four weeks: Growth slows down. Quickening (fetal movement) are commonly felt by the mother. The skin is covered with vernix caseosa and lanugo. Eyebrows and head hair are visible at twenty weeks. By twenty four weeks, the secretory epithelial cells or type II pneumocytes in the interalveolar walls of the lung begin to secrete surfactant. Finger nails appear by twenty four weeks **(Page et al., 1981).**

Twenty five to twenty nine weeks: During this age, a fetus may survive if born prematurely and given intensive care, because its lungs are capable of breathing air. In addition, the central nervous system has matured to the stage at which it can maintain rhythmic breathing movements and control body temperature. Erythropoiesis in the spleen ends by 28 weeks. The bone marrow becomes the major site of this process **(Balsam and Weiss, 1981).**

By full term (38 weeks after fertilization, or 40 weeks after last menstrual period (LMP)), the skin is usually white or bluish pink, the chest is prominent and the breasts protruded slightly in both sexes **(Moore, 1988).**

Several factors affect the rate of fetal growth, namely, maternal malformation, smoking, multiple pregnancy, alcohol or narcotics,

impaired uteroplacental blood flow, placental insufficiency and Genetic factors **(Golbus, 1980; Page et al., 1981 and Thompson, 1986).**

The changes occurring during the fetal period are not so dramatic as those appearing in the embryonic period, but they are very important. The fetus is less vulnerable to the teratogenic effects of drugs, viruses and radiation, but these agents may interfere with normal functional development, especially of the brain and eyes **(Moore, 1988).**

2.1.2. Embryonic Development in Rats

The duration of pregnancy is the period of time elapsing between fertilization of an ovum and the birth of the young. Internal changes, which accompany gestation, include the increase of blood supply to the uterus, the rise in the overall metabolism and the basal metabolic temperature of the mother, the development of the placenta which enables the uptake of nutrients and excretion of metabolic wastes from the conceptus and all the processes concerned with the development and growth of the embryo and fetus.

Both internal and external environmental factors have an effect on the gestation period. These environmental factors include the age, weight and general physiological condition of mother, the size and weight of the fetus as well as litter number and size. For the proper understanding of the exact sequences of the processes of gestation, it is imperative that a synopsis of these processes be reviewed **(Ratcliffe et al., 1993).**

The Estrus Cycle.

The estrus cycle starts at the attainment of puberty, occurring in non pregnant female in a species-specific rhythmic cycle. In the rat, it is characterized by four major phases, namely, estrus, metestrus, diestrus and proestrus. The rat normally tends to display signs of estrus every 4 or 5 days **(Fox and Laird, 1970).**

The estrus phase is the time of ovulation. Mating will result in fertilization. This phase may last from nine to fifteen hours. Metestrus phase follows estrus and occurs shortly after ovulation. It lasts about 21 hours. The diestrus phase is the third and longest phase, which lasts for 57 hours. The proestrus phase is a preparatory phase preliminary to the next estrus period.

Ovulation, which occurs during the estrus phase, refers to discharge of the mature ovum from the grafian follicle. It occurs spontaneously during estrus whether or not mating has occurred.

The periodicity of estrus in mature females is a direct result of cyclic changes that occur in the ovary which, in turn, reflects altered hypothalamic activity and changes in gonadotropin secretion. **(Ratcliffe et al., 1993).**

Mating and Fertilization.

Fertilization must be preceded by the condition of mating. Mating in rat is detected by the occurrence of vaginal plugs. Such plugs are formed by a mixture of the secretions of the vesicular and coagulating glands of the male and usually fill the vagina from cervix to vulva. Plugs persist for 16-24 hours and may last as long as 48 hours **(Fox and Laird, 1970).**

In rat, coitus usually precedes ovulation by only few hours. The passage of sperm into the oviduct prior to uptake by the ova insures that the ova are relatively fresh or "young". Fertilization starts with the penetration of the sperm into the cytoplasm of the ovum and ends with the formation of the metaphase plate of the first cleavage of the zygote. The fertilized ovum moves through the first coil of the ampulla **(Enders, 1970).**

Cleavage and Implantation.

The fertilized ovum forming the zygote undergoes cleavage and divides by mitosis, to the two-cell, the four-cell, the eight-cell and the multiple cell stages. The morula (clustered group of cells) and the blastocyst (stage with a contained cavity) are the final stages of the blastocyst formation. The dividing morula enters the uterus on the third

day after end of fertilization and by the fourth day all the blastocyst becomes intra-uterine.

The blastocysts swell after the fifth day and their subsequent expansion results in formation of the implantation chamber and "Fix" the blastocyst in position. Arrangement of the blastocyst in individual cornua of the bicornuate uteri constitutes random spacing through the length of each cornu.

Implantation starts by apposition of the trophoblast and uterine luminal epithelium, then adhesion and penetration by which the trophoblast passes through the uterine luminal epithelium **(Enders, 1970).**

Placentation.

The term placenta is applicable to any combination of embryonic and maternal tissues, which serve as the medium for physiological interchanges between the mother and conceptus. The preplacentation period includes the periods of ovum fertilization, cleavage, implantation and part of the early embryonic period during which placentation takes place. The ultimate stage of placental growth is considered around day eleven **(Macdonald, 1980).**

Organogenesis.

Organogenesis is the period during which the major organs are developed. This stage ends at the phase of transition when organ differentiation is complete and the fetus has attained the characteristic morphological features of its species. Some process of organogenesis of the central nervous system, the special senses and behavioral peculiarities continue to develop and organize during the fetal growth period up to full term. The endoderm, is formed by migration of cell mass, together with the outer layer, which is the ectoderm. Both rise to a mass of cells which is the primitive streak. The cells of the mesoderm, which is the middle layer originate from this streak and come to lie between the ectodermal and endodermal layers **(Hendrickx and Houston, 1970).**

The ectoderm forms an elongated plate in the medial axis of the germ disc. This plate, the neural plate will give rise to the brain and spinal cord. Other derivatives of the ectoderm include the skin coat cover, sensory organs and most of the glands. The mesoderm proliferates as it migrates from the primitive streak and differentiates into somites and the notochord in the early period of organogenesis. The somites differentiate into vertebrae, muscles of the trunk and dermis of the skin. The notochord is incorporated into the intervertebral discs. The endoderm in early stages forms the lining of the alimentary and respiratory passages apart from the nose, mouth and the lower part of the anal canal. The liver, the pancreas, the serous, mucous and gastric glands progressively differentiate from the alimentary canal **(Hendrickx and Houston, 1970).**

While the various organs are formed, the shape of the embryo changes. The main changes during the period of organogenesis are elongation of the body, subdivision of the body into head, trunk and tail, development of the appendages and the separation of the embryo from the extra-embryonic parts. The changing appearance of the embryo makes it possible to distinguish certain stages. Three criteria are used to distinguish one stage from another, which are, age, size and selected morphological features of the embryo. Age determination of embryos and fetuses is based on copulation and fertilization time. The preferred and accepted method is the normal stages on morphological properties of the embryo, especially the external features.

During gastrulation, the shape of the primitive streak may be used and after gastrulation, the neural plate is an easily recognizable feature. The number of pairs of somites used to define the stage of development during early organogenesis. In later stages, the development of the appendages is easily distinguishable and are reliable characters for the definition of normal stages. The development of different organs of the embryo is not

strictly coordinated in time and therefore all the organs may not achieve the same degree of development for a given stage, or at a given period **(Hendrickx and Houston, 1970).**

Fetal Growth.

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. Two designations for describing growth are used, namely, absolute growth and relative growth. Absolute growth is the increment in dimensions (volume, crown-rump length, weight and similar parameters) of the fetus in a unit of time. Relative growth is the increment changes in dimension for a unit of time divided by the dimension attained at the time of measurement. Absolute growth increases throughout pregnancy, but relative growth begins to decrease about the middle of pregnancy. This period takes from day 17 to day 20 of gestation. The day 17 of development is the beginning of fetal period and a rapid increase in linear dimension and weight of the fetus begins at that time**(Macdonald, 1980).**

Changes During Pregnancy.

Consideration of the physiology of pregnancy rests on a careful understanding of the embryological developments that take place. Several interacting mechanisms and processes have to be organized and coordinated to bring about a successful pregnancy. The general body metabolism of the maternal organism must also change to accommodate the stress of pregnancy **(Ratcliffe et al., 1993).**

Uterine Changes.

During pregnancy the uterus must expand many times beyond its non gravid size dependent on the number of fetuses present. However, this is not entirely the result of stretching by the growing embryo. Several changes occur, the most important are the following: *Endometrial Proliferation:* During this time the endometrium undergoes a general increase in thickness along with increased vascularity, growth and coiling of the uterine glands and leukocytic infiltration. *General Uterine Growth*: After implantation, the uterine tissues of both endometrium and myometrium increase rapidly. Muscular hypertrophy as well as extension in the connective tissue, fibrillar elements and collagen adds to the actual tissue content of the uterus. In addition, marked increase in vascularity of the tissue and the amount of interacellular fluids accounts for an appreciable amount of increases in size. *Uterine Stretching*: Actual addition of tissue to the uterus diminishes but its actual volume is increased by its rapidly growing fetal contents **(Hendrickx and Houston, 1970).**

Vaginal Changes.

The finding of a copulation plug is the criterion commonly used to infer that pregnancy has commenced and from which gestation time is calculated. The plug is a hard horny mass that may be seen or felt in the vagina with the aid of a probe. The formation of the plug might play a part in the nervous stimulation of the anterior pituitary of the female and determine an actively secreting corpus luteum until placentation **(Bennet and Vickery, 1970).**

Physiological Changes.

Water intake increases from day thirteen of pregnancy onwards, to reach 37% increase during the final week of pregnancy. Urine output also increases in pregnant rats only on day 13 and 15 of pregnancy. Sodium excretion increases in urine during the first two weeks of pregnancy. During the third week, however, urinary sodium output decreases to end up on day 21. Daily changes in urinary chloride output have a similar pattern to that of sodium. Daily changes in urinary potassium output shows significant increase during the three weeks of pregnancy. The retention of potassium in pregnant rats is greater than sodium or chloride. Plasma volume increases significantly on day 6 of gestation. The increase continues until closes to term, where pregnant animals possess a plasma volume approximately 30% higher than virgin animals. The blood volume increases significantly on day 14 and 21 of pregnancy. **(Atherton et al., 1982 and Barron et al., 1984).**

2.1.3.Comparison of Embryonic Development in Human and Rat.

Period	Rat Day of Gestation	Development	Human Day of Gestation
preimplantation	1	Fertilization	1
	2	Formation of 2-cell stage	2
	4	Formation of 16-cell stage (morula)	3
	5	Formation of blastocyst	4 -10
	Late 5	Implantation of blastocyst	
	6	Blastocyst implanting with trophoblast and inner cell mass	
Early Organogenesis	7	Appearance of chorionic villi	14
		Differentiation of embryonic disc into embryonic and extraembryonic parts	
	8	Differentiation of trophoblast	15
		Appearance of primitive streak,	
	9	Start of extraembryonic mesoderm	
		Start of intraembryonic mesoderm	
Major Organogenesis	10 – 10.5	Appearance of occipital somites	18-30
		Appearance of neural somites	
		Appearance of early neural folds	
		Closure of neural tube	
		Formation of heart	
		Differentiation of primitive gut	
		Liver primordium	
		Development of optic and otic primordia	
	11-11.5	Organization of arm and leg buds	26
	12-12.5	Differentiation of hand plates	32
Fetal Growth	13-13.5	Formation of foot plates	37
	14 – 14.5	Appearance of auricular hillock	40
		Eyes shifting anteriorly	
	16	Ossification of skeleton begins	80
	17 – 21	Fetal growth complete	63 - 266
		Increase in size and weight	
Iman I. Abdel-Gawad, (1995).			Moore, (1988).

2.2.CAUSES OF HUMAN CONGENITAL MALFORMATIONS

Congenital malformations are anatomical or structural abnormalities of the neonate that are present at birth, or those that may be diagnosed later. They may be macroscopic or microscopic, external or internal. Congenital malformations result from defective embryogenesis. Teratology is the study of abnormal development of embryos and the causes of congenital malformations. A fundamental concept in teratology is that certain stages of embryonic development are more vulnerable than others.

It is customary to divide the causes of congenital malformations into genetic factors (e.g., chromosomal abnormalities) and environmental factors. However, many common congenital malformations are caused by genetic and environmental factors acting together. This is called multifactorial *inheritance* **(Persaud et al., 1985 and Moore, 1988).**

Congenital malformations may be single or multiple and of major or minor clinical significance. Single minor malformations are present in about 14% of newborns. The estimated incidence of causes of major congenital malformations, based on data from Connor and Ferguson-Smith (1984), Persaud et al., (1985) and Thompson (1986), are given in Table (1).

Table (1) Estimated Incidence of Causes of Major Congenital Malformations

Cause	Incidence (%)
Chromosomal aberrations	6
Environmental factors	7
Monogenic or single gene defects	8
Multifactorial inheritance	25
Unknown etiology	54

Ninety per cent of infants with multiple minor malformations have an associated major malformation. Of the three per cent of infants born with congenital malformations, 0.7% have multiple major malformations. Most of these infants die. Major malformations are more common in early embryos (10-15%), but most of them are spontaneously aborted **(Connor and Ferguson-Smith, 1984).**

2.2.1.Malformations Caused by Genetic Factors.

Numerically, genetic factors due to numerical and structural changes in chromosomes are the most important causes of congenital malformations. Genetic factors cause over one third of all congenital malformations and nearly 85% of all those of unknown causes **(Moore, 1988).**

Chromosome complements are subject to numerical and structural changes. These may affect either the sex chromosomes or the autosomes and in rare cases, both kinds of chromosomes are affected. Genetic factors initiate malformations by biochemical or other means at the subcellular, cellular, or tissue levels. The mechanism initiated by the genetic factor may be identical or similar to the causal mechanism initiated by any teratogen. A teratogen is any agent that can produce a congenital malformation or raise the incidence of the malformations in the population **(Moore, 1988).**

Numerical Chromosomal Abnormalities.

Numerical abnormalities of chromosomes usually arise as the result of nondisjunction. Changes in chromosome number represent either aneuploidy or polyploidy.

Aneuploidy: represents a deviation from the diploid number of 46 chromosomes. An aneuploid is an individual or a cell that has a chromosome number that is not an exact multiple of the haploid number of 23. As a result the cells of the embryo may be hypodiploid monosomy (45) as in Turner syndrome, or hyperdiploid trisomy (47) as in Down's syndrome (trisomy 21), there is also trisomy 18; 13; and sex chromosomes. There is also Tetrasomy and Pentasomy of the sex chromosomes.

Mosaicism: A mosaic is a person derived from one zygote that has cells with two or more different genotypes (genetic conditions). Usually the malformations are less serious than persons with monosomy.

Polyploidy: Polyploid cells contain multiples of the haploid number of chromosomes (i.e., 69, 92 and so forth). Polyploidy is a significant cause of spontaneous abortion **(Moore, 1988).**

Structural Chromosomal Abnormalities.

Most structural abnormalities of chromosomes result from chromosome breaks that are induced by various factors, such as radiation, drugs, chemicals, viruses and others. The type of chromosome abnormality that results depends upon several factors including the DNA repair mechanisms. The only aberrations of chromosome structure that are likely to be transmitted from parent to child are the structural rearrangements of the inversion and translocation types.

Translocation: This is the transfer of a piece of one chromosome to a nonhomologous chromosome, if two nonhomologous chromosomes exchange pieces, it is called reciprocal translocation.

Deletion: This results when a portion of the chromosome is deleted. A ring chromosome is a type of deletion chromosome from which both ends have been lost and the broken ends have rejoined to form a ring-shape.

Inversion: This is a chromosomal aberration in which a segment of a chromosome is inverted.

Isochromosome: This abnormality results when the centromere divides transversely instead of longitudinally **(Hall, 1996).**

Malformations Caused by Mutant Genes.

Probably mutant genes cause 8% of congenital malformations. A mutation usually involves a permanent loss or a change in the function of a gene. Because a random change is unlikely to lead to an improvement in development, most mutations are deleterious and some are lethal. The mutation rate in a population can be increased by several agents, e.g., large doses of radiation and many chemicals, especially carcinogenic ones **(Moore, 1988).**

2.2.2.Malformations Caused by Teratogenic Factors.

Although the human embryo is well protected in the uterus, certain agents called teratogens may induce congenital malformations during embryonic development. The organs and parts of an embryo are most sensitive to teratogenic agents during process of cellular proliferation and differentiation. Teratogenic agents cause about 7% of congenital malformations. Because biochemical differentiation precedes morphological differentiation, the period during which structures are sensitive to interference often precedes the stage of their visible development by few days. Teratogens do not appear to be effective in causing malformations until cellular differentiation begins. However, their early action may cause the death of the embryo before malformations are established **(Tubiana et al., 1990).**

Six mechanisms can cause congenital malformations: (1) too little growth, (2) too little resorption, (3) too much resorption, (4) resorption in the wrong locations, (5) normal growth in an abnormal position and (6) local overgrowth of a tissue or structure **(Moore, 1988).**

Teratogens and Human Congenital Malformations.

A teratogen is any agent that can induce or increase the incidence of congenital malformations. They may be drugs, chemicals, radiation and infectious agents e.g., viruses or bacteria **(Moore, 1988).**

Radiation as a Teratogen.

Exposure to ionizing radiation may injure embryonic cells, resulting in embryonic cell death, chromosome injury, mental retardation and disturbance of proliferation, differentiation and growth. The severity and type of embryonic damage is a function of the absorbed dose, the dose rate and the stage of embryonic or fetal development during which the radiation exposure occurs **(Brent, 1986).**

In the past, large amounts of ionizing radiation were given inadvertently to embryos and fetuses of pregnant women who were treated for cancer of the cervix. In all cases, their embryos were severely malformed or killed. Marked microcephaly, spina bifida cystica, cleft palate, skeletal and visceral abnormalities and mental retardation were observed in the infants who survived. Development of the central nervous system, skeletal and muscular tissues were nearly always affected **(Persaud, 1979).**

Observations of Japanese atomic bomb survivors suggest that ten to 18 weeks of pregnancy (eight to 16 weeks after fertilization) is the period of greatest sensitivity for radiation damage to the brain leading to severe mental retardation **(Mole, 1982).**

Teratologists agree that large amounts of ionizing radiation produce congenital malformations. It is generally accepted that doses of radiation (0.25 Gy) are harmful to the developing central nervous system **(Moore, 1988).**

There is no proof that human congenital malformations have been caused by diagnostic levels of radiation. It is prudent, however, to be cautious during diagnostic examinations of the pelvic region in pregnant women using x-rays or radioisotopes. These may result in radiation induced congenital abnormalities with certain probability **(Miller and Merke, 1996).**

Mechanical Factors as Teratogens.

It is generally accepted that congenital abnormalities caused by external injury to the mother are extremely rare, but possible. Intrauterine mechanical forces, particularly in a malformed uterus may cause congenital dislocation of the hip and clubfoot. Such deformations may be caused by factors that restrict the mobility of the fetus, thereby causing prolonged compression in an abnormal posture **(Connor and Ferguson-Smith, 1984).**

A significantly reduced quantity of amniotic fluid (oligohydramnios) may result in mechanically induced abnormalities of the fetal limbs. Intrauterine amputations or other malformations may be caused by local constrictions during fetal growth which may result from amniotic bands or fibrous rings, presumably formed as a result of rupture of the fetal membranes (amnion and chorion) during early pregnancy **(Behrman et al., 1996).**

2.2.3.Malformations Caused by Multifactorial Inheritance.

Most common congenital malformations have familial distributions consistent with multifactorial inheritance. This may be represented by a combination of genetic and environmental factors, with a developmental "threshold" dividing individuals with the malformation from those without it. Multifactorial traits are usually single major malformations such as cleft lip, isolated cleft palate, neural tube defects **(Moore, 1988).**

2.3.BIOLOGICAL ASPECTS OF CELLULAR BEHAVIOR.

2.3.1.Cell Proliferation

Cell proliferation is a very essential process for the continuity of biological life. The rate of this process varies according to cell type and species of the organism, it is a unique specific property of the cell. The process of cell proliferation is maintained by cell division. Cell division can occur in two ways. (1) Mitosis, occurs in most somatic cells and results in the distribution of identical copies of the genome of the parent cell to the resulting cells. (2) Meiosis, occurs in cells of the gonads and results in the number of chromosomes being halved to the haploid number, preserving all the genetic properties of the parent cell **(Alberts et al., 1994).**

Mitosis.

This is divided into five stages called: interphase, prophase, metaphase, anaphase and telophase.

Interphase: New DNA is synthesized during the S phase of interphase, so that in diploid cells the amount of DNA is doubled to the tetraploid value by the onset of mitosis, although the chromosome number is still diploid. During mitosis, this amount is halved between the two daughter cells, so that DNA quantity and chromosome number are diploid in both.

Prophase: The strands of chromatin, highly extended during interphase, begin to shorten, thicken and resolve themselves into recognizable chromosomes; each made up of two chromatids joined at the centromere. Outside the nucleus, centrioles begin to separate, moving to

opposite poles of the cell, central spindle appears the nucleoli disappear and finally the nuclear envelope disintegrates. This event marks the end of prophase.

Metaphase: The spindle microtubules invade the central region of the cell and the chromosomes move towards the equator of the spindle.

Anaphase: The centromere is separated lengthwise, both carrying an attached chromatid; each of them duplicated into two new chromosomes. These move apart, one towards each pole.

Telophase: The chromosomes now re-extend and the nuclear envelope appears. Nucleoli also reappear **(Bannister, 1995).**

Meiosis

During meiosis there are two cell divisions: (a) meiosis I, in which the DNA is reduced to diploid amount in each resultant cell, although the chromosome number is halved to the haploid value. (b) Meiosis II, the DNA in each new cell formed is reduced to the haploid amount; the chromosome number remains haploid.

Meiosis I

This division of meiosis constitutes four stages, namely, prophase, metaphase, anaphase and telophase.

Prophase I :

Prophase I is a long and complex phase which differs considerably from mitotic prophase and is customarily divided into five substages: ***Leptotene stage***: Chromosomes appear as individual threads attached at one end to the nuclear envelope and show characteristic beads. ***Zygotene stage***: Chromosomes come together side by side in homologous pairs.

Pachytene stage: Spiralized shortening and thickening of each chromosome progresses and its two chromatids have join at the centromere. Each bivalent pair of four chromatids forms a tetrad. ***Diplotene stage:*** Homologous pairs, now much shortened, separate except where crossing over has occurred (chiasmata). ***Diakinesis:*** Remaining chiasmata finally resolve and the chromosomes, still as bivalents. During prophase, the nucleoli have disappeared and the spindle and asters have formed as in mitosis. At the end of prophase, the nuclear envelope disappears and bivalent chromosomes move towards the equatorial plate (prometaphase).

Metaphase I

This stage resembles mitotic metaphase except that the bodies attached to the spindle microtubules are bivalents and not single chromosomes.

Anaphase I and telophase I

These also occur as in mitosis, except that in anaphase the centromeres do not split, therefore, instead of the paired chromatids separating to move towards the poles, whole homologous chromosomes made up of two joined chromatids go to opposite poles.

Meiosis II

Meiosis II commences after only a short interval during which no DNA synthesis occurs. This second division is similar to mitosis, with separation of chromatids during anaphase. It is more evident in spermatogenesis than organogenesis **(Bannister et. al, 1995).**

2.3.2.Cell Differentiation.

Differentiation denotes the appearance of highly distinctive cell types which become integrated to form a functioning tissue. Fully differentiated

cells; because of their size, shape, ultrastructure, chemical constitution and function are completely distinct with no intermediaries; and there is no situation in which a type changes into another. Differentiation which occurs during embryogenesis stands two opposing views. One claims the presence of preformation in the early embryo and the other claims that epigenesis take place.

Preformation holds that all structures of the mature body were present in the zygote and simply enlarged and revealed in a subsequent development.

Epigenesis holds that the various organ primordia appearing during development are essentially new formations.

Relative movements of cells and tissues are a fundamental and common feature of embryonic development and fetal growth. This is essentially controlled according to specific time scales by several factors of differential growth rates and directions in the different parts of the embryonic system. The relative movement of cells and tissues is known in human embryonic development as manifestation that takes place throughout the whole period of gestation.

Each differentiated cell type has its own characteristic repertoire of proteins, which are associated with the specialized function of that cell. Cell expression is the result of differential gene regulatory events. Such events are regulated by signals in the local environment of the cell.

Initially, all cells possess rather similar properties but, as embryogenesis gathers momentum, they begin to diversify, first, separating into broad categories (e.g. the principal germ layers, etc.) and then into narrower categories (tissues and subtypes of tissues) until finally they mature into the `end cells' of their lineage **(Gurdon, 1973).**

Some cells, which are capable of giving rise to others throughout life (Stem cells) never, proceed to the ultimate point of this progression of differentiation and retain some embryonic characteristics. However, in all cases there is a sequential pattern of gene expression, which changes and limits the cell to a particular specialized range of activities. Stem cells remain at a level of partial differentiation, although some of their progeny will be committed to full differentiation. In general, as the degree of differentiation progresses, cell division becomes less frequent **(Bannister, 1995).**

2.3.3.Cell Growth.

Growth basically implies an increase in size and mass resulting from synthesis of specific tissue components. Growth of the tissue is classically considered to be multiplicative, auxetic, accretionary, or a combination of these.

Auxetic growth implies an increase in the size of the individual cells in tissues. Growing striated muscle fibers, oocyte, the smooth muscle cells of the pregnant uterus are examples of auxetic growth.

Accretionary growth denotes an increase in the amount of structural intercellular material between the cells of a tissue, bone and cartilage are common examples. Fibers of connective tissue and tendon are another examples.

These types of growth are often welded together in various patterns with differential growth rates and directions. Furthermore, they overlap with and merge into the phases of cell differentiation, functional activity, aging and death.

The transition from the single cell to the multicellular adult, i.e., the growth of the organism, is accomplished by controlled cell growth and cell division processes , which in many tissues continue throughout the life of the individual. Each organ and tissue of a newborn mammal has a certain genetically determined shape and size. **(Karp, 1979).**

Growth factors: It is generally believed that the response that cells make to their environmental stimuli is mediated by the cell membrane. Recent analyses have uncovered a large and growing number of factors that appear to be able to promote growth **(Gardner et al., 1985).**

The polypeptide growth factors (PGFs) promote the proliferation and differentiation of various cell types. Typically, they increase the size and number of the cells they regulate. During embryonic development, when growth is complete the cells have become differentiated. PGFs also play an important role in cell repair in tissues that are maintained by continued or intermittent cell turnover, such as epithelium and hematopoietic tissues **(Lillien and Claude, 1981).**

Platelet-derived growth factor (PDGF) stimulates general protein synthesis and collagen synthesis in responsive cells. It also stimulates the production of enzymes active in the hydrolysis of these proteins. So far, PDGF receptors have been demonstrated only in connective tissue components such as fibroblasts, vascular tissue, smooth muscle, glial cells, and chondrocytes, where PDGF stimulates cell proliferation. PDGF also has many indirect effects, such as enhancement of erythropoiesis and production of vasoconstriction **(Tedeschi, 1993).**

2.3.4.Apoptosis.

This is an ordinary systemic and programmed process of self destructive death of the cell. This is probably the result of genetic alterations by which the cell enters a period of cytoplasmic basophilia and nuclear condensation, followed by cell fragmentation, dissolution and phagocytosis by phagocytes. Apoptosis is an orderly cellular process of self destruction, which can be initiated by any cause at any moment in the cell life. Apoptosis is different to cell terminal differentiation, which is the cessation of cell replication; and is also different to cell senescence (death) which is manifested only at the end of the cell life span. Apoptosis is also different to disorganized cell death by necrosis.

2.4.PHYSICAL CONSIDERATIONS OF IONIZING RADIATION.

2.4.1.Sources and Types of Ionizing Radiation.

The term radiation in general means transmission of energy. This may take several forms depending on the nature of radiation. Ionizing radiation are those that are characterized by inducing excitation and ionization within the medium which they traverse. The types of ionizing radiation are photons and particle radiation. The differentiation between these two types depends on the mode of propagation and energy transmission, the form of radiation and the presence or absence of mass and charge.

Photons that have the property of inducing ionization are X-rays and gamma rays. The energy associated with photons depends on the frequency of oscillations of the wave form of the photons, the higher the frequency the higher the energy associated with the wave and the shorter is its wave length.

The source of X-rays is mainly machine construction operated by the principle of stopping fast moving electrons by a target of high atomic number material. The interaction of the fast moving electrons with the target material results in the conversion of the kinetic energy of the electrons into great amounts of heat and smaller amounts of X-rays. The energy associated with the X-ray photons is dependent on the kinetic energy of the fast moving electrons which is a function of the voltage applied to the machine during operation.

Gamma rays on the other hand are emitted during the process of radioactive disintegration of gamma emitting radionuclides. The phenomenon of radioactivity is a complicated process depending on

nuclear stability, which in turn depends on the neutron constitution of the nuclide of any element. During the radioactive process, both gamma radiation and particle radiation are emitted with varying intensities. Each gamma emitting radionuclide has a specific Gamma energy spectrum which is characteristic of the radionuclide. The essential features of both X-rays and gamma rays are similar **(Park, 1995).**

Particle radiations are characterized by possessing mass and charge. The most common and popular particles are Alpha and Beta particles, which are emitted from unstable (radioactive) nucleus during radioactive disintegration. The Alpha particle is formed of two protons and two neutrons, carries two positive charges. The Beta particle has a mass of an electron and carries a negative charge, or a positive charge in case of a positron. Several other particle radiations are known such as protons, mesons, pions, leptons and others which are constituents of the atomic nucleus. The neutron, is a neutral particle constituent of the atomic nucleus having approximately the same mass as the proton and carries an equal positive and negative charges. Neutrons are produced by certain specific nuclear reactions, or spontaneously during the process of nuclear fission. The energy associated with the neutrons is specific for the type of reaction from which they are produced. The relative penetrating power of ionizing radiation differs from one type to another. Photons are known to have more penetrating power than particles. In biological media photons are able to penetrate a thickness of several centimeters. Several other types of nuclear fundamental elementary particles are known in the science of nuclear physics, however this matter is outside the scope of this presentation **(Park, 1995).**

In the context of this thesis, the radiation used were gamma rays from a Cobalt-60 source. The Gamma energy spectrum emitted from Cobalt-60 has two energy peaks of 1.33 and 1.17 MeV with average energy of 1.25 MeV when considering its interactions with biological media.

2.4.2.Interactions of Ionizing Radiation with Matter.

The word interaction is applied to processes in which the energy and/or the direction of the radiation are altered. Such processes occur at random and it is therefore only possible to speak of the probability of interactions occurring. This probability can be expressed in terms of cross sections or of various interaction coefficients.

Interactions of Photons with Matter

Photons can, in principle, interact with planetary electrons or atomic nuclei or the electric fields round these electrons or nuclei. In so doing they may lose all, part, or non of their energy. Of the several possible processes of interaction, in most circumstances only three are of great importance when photons interact with biological media **(Ball and Moore, 1997).**

Photoelectric Effect.

In this process, a photon gives up all its energy to an inner bound electron of atoms of the absorbing media, which is then ejected from the atom with a certain kinetic energy. The initial photon energy is expended in overcoming the binding energy of that inner bound electron and in giving the ejected photoelectron its kinetic energy. The ejection of a photoelectron from an atom leaves a vacancy in one of the inner electron orbits. This is filled by an electron falling in from an outer orbit. The energy given up by this electron jump, sometimes appears on the X-Ray spectrum as a characteristic X-Ray photon. The photon energies are characteristic of the atom from which they come and the photons are therefore called characteristic radiation. In this photoelectric process, the initial incident photon energy is absorbed in the medium **(Greening, 1985).**

Compton Effect.

In this process, the photon iteracts with an outer free electron, which is regarded as free because its electron binding energy is negligible. The incident photon transfers some of its energy to the electron, which recoils outside the atom and the remainder of the incident energy appears as the energy of a scattered photon of less energy and therefore of longer wave length. The incident photon energy in the compton process is partly absorbed in the biological medium and partly scattered.

Pair Production.

In this process, the incident photon interacts with the electric field round the nucleus of the atom. The whole incident photon energy becomes converted to the mass and kinetic energy of positive and negative particles (electron and positron). This process is not possible except at photon energy equivalent to the mass of 2 particles, (i.e. $2mC^2$=1.02 MeV). Once the threshold energy of 1.02 MeV is exceeded, the probability increases with the increase of the photon energy. The probability decreases with the increase of the atomic number of the absorbing material. When the positron has slowed nearly to rest, it annihilates with an electron giving two photons, each of energy mC = 0.51 MeV which travel in opposite directions **(Ball and Moore, 1997).**

In all photon interaction processes with matter, there is conservation of energy and momentum of the system before and after the interaction takes place. The photoelectric cross section per atom varies roughly as Z^4. For compton effect, the cross section per atom varies with Z. For pair production, the cross section per atom varies approximately as Z^2. However, for mass attenuation coefficient is approximately to Z. From such considerations, it is found that high atomic number (Z) materials are considered good absorbers to photon and vice versa **(Greening, 1985).**

2.4.3. Radiation Units.

Exposure Unit (Roentgen)

It is defined as that quantity of X- or γ radiation that produces ions carrying one statcoulomb of charge of either sign per cubic centimeter of air at 0 °C and 760 mm Hg. According to the SI units, the roentgen equals the generation of 2.58×10^{-4} coulomb per kilogram air **(Cember,1985).**

Absorbed dose (Gray).

The SI unit of radiation energy absorption in matter is the Gray (Gy). This is defined as the radiation energy absorption of one Joule of energy per one kilogram of the biological medium. This means that the term absorbed dose is defined as the quotient of unit of energy absorbed per unit of mass of the medium.

Since

1 erg = 10^{-7} joule. 1 Kg = 1000 gram

Rad = absorption of 100 ergs in 1 gm.

Therefore: 1 Gray = 100 Rad.

Equivalent Dose (Sievert - Sv).

It equals the absorbed dose multiplied by the Radiation Weighting Factor (W_R). this factor takes in consideration the type and energy of radiation.

The old unit was the rem = 1/100 Sievert **(ICRP, 1991).**

Effective Dose (Sievert - Sv).

This unit is defined as the product of the equivalent dose multiplied by the Tissue Weighting Factor (W_T). This factor takes in consideration the differential radiosensitivities of the body tissues **(Cember,1985).**

2.5.EFFECTS OF IONIZING RADIATION ON BIOLOGICAL SYSTEM.

2.5.1.Basic Concepts.

The sequential development of radiation injury in biological systems is primarily initiated at the molecular level. The nucleic acids are considered the primary site of radiation injury to the cell, followed by the molecules of the cell membrane and other critical biomolecules of the cell system. Since biomolecules are the target for radiation energy absorption, this results into a population of excited and ionized physicochemical bonds of molecules. The number of affected molecules depends on the amount of radiation energy absorbed in a specific mass of biological media.

The ultimate outcome will also depend on the radiosensitivity of the cells and tissues of the biological system involved in the radiation exposure. The most important biological factors that determine cellular radiosensitivity are cell division, processes of cellular differentiation, proliferation, cellular organization and biochemical activity of the cell in particular during synthesis of critical molecules. Completely differentiated cells are considered relatively radioresistant **(Yarmonenko, 1988).**

The ultimate response of cells and tissues to radiation injury is invariably dependent on the radiation dose and the ability of the cells to repair sublethal damage. High radiation doses usually result in mitotic arrest and high incidence of cell death, with little chance of regenerative cellular repopulation. In this situation, there will be arrest of tissue development and cellular replacement In case of exposure to high doses of radiation, the various cell types in body tissue will suffer radiation induced cell death in proliferating cells; or radiation induced

physiological and functional disturbances in non-proliferating differentiated cells. At relatively lower radiation doses, some primordial cells may survive the radiation injury and proceed towards regeneration and reconstitution of the tissue cellular population. Lower doses of radiation fail to produce cell killing, but succeed in producing radiation induced mutations and other molecular alteration resulting in cellular abnormalities that become inherited in the genetic cell line of the cells composing the tissue and ultimately produce tissue and organ abnormalities **(UNSCEAR, 1986; El-Naggar, 1990).**

In this respect, two essential radiobiological principles should be considered. The first is the Linear Energy Transfer (LET), which is defined as the average amount of energy imparted from the incident radiation to the biological system in a unit length of the linear track. The dimensions of the LET are given in terms of electron volts per micron of linear track. On the basis of such consideration, radiation may be classified as those of high LET such as heavy charged particle radiations; and those of low LET such as photon radiations. The biological effects induced at the molecular level are distinctly different in both situations.

The second concept is the Relative Biological Effectiveness (RBE) of the various types of ionizing radiations. The RBE is defined as the quotient of the doses from a specific radiation as related to a standard radiation, to produce the same biological end point in both situations. This will provide a differential understanding of the ability of the different types of radiation to cause biological damage and will also give an insight of the differential radiosensitivity of the biological system in its response to the incident radiation. These two concept are fundamental in the proper understanding of the radiation induced alterations in cells initiated at the molecular level **(El-Naggar, 1990).**

The effects of radiation on the cell in a biological system are essentially derived from the damage caused to the biomolecules constituting the cell. In case of exposure to low radiation doses, damage to the Deoxyribonucleic acid (DNA) present in the cell nucleus is of great concern. Directly or indirectly by the action of chemical radicals, radiation can induce changes in the base sequence and can therefore alter the genetic code script. The radiation induced DNA damage is expressed as DNA mutation occurring in genes of chromosomes which alters the genetic information that is transmitted from the cell to its progeny. The DNA molecule is known to possess an efficient potential for repair mechanisms, however, this repair is not always error free. Most damage is repaired, however, some damage remains or is badly repaired. This initial DNA damage has consequences on the cell and its progeny **(El-Naggar, 1996).**

The process by which DNA mutations can be reduced by a small prior conditioning dose of radiation is called **Adaptive Response.** It has been postulated on experimental evidence that this conditioning dose probably causes stimulation of the repair mechanisms in the cell. Such process of adaptive response has been demonstrated in human lymphocytes and in certain mammalian cells. Adaptation is likely to occur together with the processes of DNA mutation and its subsequent effects. The balance between the stimulated cellular repair and residual damage is not yet clear. In vitro, adaptive response of lymphocytes takes place between 4 and 6 hours after a Conditioning Dose in the range between 5 mGy to 200 mGy and remains effective for about three cell cycles. Following a Challenge Dose after a Conditioning Dose, stimulation of repair is manifested as reduction below the expected frequency of chromosomal aberrations, sister chromosome exchanges, induced micronuclei and specific locus mutations as compared to cells exposed to Challenge Dose alone. The exact mechanisms involved in the cell adaptive response remain not clear and the phenomenon is still questionable **(UNSCEAR, 1993).**

2.5.2.Radiation Effects on Adult Mammals.

Radiation effects can be classified into Stochastic Probabilistic Effects and Non-stochastic Deterministic Effects. This recent realistic classification depends on the concept of the threshold dose to produce an effective response. This classification was adopted by the International Commission on Radiological Protection (ICRP) since 1977 and was elaborated upon to gain its present dimensions in 1991 **(ICRP, 1977; ICRP,1991).**

Delayed Stochastic Probabilistic Effects.

They have the features of: no threshold dose, latent period, probabilistic nature of all mechanisms involved and dose response relationship (increase probability with increase of dose). The populations at risk are atomic energy workers, staff of medical radiation (diagnostic and therapeutic), mining workers and others similar to the above groups. These include hereditary, congenital and teratogenic genetic, cancer transformation, premature aging, cataract and infertility.

Hereditary effects are effects that are transmitted to the progeny of parents who have developed radiation injury to the gonadal cells. These effects may be expressed in the first generation or later.

Congenital malformations and teratogenic effects are effects that may be produced in the developing embryo-fetus during intrauterine life, induced by exposure of the abdomino-pelvic region of the pregnant mother to radiation. The type and degree of malformation depends upon the magnitude of the radiation dose and more specifically on the stage of gestation at which radiation exposure took place. Teratogenesis are those effects expressed and permanently present in the organism. The origin must be genetic, congenital or induced **(Cotran et al., 1994).**

Genetic effects are produced by radiation induced injury to genetic material (DNA) in the cell. They are termed mutations, which are defined as any permanent change in the chemical, physical, functional or structural properties of the DNA molecule. Mutations are divided into gene mutation and chromosome aberrations.

Cancer transformation may occur due to permanent change to the DNA molecule which is called initiation process. If clones of mutant cells are presented (due to inactivation of tumor suppressor genes) this stage is called promotion process. When the cell become committed to the malignant process, it is called the conversion stage. The last stage is called progressive stage in which there is increase in tumor mass, direct extension and distal metastasis.

Premature Aging, Cataract and Infertility are also considered as stochastic probabilistic effects

Acute Non-stochastic Deterministic Effects.

These effects occur only after relatively high threshold dose of radiation, below which the particular effect does not occur. The occurrence and severity of effect produced is a function of the magnitude of dose and dose rate. The pathogenesis of induction and mechanisms of development are non-stochastic i.e. deterministic in nature. These effects appear within hours or days after exposure without a latent period.

Major examples of non-stochastic deterministic effects are all forms of acute radiation injury to tissues or organs. All forms of Acute Radiation Syndromes. ***Haemopoitic*** "Bone Marrow" syndrome, the threshold dose is about 2 Gy, manifested by pancytopenia, increase bone marrow proliferation and differentiation of stem cells. ***Gastro-intestinal*** syndrome, threshold dose is 4.5 Gy, manifested by gastro-enteritis, which

leads to dehydration. ***Cardio-vascular*** syndrome, the threshold dose is 6.5 Gy, manifested by disturbance in microflow, capillary fragility, petecial hemorrhages, myocardial ischaemia, hypotension and cardiac shock. ***Oro-respiratory*** syndrome, the threshold dose is 8 Gy, manifested by petechial hemorrhages, constriction of the bronchioles, pulmonary edema and respiratory distress. ***Central nervous system*** syndrome, the threshold dose is about 10 Gy, manifested by disturbance of the physiology and function of the cerebral cells, leads to loss of reflexes, convulsions, coma, it has very bad prognosis. Associated syndromes include skin burns, depression of immune response and psychosomatic disturbances.

2.5.3.Radiation Effects on Embryonic Development and Fetal Growth.

The following considerations outline the main features of the response of cells and tissues of embryo and fetus after exposure to ionizing radiation. From available knowledge it is justified to consider the embryo and fetus as the most radiosensitive stage in the entire life of any mammal. The fertilized ovum is highly radiosensitive owing to the radiation induced interference with the syngamic process. The particular hypersensitivity of the embryo is attributed to the relatively high level of hydration, oxygenation, biochemical activity, cellular organization and high rate of cellular proliferation. The differentiating cells of the fetus are most radiosensitive and result in radiation induced teratologies. Maximum tissue and organ damage occurs when the radiation insult is imposed at the time of cellular differentiation. However, radiation injury will ultimately be a balance between the initial effect of radiation and the ability of the cells and tissues to repair the damage **(NCRP, 1985).**

The response of the development and growth of the mammalian embryo and fetus to ionizing radiation varies greatly according to the stage of gestation at the time of exposure. An embryo is a mosaic of several cell colonies undergoing rapid division, organization and

differentiation resulting in the ultimate formation of embryonic tissues and organs. These mosaic cellular populations are very rapidly changing from day to day **(Tubiana et al., 1990).**

Five main processes of gestation are identified, namely, fertilization, implantation, placentation, organogenesis and fetal growth. The duration of gestation commences with the process of fertilization and terminates with delivery of offspring. The process of fertilization starts with the penetration of sperm into the cytoplasm of the ovum and ends with the formation of the metaphase plate of the first cleavage of the zygote. Cleavage of the zygote by mitotic divisions will give the two-cell stage, the four-cell stage, the multi-cell stage (the morula) and finally the blastocysts. The blastocysts are then distributed to their sites of implantation, a process of rooting adhesion, which terminates the stage of preimplantation.

The stage of placentation starts when the placenta begins to develop from a combination of embryonic and maternal tissues. The medium of placental tissue serves the mechanisms of physiological interchanges between the maternal uterus and the implanted embryonic tissues. The process of placentation is generally considered part of the stage of organogenesis, during which the implanted embryonic tissues proceed to develop in sequential complicated processes of organ formation.

During the stage of organogenesis, the three germ layers namely ectoderm, mesoderm and endoderm) are further subdivided into smaller groups of cells, which ultimately develop by division, organization and differentiation to form the various organs whose origins are the three germ layers. Further development of organogenesis is the ultimate formation of the various body organs. Complete differentiation of most tissue cells and final organization of body structure mainly characterize the stage of fetal growth. Growth of fetal structure generally takes place

to enable the growing fetus to achieve normal size of its species by the end of the fetal growth period. This is considered full term **(Hendrickx and Houston, 1970).**

The various complicated mechanisms that take place at the cellular and tissue levels during the different phases of gestation provide a distinct grade of difference in the radiosensitivity of the various embryonic and fetal tissues. This differential radiosensitivity of embryonic and fetal tissues is the main and crucial factor that determines the radiation induced effects on the embryo and fetus during the various developmental stages. The radiation induced effects therefore differ according to the stage of gestation at which the embryo or fetus had been exposed to radiation **(Tubiana et al., 1990).**

Radiations have a wide range of effects on the preimplantation stage most important of which is disruption of mitotic spindle during cell division, disturbance of biochemical activities, ultimate disorganization of the processes of cleavage and blastocyst formation, possibility of arrest of cellular organization, failure of development and resorption of cellular remnants. Irradiation during the pre-implantation stage will result mostly in embryonic death and absorption of the primitive cellular elements of the embryo at this stage **(Ratcliffe et al., 1993).**

Radiation exposure during the stage of organogenesis is expected to result in production of several types of malformations depending on the type of tissue bearing the impact of irradiation and the condition of division or differentiation taking place in a particular tissue. The tissues mostly affected by irradiation during the stage of organogenesis and in which most malformations occur are the nerve tissue, skeletal tissue and tissue of the special senses. Embryonic death during the stage of organogenesis usually occurs at thresholds of relatively high doses.

Irradiation during the period of fetal growth is mainly characterized by the occurrence of malformations of the central nervous system, mental retardation, delay of growth and some cerebral functional deficiency **(Tubiana et al., 1990).**

2.5.4.Pathological Effects of Radiation on Adult Tissues.

The studies performed in this thesis deal with radiation effects induced during embryonic development and fetal growth. These effects are very different to those induced by radiation on adult cellular populations, tissues and organ systems. The main reasons for this difference are the processes of cellular organization, proliferation, differentiation and growth. These processes assume basic patterns of differences when they occur during intrauterine life and when they occur in adult cellular population. However, in spite of these great differences, it is found logic to include a short synopsis that deals with radiation effects on adult tissues.

Effects on Cells and Tissues.

Although radiant energy can affect cytoplasmic enzymes, macromolecules and organelles, the most vulnerable target is nuclear DNA. The nucleus is the prime target of radiation injury. With sufficient exposure, the nucleus appears swollen and the chromatin is clumped. At higher levels, there is pyknosis and even fragmentation of the nucleus. The cytoplasmic changes include cell swelling, mitochondrial distortion and degeneration of the endoplasmic reticulum. Plasma membrane focal defects and breaks may appear and indeed the cell may be disrupted.

At ***sufficient dosage*** radiation can inhibit indefinitely the cells' capacity to divide. This inhibition of cell proliferation is the usual mechanism by which radiation kills cells (except at extremely high levels

of exposure). Selective inhibition of cell proliferation leading to cell killing during fetal development accounts for the somatic effects and teratogenicity of radiant energy.

Smaller doses of radiant energy may induce mutations and heritable or nonheritable alterations in metabolism that are compatible with cell survival and continued reproduction. When such injuries are heritable and involve germinal cells, overt or occult defects are transmitted to offspring. Radiation is a potent cause of mutation and oncogenic transformation **(Cotran et al., 1994).**

Effects on Organ System.

The effect of radiation upon organs depends on the dose, type of tissue irradiated and time lapse since irradiation. Injury may become apparent sometimes within days to months, or only after some time lapse (latency), which may be as long as many years **(Cotran et al., 1994).**

Vascular changes: vessels in the skin may show only dilatation, producing some erythema. Later or with higher doses, there is endothelial swelling and vacuolation or even destruction of endothelial cells, particularly in the microvasculature, with secondary thromboses or hemorrhages. At a later stage, intimal hyperplasia and collagenous hyalinization with thickening of the media develop. Such changing in arterioles and small arteries result in marked narrowing or even obliteration of the vascular lumina **(Cotran et al., 1994).**

***Skin*:** the skin is in the pathway of all externally delivered radiation. A range of changes may appear, from mild post irradiation erythema (2-3 days), sometimes followed by edema (2-3 weeks), to epithelial blistering and desquamation (4-6 weeks), to a chronic

radiodermatitis (months to years) or even the development of skin cancer. The radiodermatitis takes many forms, including blotchy increased pigmentation or depigmentation, hyperkeratosis, epilation, skin atrophy, dermal and subcutaneous fibrosis and in some instances, telangiectasia and ulcerations **(Mettler and Moseley, 1985).**

Hematopoietic and lymphoid systems: The hematopoietic and lymphoid systems are extremely susceptible radiant injury. With high dose levels and large exposure fields sever lymphopenia may appear within hours, with shrinkage of the lymph nodes and spleen. Radiation directly destroys lymphocytes, both in the circulating blood and in tissues (nodes, spleen and thymus, gut) and causes cytological disorganization. Regeneration may occur within weeks to months. The circulating granulocyte count begins to fall toward the end of the first week, with possibly disappearance of these cells in the circulating blood during the second week. Recovery may require two to three months. Neutrophil count returns within 2-3 months. Platelets are similarly affected, with the nadir of the granulocytes. Erythrocytes are radioresistant, but anemia may appear after two to three weeks and be persistent for months because of marrow damage. The hematopoietic cells in the bone marrow are also quite sensitive to radiant energy, including the red cell precursors **(Finch, 1979).**

Kidney: the kidneys are moderately radiosensitive. Irradiated kidneys of experimental animals or man show: degeneration, necrosis or atrophy of the tubular epithelium. Increase interstitial connective tissue. Thickening of basement membranes. Hyalinization of connective tissue. Replacement fibrosis of renal structures. Degeneration, necrosis, swelling or proliferation of endothelial cells. Intimal vascular thickening or endartritis. Medial degeneration, necrosis or thickening of vascular walls and narrowing of lumen. Degeneration, necrosis, atrophy or scarring of glomeruli **(Robin and Casarett, 1968).**

Gonads: in both the male and the female, particularly the germ cells, are highly vulnerable to radiation injury, and sterility is a frequent residual of such damage. Sclerosis of the germinal tubules may be evident. Sclerosed follicles occurred in ovaries. Indeed, for given dosage of the same form of radiation, sterility is more frequent in the female than in the male, principally because of radiation destruction of the ovarian follicles **(Mettler and Moseley, 1985).**

Lungs: because of their rich vascularization, are vulnerable to radiation injury. During the acute phase, the endothelial cell changes in the blood vessels are seen in the alveolar capillaries. The increase vascular permeability may lead to marked pulmonary congestion, edema, fibrin exudation, the formation of hyaline membranes and even total filling of the air spaces by a rich proteinaceous and cellular debris, creating changes very similar to those seen in acute respiratory distress syndrome. Later changes include fibrosis of the alveolar walls and the described vascular wall thickening and luminal narrowing. The respiratory dysfunction may be crippling or fatal since the "radiation pneumonitis" creates a profound alveolocapillary block **(Upton, 1982).**

Gastrointestinal tract: is quite radiosensitive and is frequently affected in all forms of deep radiation. Different portions of the gastrointestinal tract show different sensitivities - the esophagus and rectum being relatively resistant (the lining epithelium is squamous type) while the midportions of the tract, especially the crypt cells of the small intestine are quite sensitive(the lining epithelium is columnar type). Soon after exposure, patients often have loss of appetite, nausea and vomiting and many develop sever diarrhea for a period of days. As might be expected, the intestinal epithelium is vulnerable because of its high turnover rate and all forms of nuclear and cellular pleomorphism along with mitotic abnormalities are seen in mucosal cells in the postirradiation period. Mucosal edema, hyperemia and ulcerations may appear,

accompanied by vascular and connective tissue changes in the submucosa at all levels from the mouth to the anus. Later effects comprise mucosal and submucosal atrophy and fibrosis, accompanied sometimes by similar atrophy and fibrosis of the muscularis. These changes may indeed cause intestinal and esophageal strictures or even complete obstruction **(Cotran et al., 1994).**

Central nervous system: in the developing embryonic brain is radiosensitive; mature nervous tissue is radioresistant. Exposure to high doses of radiation may show areas of demyelination and ganglion cell degenerative changes secondary to radiation induced ischemia. After sometimes cancers may appear. There is suggestion that the brain contiguous to a neoplasm may be more vulnerable to radiation injury. The effects to the brain are considered delayed effects and subdivided into early and late delayed effects. The early delayed effects occur 3 months after irradiation. They consist of multiple punched out foci of demyelination, accompanied by perivascular infiltrations by lymphocytes and plasma cells; the blood vessels show no degenerative changes, the primary process possibly being either in the nature of an autoimmune response or due to direct injury to oligodendroglia **(Cotran et al., 1994).**

The late delayed effects, usually seen several months or years after irradiation. In the cerebrum, the most frequent site of involvement is the central white matter. In some cases it is softened as well as expanded and shows a yellow waxy discoloration occasionally tinged with pink, with isolated red or brown pinpoint hemorrhages. In others, the softening is more severe and the white matter is granular and apt to crumble. Occasionally, cystic cavitation is present. The arcuate fibers tend to be spared. In extreme, long-standing examples the affected lobe is reduced in size because of the loss of white matter and the later is grey as well as cystic. The cortical ribbon usually is grossly normal, even in advanced cases, although changes may be found of histological

examination. The brain parenchyma is replaced by a firm, ill defined space-occupying mass which resembles a diffusely infiltrating astrocytoma: there is loss demarcation between grey and white matter, when the lesion involves the basal ganglia, the outline of their normal anatomy is blurred. The brain stem may occasionally be the chief site of radionecrosis **(Manz et al., 1979).**

The microscopical appearance is that of simple coagulative necrosis with little or no accompanying inflammatory cellular reaction. In others, demyelination, characterized by loss of oligodendroglia and myelin sheathes, may be the chief feature. Usually there is severing reduction in the number of axons. Fibrinoid necrosis of the blood vessel walls, is repeatedly emphasized. Thrombotic occlusions, are frequent and may also result in occlusive fibrosis. Focal irregular calcification is frequent: it may or may not be related to the blood vessel. Vascular alterations also often take the form of large irregular capillary telangiectases, which may contain laminating thrombotic material **(Diengdoh and Booth, 1976).**

Extensive and relatively acellular fibrosis may be notable. Hypertrophy and increased fiber formation of the reactive astrocytes are usually demonstrable. It should be noted that the extent and severity of radiation damage to the brain cannot always be exactly correlated with the area exposed to radiation and the topographical distribution of the microscopical changes may apparently extend well beyond it. Radiation myelopathy: both the gross and microscopic features essentially parallel those found in cerebral radionecrosis **(Russell and Rubinstein, 1989).**

Other forms of radiation damage to the brain: sudden onset of dilatation of the third ventricle may occur. The sudden onset blindness, probably due to demyelination, axonal loss and vascular hyalinization of

the anterior visual pathways, has also been reported in patients treated with low doses of cranial radiation **(Wilson and Kleinschmidt, 1987).**

In childhood radiation induces hypothalamic-pituitary pathways damage. In the peripheral nerves, there is also epineurial fibrosis, with the traversing nerve fascicles showing demyelination, axonal loss and endoneurial fibrosis **(Henson and Urich, 1982).**

2.6. SYNOPSIS OF PREVIOUS WORK.

Several reports in the literature deal with radiation induced effects on embryonic and fetal development. The data cited in this text are the most relevant to the subject matter of this thesis.

2.6.1.Human Relevant Work.

In an extensive human study by **Lazjuk et al. (1993)** reported that an investigation of over 21000 embryos and fetuses from medically induced abortions was conducted from 1980 through 1991 in the republic of Belarus. More than half of the abortions studied were carried out after the Chernobyl nuclear accident, including 1176 from districts with radioactive Cesium-137 soil contamination with level over 0.6 TBq/Km^2 (Tera Becqurel = 10^{12} Becqurel). Congenital malformations in 7325 newborn children were also analyzed. The study showed that during the 5 years after Chernobyl accident, the frequency of abnormal developments in aborted fetuses from contaminated areas was significantly higher than in aborted fetuses from uncontaminated areas. Additionally, the congenital malformation incidence in newborn children increased in Belarus compared to the incidence before the accident; the increase was most significant in the heavily contaminated areas.

Lazyuk et al. (1994) reported in another study on human population after Chernobyl accident that the incidence of developmental abnormalities among 5 to 12 week old human embryos collected in Minsk during abortions before the Chernobyl accident was compared to that in Minsk, Mogilev and southeastern districts of Gomel and Mogilev oblasts before and after the accident. The incidence of developmental abnormalities among human embryos from the highest radioactive contaminated regions of Belarus exceeded that of control group and of urban population after the Chernobyl accident by a factor of 1.5 - 2 . The

mutagenic effect of irradiation is the most probable cause of the increased of frequency developmental abnormality. These data suggest that recording of developmental abnormalities in embryos obtained by medical abortions is a new promising approach to the monitoring of genetic consequences of irradiation in human population.

Minoru (1995), concluded that the developing mammalian brain is highly susceptible to ionizing radiation. A significant increase in number of neonates have small head size and mental retardation has been noted in prenatally exposed survivors of the atomic bombing, with the highest risk in those exposed during 8-15 weeks after fertilization. The high sensitivity of neural cells to the effect of radiation may constitute the causative defense mechanism.

Streffer, (1995) reported that the embryo and fetus are very radiosensitive during the total prenatal developmental period. The quality and extent of radiation effects depend strongly on the developmental stage at which the exposure occurs. During the preimplantation period, radiation exposure can cause death of the embryo after radiation doses of 0.2 Gy and higher. Malformations are only observed in very rare cases when genetic predispositions exist. Macroscopic-anatomical malformations are induced only after irradiation during the major organogenesis. Based on experimental data with mammals it was assumed that a radiation dose of about 0.2 Gy doubles the malformation risk. Studies on humans give rise to the assumption that the human embryo is more radioresistant than the embryo of mice and rats. Radiation exposure during the major organogenesis and the early fetal period lead to disturbances in the growth and developmental processes. During early fetogenesis (week 8-15 post coitus) high radiosensitivity exists for the development of central nervous system. Radiation doses of 1 Gy cause severe mental retardation in about 50% of exposed fetuses. Analysis of the dose-effect curves shows that there is probably

a dose-effect curve with a threshold for this effect. It must be taken into account that radiation exposure during the fetal period also induces cancer. The studies, however, do not allow quantitative estimate of this radiation risk at present. It is therefore generally assumed that the risk is about the same level as for children.

2.6.2.Animal Relevant Work.

Russell and Russell (1954) reported the effects of 200 rads (2 Gy) of X-ray during the different stages of gestation in the mouse. Exposure during the preimplantation period resulted in high incidence of prenatal death with almost no abnormalities observed in survivors to term. Irradiation during the period of major organogenesis resulted in a high incidence of abnormalities at birth with lower incidence of mortality. Irradiation during the fetal period did not cause prenatal death and no gross abnormalities at birth.

In a study by **Ohzu (1965)** pregnant mice were exposed at 0.5 and 1.5 days after fertilization with doses 5, 15 and 25 rads (0.05, 0.15 and 0.25 Gy respectively). The results showed that an increase in number of resorbed embryos, as a dose-dependent effect, independent of time of exposures. Some malformations appeared in survivals to term.

Rugh and Wohlfromm (1965) exposed pregnant mice to X-rays at various stages of gestation. When pregnant mice were irradiated during the first 5 days of development to doses ranging from 125 to 400 rad (1.25 to 4 Gy). The litter number was reduced from 9, the average control number to 3 for the average irradiated embryos. Irradiation on days 6, 7 and 9 of gestation to doses ranging from 120 to 610 rad (1.2 to 6.1 Gy) resulted in the death of half the embryos in utero.

In a study by **Brent and Bolden (1967)**, pregnant rats were exposed on the first and sixth day of gestation with doses of 150 rad (1.5 Gy) using shielding techniques which differentiate the effects of irradiating the uterus, ovary and oviduct. All the animals were sacrificed after 21 days of gestation. Results indicated that animals irradiated on the first day of gestation showed fetal mortality due to direct irradiation of oviduct and ova contained within it, with no growth retardation and low incidence of malformations. Animals irradiated on the sixth day of gestation showed increased fetal mortality and decreased fetal weight due to irradiation of the embryonic site, the embryos were retarded in growth at term, with low incidence of malformations.

Rugh et al. (1969) reported that preimplanted zygotes in mice were exposed to 10, 15, 25 and 50 rad (0.1, 0.15, 0.25 and 0.5 Gy) at various stages of 12, 18, 24 and 30 hours after insemination. The animals were sacrificed on day 18 of gestation. At 25 and 50 rad (0.25 and 0.5 Gy) the decrease in normal live fetuses was observed over a wide range of times from 5 to 10 hours post-conception. However, at 18 hours the decrease in the percentage of normal live fetuses was significant. At 24 and 30 hours post-conception it did not matter much whether the exposure was 0.1 or 0.5 Gy, the variations in fetal death were minor.

Philippe (1975) exposed pregnant mice to single doses of Cobalt-60 gamma rays from 50 to 500 rads (0.5 to 5.0 Gy). Animals received whole body exposure at 9, 10, 11 and 12 days of pregnancy. The embryos and their placentae were weighed and examined from day 13 up to day 18 postcoitus.

Irradiation on **day 9**: was sensitive only to 15 rad (1.5 Gy) and above. Lower doses did not produce any significant change, whereas higher doses were lethal to the embryos.

Irradiation on **day 10**: the radiation effect manifested itself by decrease in fetal and placental weights. Malformations were observed at

125 rad (1.25 Gy). The fetal mortality rate at 175 rad (1.75 Gy) was high, 64.5 % of the embryos died and surviving fetuses were malformed. At 200 rad (2 Gy) fetal loss was almost 100%.

Irradiation on **day 11**: although no malformations were observed at doses lower than 150 rad (1.5 Gy), the fetus and placenta were small compared to controls at a dose as low as 75 rad (0.75 Gy). At 200 rad (2 Gy), prenatal death reached 63 % and all survivors were malformed. At 300 rad (3 Gy) prenatal loss come close to 100 %.

Irradiation on **day 12**: resulted in reduction of fetal and placental weights at dose levels between 125 to 450 rad (1.25 to 4.5 Gy). Various types of malformations occurred even at 150 rad (1.5 Gy). The highest dose administered was 50 rad (5.0 Gy) which resulting in 100 % fetal death.

Knauss (1980) exposed mice on days 7, 10 and 13 postcoitus to X-rays at doses in the range of 5 to 250 rad (0.05 to 2.5 Gy) and examined the animals on day 19 postcoitus. Day 7 postcoitus showed maximum sensitivity and day 13 showed minimum sensitivity. Exposure to 6.9 Gy at day 7 postcoitus and exposure to 140 rad (1.4 Gy) at days 10 and 13 postcoitus and exposure to 140 rad (1.4 Gy) at days 10 and 13 postcoitus induced malformations in 50 % of the litters of irradiated animals. The author proposed a linearity of the dose-response relationship for the induction of malformations at the most sensitive stages of development, which was considered as the days 7 and 10 postcoitus.

Zhous and Wang (1982) investigated mouse embryos in the preimplantation period to single or fractionated exposures of 1.0 Gy of gamma radiation. Among early effects, they reported increased mortality (increased number of dead fetuses and resorption sites) and a decreased mean fetal weight of irradiated litters.

Mazur (1984) exposed pregnant mice to single dose of 2 Gy of X-irradiation on 1, 2, 3 and 4 day of the pre-implantation period; and examined on day 19 of gestation. The author concluded that the highest deaths of embryos occurred before implantation of blastocyst.

Roux et al. (1986) irradiated pregnant rats on day 10 of gestation by gamma rays from Cobalt-60 at doses of 0.4 and 0.75 Gy. The fetuses were examined on day 21 of gestation. Results indicate that at 0.4 Gy, fetal mortality was observed to be (32.2 %). Ocular anomalies appeared in 2.5 % of the fetuses but no skeletal anomaly was observed. At a dose 0.75 Gy, the fetal mortality increased to (37%). Malformations as neural tube defects, hydrocephalia, ocular anomalies, cardiopathy and facial cleft were observed in 69.2 % of fetuses. No skeletal anomaly was reported.

In a study by **Auerbach et al. (1986)** pregnant mice exposed to 0.8 Gy of gamma radiation on the day 8 of gestation and sacrificed the animals on the day 18 of gestation. Results indicate that irradiation neither increase the percentage of resorbed fetuses nor decreased the litter size. However, increased number of skeletal malformation was observed.

Jensh and Brent (1986) exposed pregnant rats to 0.6 Gy of X-rays on the days 9 and 17 of gestation, sacrificed half the mothers on day 21 and allowed the remaining to deliver. The results showed that this doses level of 0.6 Gy does not cause significant alterations in postnatal physiologic development. Exposure on day 9 of gestation did not cause growth retardation, or anatomic malformations, or any major central nervous system effects. Exposure on day 17 did not produce major anatomic malformations since this stage is well beyond the period of major organogenesis; however, postnatal growth retardation was observed.

Jensh and Brent (a) (1988) carried out another study using fractionated doses of 0.15 Gy and 0.30 Gy per day of X-rays with total exposure of 0.75 Gy and 1.50 Gy, from day 14 to day 18 of gestation. Group of animals sacrificed on day 21 of gestation and groups were allowed to deliver their offspring. The litters were examined on the first day of life. The authors reported a dose-related weight reduction in full term fetuses and offspring throughout the 86-day postnatal period. Adult offspring brain, gonadal, organ and body weights were reduced.

In another experiment by **Jensh and Brent (b) (1988)** pregnant rats were exposed on days 9 and 17 of gestation to doses of 1, 2, 3, 4, 6 and 8 Gy. Fetuses were examined on first day of postnatal life. Authors reported that exposure on the day 9 increased anatomic malformation. Exposure on day 17 did not produce major anatomic malformations. However, growth retardation, cellular changes and neurophysiological alterations were observed.

In a report by **Tomoko and Yasunari (1993)** pregnant mice were exposed to 1.5 Gy gamma radiation at 6-hour intervals during the period of organogenesis. All animals were sacrificed on day 18 of gestation. Results indicated that death of embryo/fetus, especially during early period of organogenesis, was most frequent in mice irradiated between day 6.75 and 8.25 of gestation. The most highly sensitive period for each malformation lasted no more than 12 hours. Reduction of fetal body weight was observed mostly in the groups irradiated between days 9.75 and 11 of gestation.

Hong et al. (1993) exposed pregnant mice on day 8 of gestation with 1.0 watt ultrasound after exposure to 1.5 Gy radiation immediately or irradiated with time interval of one hour. The incidences of external malformations synergistically increased in the group irradiated with both agents. Especially in the group treated with time interval of one

hour, the incidences of external malformations reached maximum. The conclusion is the combined effects of radiation and ultrasound malformations and the histological changes in mouse embryos were synergistic-sensitization effects.

Huuskonen and his colleagues (1993) studied the effects of magnetic fields on the embryonic and fetal development of rats. They found that the mean numbers of implantation and living fetuses per litter were significantly increased. The incidence of fetuses with minor skeletal anomalies was significantly increased. One serious malformation (anophthalmia) and a few minor visceral malformations were found.

Devi et al. (1994) carried out a study in which the abdominal region of pregnant mice was exposed to 0.05 to 0.5 Gy of gamma radiation on day 11.5 postcoitus. The animals were sacrificed on day 18 of gestation and the fetuses were examined for mortality, growth retardation and changes in head size, brain weight and incidence of microphthalmia. No marked increase in fetal mortality or growth retardation was observed below 0.25 Gy. The increase in these parameters was significant only at 0.5 Gy. A significant reduction in head size and brain weight and a significant increase in the incidence of microphthalmia were observed at doses above 0.15 Gy. Detectable levels of microphthalmia and microcephaly were evident even at 0.1 Gy. It was concluded that the late period of organogenesis in the mouse especially between days 10 and 12 postcoitus, is a particularly sensitive phase in the development of the skull, brain and eye.

In a report by **Sun-Xuezhi et al. (1995)** morphogenetic changes in the developing brain induced by doses of Co-60 gamma irradiation ranging from 0 to 1.5 Gy on day 13 of pregnancy were studied in 6 week old mice. Dose-related reduction in brain weight and cortical thickness were significant for all irradiated groups, but abnormal cortical architecture was

evident only in mice exposed to 1.0 and 1.5 Gy. Ectopic gray matter, enlarged lateral ventricles and the absence of trunks from the corpus callosum were observed respectively in 23%, 30%, and 10% of the mice exposed to 1.0 Gy, irradiation was applied. Brain malformations identical to the small heads and ectopic gray matter typically observed among atomic bomb survivors were reproduced in mice exposed to 1.5 Gy irradiation on day 13 of pregnancy.

From all of the above data from both human and experimental animal observations, the following considerations must be taken:

- The embryo and fetus are very radiosensitive during the total prenatal developmental period. The quality and extent of radiation effects depend strongly on the developmental stage at which the exposure occurs, total dose of exposure and other radiation factors such as dose rate and dose fractionation **(NCRP, 1985).**

- Exposure during the preimplantation period resulted in high incidence of prenatal deaths with almost no abnormalities observed in survivors to term. Irradiation during the period of major organogenesis resulted in a high incidence of abnormalities at birth with lower incidence of mortality. Irradiation during the fetal period did not cause prenatal death and no gross abnormalities at birth.

- The malformations that appear extensively were: Decrease in fetal weight and size. Skeletal deformities e.g. polydactyly. Many CNS changes including, reductions of head size, facial clefts, exencephaly, microcephaly, hydrocephaly, malformations of neural tube defects and behavioral alterations. There are also some ocular abnormalities such as microphthalmia.

Experimental Methods

3. EXPERIMENTAL METHODS.

3.1. SCOPE OF EXPERIMENTS.

Series of experimental procedures were carried out for the purpose of conducting a detailed study on the effects of ionizing radiation on the various stages of gestation in female albino rats. The aim of these experiments was to procure data related to the effects and congenital malformations induced after exposure of pregnant female rats to doses of ionizing radiation at different phases of gestation. This data will further be used to extrapolate the result on humans in case of radiation exposure during pregnancy.

Cobalt-60 gamma radiation doses of 0.5, 1, 2 and 3 Gray were delivered to several groups of pregnant female animals at specific times of gestation. All animal groups were sacrificed and dissected on the 21^{st} day.

To study the effects of irradiation during the stage of **preimplantation**, groups of animals were irradiated on the 9^{th} day of gestation. This allowed observation of radiation effects on the preimplantation processes itself, and on the subsequent development of these effects during stages of organogenesis and fetal growth.

To study the effects of irradiation on the stage of **organogenesis**, groups of animals were irradiated the 12^{th} day of gestation. This allowed the observation of radiation effects on the processes of organogenesis itself and on the subsequent development of these effects during stage of fetal growth.

To study the effects of radiation on the stage of **fetal growth**, groups of animals were irradiated on the 15th day of gestation. This allowed the observation of radiation effects on the processes involved in fetal growth, and the subsequent development of these effects on fetus to reach full term.

The experimental protocol offered a systemic approach for observing the radiation induced changes at each individual stage of gestation, and also the subsequent changes occurring to embryo and fetus throughout the whole period of pregnancy.

The parameters studied in all groups of animals included observations regarding absorption sites, number of litters and morphological malformations. For each litter the weight in gram, size in milliliters. Lateral body length, circumference at girth, tail length and skull dimensions (antro-posterior and biparietal) in millimeters were measured.

Congenital malformations were observed, recorded and photographed.

Histopathological studies were performed on tissues of the brain, spinal cord, bone, skeletal muscles, and internal organs, e.g., the heart, lung, liver, spleen, stomach, intestine, kidney and suprarenal gland.

3.2. ANIMALS.

Seventy five virgin female albino rats (Rattus rattus), 3 to 4 months old, of body weight ranging between 130 and 150 grams at the start of the experiment were randomly selected from a larger population of about 280 animals. however, the data obtained was collected from 403 neonates. The measurements for each neonate was 7 parameters (size, weight, lateral body length, circumference girth at umbilicus, tail length, antro-

posterior and biparietal dimensions of skull). The total number of measurements for the parameters that were studied amounted to about 2821 measurements.

All animals were housed in galvanized metal cages of dimensions of 421 x 26w x 22h centimeters. The mean ambient temperature in the housing facility was 28°C (ranging from 26°C to 32°C), and the mean relative humidity was 64% (ranging from 50 to 74%). The animals were freely fed on balanced diet consisting of corn, soya-bean and fish meal with dicalcium phosphate, sodium chloride, methionine and multivitamins mixture. The diet contained at least 17.7% crude protein, 3% fat and 3% crude fiber. Tap water was offered liberally.

3.3. MATING AND TESTING OF PREGNANCY.

The estrus phase was tested by vaginal smear from virgin females. Mating was allowed at a ratio of one male to one female rat in every cage during the estrus phase. The detection and confirmation of pregnancy was carried by both the following two methods; and animals were considered pregnant when both tests were confirmed positive.

a- ***The vaginal smear***: A vaginal smear was spread on a glass slide with a drop of distilled water, then dried in air. The dried smear was stained by hematoxylin 0.2%, dried in air and examined microscopically for sperm detection. The day on which the spermatozoa were seen in the vaginal smear was recorded as the first day of gestation **(Jensh and Brent, 1988).**

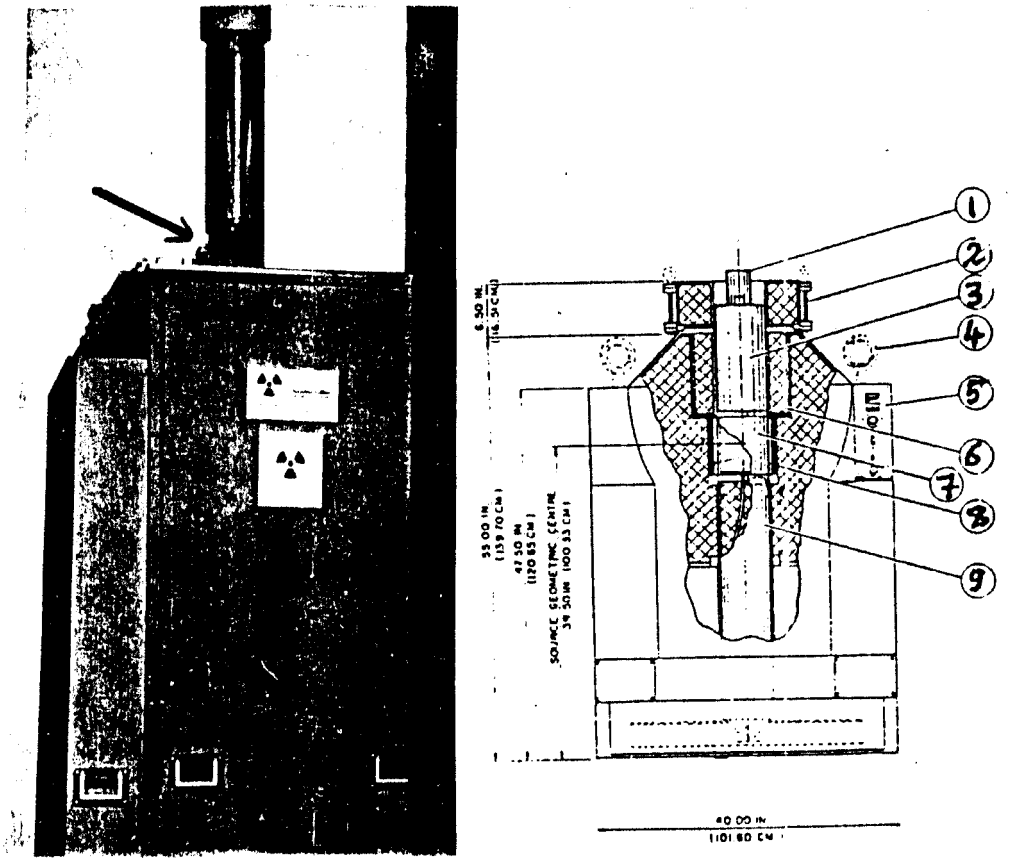
b- ***The vaginal plug***: The presence of a plug in the vagina confirmed the occurrence of mating and was recorded as the first day of gestation **(Devi and Hande, 1990).**

3.4. IRRADIATION.

The irradiation source used was Cobalt-60 (Gamma-cell 220), Atomic Energy of Canada Limited, installed at Radioisotope Department of the Egyptian Atomic Energy Authority. Basically, the unit consists of an annular shaped source, a lead shield around the source, and a long cylindrical drawer free to move vertically through the center of the source. The drawer carries a cage which descends to the center point of the source. In this cage, the animals to be irradiated are placed. The source consists of forty eight stainless steel Cobalt-60 slugs completely sealed in by welded end capsules. The unit is provided with a special electrical mechanism to facilitate its operation and manipulation and shielded by lead jacket (plate 1).

Cobalt-60 is a radioactive isotope of Cobalt which the physical half life is 5.27 years. It decays by Beta particle and Gamma ray emission. The gamma ray energy spectrum of Cobalt-60 gives two peaks of 1.33 and 1.17 MeV. The average gamma energy of the two peaks of Cobalt-60 equals 1.25 MeV. This source provided an average exposure rate of 3.1 Gy per minute in the center of the cage of the machine of irradiation. Dose rate estimate was calculated by Cobalt-60 decay calculations and also by thermoluminescense dosimetry (TLD), which was carried out at the dosimetry laboratory of the National Center of Nuclear Safety and Radiation Control, Atomic Energy Authority.

The study was designed to satisfy the requirements to obtain data on the radiation effects on embryonic and fetal development at the various stages of gestation. Several groups of animals were required for this study, including control and irradiated groups at 0.5, 1, 2 and 3 Gray.



(A) (B)

Plate (1) shows photograph of **Gamma-cell 220** Cobalt-60 radiation source installed at the Middle East Radioisotope Center for Arab Countries. Dokki Cairo. This unit was used for irradiation of animals during the experiments performed for this thesis. Arrow points to the position of the irradiation cage. (A) external view while column was raised. (B)internal diagram while column was down.

① Top shield plug.
② Collar door hinge.
③ Drawer top.
④ Removable lifting lugs.
⑤ Control panel.
⑥ Inner head plug.
⑦ Sample chamber.
⑧ Source pencil assembly.
⑨ Drawer bottom.

3.5. EXPERIMENTAL ANIMAL GROUPS.

A total of seventy five animals were included in this study. These were divided into three groups.

Group 1. Comprised 25 animals, 5 of them were considered as control subgroup. All control animals were subject to identical experimental conditions as the corresponding irradiated subgroups except irradiation. Twenty animals irradiated on day 9 of gestation corresponding to the stage of **early organogenesis**. Those 20 animals were arranged into four irradiated subgroups each of 5 animals, according to the radiation doses of 0.5, 1, 2, and 3 Gy. All animals were sacrificed at day 21 of gestation.

Group 2. Comprised 25 animals, 5 of them were considered as control subgroup. All control animals were subject to identical experimental conditions as the corresponding irradiated subgroups except irradiation. Twenty animals irradiated on day 12 of gestation corresponding to the stage of **major organogenesis**. Those 20 animals were arranged into four irradiated subgroups each of 5 animals, according to the radiation doses of 0.5, 1, 2, and 3 Gy. All animals were sacrificed at day 21 of gestation.

Group 3. Comprised 25 animals, 5 of them were considered as control subgroup. All control animals were subject to identical experimental conditions as the corresponding irradiated subgroups except irradiation. Twenty animals irradiated on day 15 of gestation corresponding to the stage of **fetal growth**. Those 20 animals were arranged into four irradiated subgroups each of 5 animals, according to the radiation doses of 0.5, 1, 2, and 3 Gy. All animals were sacrificed at day 21 of gestation.

3.6. DISSECTION AND PARAMETERS STUDIED.

All the experimental groups of pregnant animals were sacrificed by quick decapitation on day 21 of gestation. The pregnant uteri were promptly removed outside the animal's abdomen, opened and litters taken out. Absorption sites were detected and recorded. After full count and observation of litters, several parameters were measured. These parameters were volume (in milliliters by water displacement method), weight (in grams), lateral length (in millimeters), circumference girth at umbilicus (in millimeters by thread method), tail length (in millimeters), antro-posterior and biparietal dimensions of skull (in millimeters). All measures in millimeters were carried out by vernier caliper. **Photographs** of litters and uteri with absorption sites were taken promptly after animal sacrifice and dissection.

3.7. CONGENITAL MALFORMATIONS

The congenital malformations were recorded and photographed.

3.8. HISTOPATHOLOGICAL STUDIES.

All litters were embedded in 10% buffered formalin for a minimum of 24 hours then dissected to extract the internal organs. The organs included the heart, lung, liver, spleen, stomach, intestine, thymus, kidney, and suprarenal gland were taken as one group. Another group was the nervous and skeletal systems (skull, brain, eye, vertebral column with spinal cord, and thigh muscle with femur bone).

These organs were immersed in a preservative solution (10% formalin). The sample was dehydrated by passage through a series of alcohol solutions with rising concentrations (e.g. 60%, 70%, 90%, and 100%) until all water (intrinsic tissue water and fixative water) was

removed. An organic solvent (xylol) which is miscible both with alcohol and with molten liquid paraffin wax then replaced the alcohol. The resulting specimen was immersed in paraffin wax at a temperature 60 °C (just above the melting point of the wax), which is solid at normal working room temperature. The wax acts as a physical support to the sample, allowing thin sections (3 μm) to be cut, using a microtome, without deformation of the cellular structure and architecture. The wax-impregnated sections were mounted on glass microscope slides **(Stevens and Lowe, 1997).**

The sections were dewaxed in xylol, hydrated through graded alcohols to water. Staining in an alum hematoxylin (Harrison's iron) occurred for a suitable time. Washing well in running tap water was occurred until sections became 'blue' (about 5 minutes or less). Differentiation in 1% acid alcohol. Washing well in tap water until sections are again became 'blue' (about 5 minutes or less). Staining in 1% eosin Y was performed for 10 minutes. Washing in running tap water for 1-5 minutes. Dehydration through alcohols, clarifying in xylol, mount in Canada palsam. The resulting colour of the stains are, the nuclei become blue-black; the cytoplasm become varying shades of pink; the muscle fibers become deep pinky red; the red blood cells become orange/red and the fibrin become deep pink **(Bancroft and Stevens, 1990).**

These slides were studied histopathologically and the results were recorded descriptively with statistical formulation of the findings. Microscopic photographs were taken for some representative tissue sections.

Arbitrary scores of changes were designated. These are presented in the chapter of results.

3.9. STATISTICAL STUDIES.

The statistical methods used in this thesis were mean, standard deviation, standard error and range (minimum and maximum). Student t-test was performed to compare between irradiated and control groups. The following is a brief description of these terms.

- **Measures of Central Tendency (Mean)**

Although several means may be mathematically calculated, the arithmetic, or simple mean is used most frequently in statistics and is the one generally referred to by the term mean. The mean is the arithmetic average of the observations. It is symbolized by X (called X-bar) and is calculated as follows: $\overline{X} = \sum x_i / n$ where $\sum x_i$ = summation of individual values and n= number of individuals.

- **Measures of Spread (Dispersion)** [Range, Standard Deviation and Standard Error].
  - The **range** is the difference between the largest observation and the smallest observation. It is easy to determine once the data have been organized. Many authors give minimum and maximum values instead of the range and in some ways these values are useful information.
  - The **Standard Deviation**: The standard deviation is the most commonly used measure of dispersion with medical and health data; although its meaning and its computation are complex. The standard deviation is a measure which indicates the spread of data about their mean.
  - The **standard error** which calculated as dividing the standard deviation by square root of the population number.

- **Differences Between Group Means: t-Tests**:

For t-tests, data are essentially postulated to be withdrawn from a random sample of a normally distributed population, where the mean of the sampling distribution will be equal to the mean of the population. When two groups on particular characteristics are compared. The question is: how different the groups are? Is that difference greater than that which could occur by chance alone? In this thesis: if P value was less than 0.05, it was considered significant; if its value was less than 0.01, it was considered highly significant and if its value was less than 0.001, it was considered very highly significant. If P value was more than 0.05, it was considered nonsignificant and this probability (P) of getting a large difference by chance alone.

Given the same mean difference, groups with less variability (smaller standard deviations), will be more likely to be significantly different than groups with wider variability.

Computer program "Excel 97" under windows 98 was used for the data entry, calculations and drawing of curves.

RESULTS

4.RESULTS

4.1. SCOPE.

In this chapter, the results obtained from the experimental studies performed in this thesis are presented in three separate parts.

The **first part** deals with Morphological Studies which is presented as descriptive texts and tables 2-19. It is subdivided into two sections, individual and collective results.

The first section of this part comprises individual results (tables 2-16) obtained for the various subgroups of control and irradiated animals. These tables include observations on number of absorption sites and litters, measurements of litters for size, weight, lateral body length, circumference girth at umbilicus, tail length and skull dimensions (antro-posterior and biparietal). Values for mean, standard deviation, standard error, minimum and maximum are indicated.

The second section of this part comprises collective compilation (tables 17-19) of individual results given in the first section. These collective results include statistical considerations of t-test and P values as indicated with descriptive texts.

Three groups of illustrative comprehensive curves are provided. The first group of curves (figure 1-6) relates each individual period of gestation to the radiation doses and the control for all parameters studied. The second group of curves (figure 7-14) relates the radiation doses used to periods of gestation for all parameters studied; the control are indicated. The third group of curves (figure 15-23) relates each parameter studied to the periods of gestation and the radiation doses used including the control. An appendix showing the detailed data of the parameters is provided at the end of the thesis.

The **second part** constitutes photographic representations of some congenital malformations observed in some litters (plates 2-14).

The **third part** constitutes findings of histopathological studies illustrated in tables (20-28) and microphotographs (plates 15-47).

PART 1 OF RESULTS.

4.2.RESULTS OF MORPHOLOGICAL STUDIES.

4.2.1. Individual Results.

4.2.1.1.RESULTS OF 9TH DAY GESTATION GROUP.

- **Control Subgroup.**

Table (2) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 0.40, SD ± 0.49 and SE ± 0.22. The minimum and maximum values were 0.00 and 1.00.
- The mean **number of litters** was 6.80, SD ± 0.98 and SE ± 0.44. The minimum and maximum values were 6.00 and 8.00.

Measurements of litters.

- The mean **size** was 4.02 ml, SD ± 0.50 and SE ± 0.22. The minimum and maximum values were 3.40 and 4.70 ml.
- The mean **weight** was 4.05 gm, SD ± 0.51 and SE ± 0.23. The minimum and maximum values were 3.30 and 4.90 gm.
- The mean **lateral body length** was 34.36 mm, SD ± 1.57 and SE ± 0.70. The minimum and maximum values were 32.30 and 36.60 mm.
- The mean **girth at umbilicus** was 41.58 mm, SD ± 2.43 and SE ± 1.09. The minimum and maximum values were 39.23 and 46.08 mm.
- The mean **tail length** was 13.81 mm, SD ± 0.74 and SE ± 0.33. The minimum and maximum values were 12.53 and 14.70 mm.
- The mean **antro-posterior dimension of skull** was 15.86 mm, SD ± 0.46 and SE ± 0.21. The minimum and maximum values were 15.10 and 16.50 mm.
- The mean **biparietal dimension of skull** was 10.48 mm, SD ± 0.30 and SE ± 0.13. The minimum and maximum values were 10.00 and 10.80 mm.

Table (2)

Numbers of absorption sites, litters and measurements For control subgroup at 9th day.

	MEAN	SD ±	SE ±	MIN.	MAX.
No. of absorption sites	0.40	0.49	0.22	0.00	1.00
No. of litters	6.80	0.98	0.44	6.00	8.00
Measurements					
Size ml.	4.02	0.50	0.22	3.40	4.70
Weight gm.	4.05	0.51	0.23	3.30	4.90
Length (Lat)* mm	34.36	1.57	0.70	32.30	36.60
Girth* mm	41.58	2.43	1.09	39.23	46.08
Tail length mm	13.81	0.74	0.33	12.53	14.70
Skull (AP)* mm	15.86	0.46	0.21	15.10	16.50
Skull (BP)* mm	10.48	0.30	0.13	10.00	10.80

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-0.5 Gy.**

Table (3) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 1.00, SD ± 0.00 and SE ± 0.00. The minimum and maximum values were 1.00 and 1.00.
- The mean **number of litters** was 6.60, SD ± 1.02, and SE ± 0.46. The minimum and maximum values were 5.00 and 8.00.

Measurements of litters.

- The mean **size** was 4.00 ml, SD ± 0.61 and SE ± 0.27. The minimum and maximum values were 3.10 and 5.00 ml.
- The mean **weight** was 4.03 gm, SD ± 0.43 and SE ± 0.19. The minimum and maximum values were 3.50 and 4.78 gm.
- The mean **lateral body length** was 33.74 mm, SD ± 1.02 and SE ± 0.46. The minimum and maximum values were 32.70 and 35.50 mm.
- The mean **girth at umbilicus** was 41.14 mm, SD ± 2.32 and SE ± 1.04. The minimum and maximum values were 38.27 and 44.00 mm.
- The mean **tail length** was 13.12 mm, SD ± 1.12 and SE ± 0.50. The minimum and maximum values were 11.80 and 14.50 mm.
- The mean **antro-posterior dimension of skull** was 15.39 mm, SD ± 0.56 and SE ± 0.25. The minimum and maximum values were 14.60 and 16.27 mm.
- The mean **biparietal dimension of skull** was 10.17 mm, SD ± 0.66 and SE ± 0.29. The minimum and maximum values were 9.33 and 11.03 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show very minimal decrease as compared to the control subgroup, and very minimal increase in number of absorption sites.

Table (3)

Number of absorption sites, litters and measurements.

For 0.5 Gy subgroup at 9th day.

	MEAN	SD	SE ±	MIN.	MAX.
No. of absorption sites	1.00	0.00	0.00	1.00	1.00
No. of litters	6.60	1.02	0.46	5.00	8.00
Measurements					
Size ml.	4.00	0.61	0.27	3.10	5.00
Weight gm.	4.03	0.43	0.19	3.50	4.78
Length (Lat)* mm	33.74	1.02	0.46	32.70	35.50
Girth* mm	41.14	2.32	1.04	38.27	44.00
Tail length mm	13.12	1.12	0.50	11.80	14.50
Skull (AP)* mm	15.39	0.56	0.25	14.60	16.27
Skull (BP)* mm	10.17	0.66	0.29	9.33	11.03

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-1 Gy.**

Table (4) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 1.20, SD ± 0.98 and SE ± 0.44. The minimum and maximum values were 0.00 and 2.00.
- The mean **number of litters** was 6.40, SD ± 1.36 and SE ± 0.61. The minimum and maximum values were 4.00 and 8.00.

Measurements of litters.

- The mean **size** was 3.00 ml, SD ± 0.11 and SE ± 0.05. The minimum and maximum values were 2.80 and 3.11 ml.
- The mean **weight** was 2.96 gm, SD ± 0.19 and SE ± 0.09. The minimum and maximum values were 2.70 and 3.26 gm.
- The mean **lateral body length** was 32.61 mm, SD ± 1.24 and SE ± 0.55. The minimum and maximum values were 31.47 and 34.93 mm.
- The mean **girth at umbilicus** was 40.42 mm, SD ± 2.47 and SE ± 1.11. The minimum and maximum values were 38.10 and 44.65 mm.
- The mean **tail length** was 11.83 mm, SD ± 0.86 and SE ± 0.39. The minimum and maximum values were 10.73 and 13.10 mm.
- The mean **antro-posterior dimension of skull** was 15.23 mm, SD ± 0.85 and SE ± 0.38. The minimum and maximum values were 14.00 and 16.28 mm.
- The mean **biparietal dimension of skull** was 9.79 mm, SD ± 0.21 and SE ± 0.09. The minimum and maximum values were 9.40 and 10.00 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show minimal decrease as compared to the control subgroup, and minimal increase in number of absorption sites.

Table (4)

Numbers of absorption sites, litters and measurements.

For 1 Gy subgroup at 9th day.

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	1.20	0.98	0.44	0.00	2.00
No. of litters	6.40	1.36	0.61	4.00	8.00
Measurements					
size ml.	3.00	0.11	0.05	2.80	3.11
Weight gm.	2.96	0.19	0.09	2.70	3.26
Length (Lat)* mm	32.61	1.24	0.55	31.47	34.93
Girth* mm	40.42	2.47	1.11	38.10	44.65
Tail length mm	11.83	0.86	0.39	10.73	13.10
Skull (AP)* mm	15.23	0.85	0.38	14.00	16.28
Skull (BP)* mm	9.79	0.21	0.09	9.40	10.00

(Lat) = Lateral length..*

Girth = Circumference girth at umbilicus.*

(AP) = Antro-posterior dimension of skull.*

(BP) = Biparietal dimension of skull.*

➢ **Irradiated Subgroup-2 Gy.**

Table (5) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 5.20, SD ± 1.33 and SE ± 0.59. The minimum and maximum values were 3.00 and 7.00.
- The mean **number of litters** was 1.40, SD + 1.96 and SE + 0.88. The minimum and maximum values were 0.00 and 5.00.

Measurements of litters.

- The mean **size** was 1.05 ml, SD ± 1.31 and SE ± 0.58. The minimum and maximum values were 0.00 and 3.00 ml.
- The mean **weight** was 0.97 gm, SD ± 1.19 and SE ± 0.53. The minimum and maximum values were 0.00 and 2.45 gm.
- The mean **lateral body length** was 12.39 mm, SD ± 15.19 and SE ± 6.79. The minimum and maximum values were 0.00 and 32.10 mm.
- The mean **girth at umbilicus** was 14.84 mm, SD ± 18.21 and SE ± 8.14. The minimum and maximum values were 0.00 and 38.77 mm.
- The mean **tail length** was 4.24 mm, SD ± 5.35 and SE ± 2.39. The minimum and maximum values were 0.00 and 12.63 mm.
- The mean **antro-posterior dimension of skull** was 5.97 mm, SD ± 7.36 and SE ± 3.29. The minimum and maximum values were 0.00 and 16.20 mm.
- The mean **biparietal dimension of skull** was 3.58 mm, SD ± 4.39 and SE ± 1.96. The minimum and maximum values were 0.00 and 9.33 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show significant decrease as compared to the control subgroup, and significant increase in number of absorption sites.

Table (5)

Numbers of absorption sites, litters and measurements.

For 2 Gy subgroup at 9th day.

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	5.20	1.33	0.59	3.00	7.00
No. of litters	1.40	1.96	0.88	0.00	5.00
Measurements					
Size ml.	1.05	1.31	0.58	0.00	3.00
Weight gm.	0.97	1.19	0.53	0.00	2.45
Length (Lat)* mm	12.39	15.19	6.79	0.00	32.10
Girth* mm	14.84	18.21	8.14	0.00	38.77
Tail length mm	4.24	5.35	2.39	0.00	12.63
Skull (AP)* mm	5.97	7.36	3.29	0.00	16.20
Skull (BP)* mm	3.58	4.39	1.96	0.00	9.33

(Lat) = Lateral length.*

Girth = Circumference girth at umbilicus.*

(AP) = Antro-posterior dimension of skull.*

(BP) = Biparietal dimension of skull.*

➢ **Irradiated Subgroup-3 Gy.**

Table (6) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 7.20, SD ± 1.17 and SE ± 0.52. The minimum and maximum values were 6.00 and 9.00.
- There were no surviving **litters** for this subgroup.

Table (6)

Numbers of absorption sites and litters

For 3 Gy subgroup at 9th day.

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	7.20	1.17	0.52	6.00	9.00
No. of litters*	0.00	0.00	0.00	0.00	0.00

* No litters survived for this subgroup, therefore no measurements were recorded.

4.2.1.2.RESULTS OF 12TH DAY GESTATION GROUP.

➢ Control Subgroup.

Table (7) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 0.40, SD ± 0.49 and SE ± 0.22. The minimum and maximum values were 0.00 and 1.00.
- The mean **number of litters** was 7.40, SD + 1.74 and SE + 0.78. The minimum and maximum values were 5.00 and 10.00.

Measurements of litters.

- The mean **size** was 4.06 ml, SD ± 0.45 and SE ± 0.20. The minimum and maximum values were 3.50 and 4.70 ml.
- The mean **weight** was 4.11 gm, SD ± 0.53 and SE ± 0.24. The minimum and maximum values were 3.30 and 4.90 gm.
- The mean **lateral body length** was 34.37 mm, SD ± 1.58 and SE ± 0.71. The minimum and maximum values were 32.30 and 36.60 mm.
- The mean **girth at umbilicus** was 42.18 mm, SD ± 2.32 and SE ± 1.04. The minimum and maximum values were 39.67 and 46.08 mm.
- The mean **tail length** was 14.38 mm, SD ±. 1.09 and SE ± 0.49. The minimum and maximum values were 12.50 and 15.90 mm.
- The mean **antro-posterior dimension of skull** was 16.13 mm, SD ± 0.61 and SE ± 0.27. The minimum and maximum values were 15.13 and 16.80 mm.
- The mean **biparietal dimension of skull** was 10.61 mm, SD ± 0.31 and SE ± 0.14. The minimum and maximum values were 10.07 and 10.90 mm.

Table (7)

Numbers of absorption sites, litters and measurements.

For control subgroup at 12th day.

	MEAN	SD ±	SE ±	MIN.	MAX.
No. of absorption sites	0.40	0.49	0.22	0.00	1.00
No. of litters	7.40	1.74	0.78	5.00	10.00
Measurements					
Size ml.	4.06	0.45	0.20	3.50	4.70
Weight gm.	4.11	0.53	0.24	3.30	4.90
Length (Lat)* mm	34.37	1.58	0.71	32.30	36.60
Girth* mm	42.18	2.32	1.04	39.67	46.08
Tail length mm	14.38	1.09	0.49	12.50	15.90
Skull (AP)* mm	16.13	0.61	0.27	15.13	16.80
Skull (BP)* mm	10.61	0.31	0.14	10.07	10.90

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-0.5 Gy.**

Table (8) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 0.60, SD ± 1.20 and SE ± 0.54. The minimum and maximum values were 0.00 and 3.00.
- The mean **number of litters** was 7.20, SD ± 2.93 and SE ± 1.31. The minimum and maximum values were 2.00 and 11.00.

Measurements of litters.

- The mean **size** was 4.04 ml, SD ± 0.43 and SE ± 0.19. The minimum and maximum values were 3.60 and 4.75 ml.
- The mean **weight** was 4.09 gm, SD ± 0.42 and SE ± 0.19. The minimum and maximum values were 3.66 and 4.86 gm.
- The mean **lateral body length** was 34.10 mm, SD ± 0.75 and SE ± 0.33. The minimum and maximum values were 33.57 and 35.57 mm.
- The mean **girth at umbilicus** was 41.92 mm, SD ± 0.47 and SE ± 0.21. The minimum and maximum values were 41.00 and 42.20 mm.
- The mean **tail length** was 14.06 mm, SD ± 2.17 and SE ± 0.97. The minimum and maximum values were 11.90 and 16.90 mm.
- The mean **antro-posterior dimension of skull** was 15.45 mm, SD ± 0.74 and SE ± 0.33. The minimum and maximum values were 14.13 and 16.00 mm.
- The mean **biparietal dimension of skull** was 10.24 mm, SD ± 0.89 and SE ± 0.40. The minimum and maximum values were 9.47 and 11.60 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show very minimal decrease as compared to the control subgroup, and very minimal increase in number of absorption sites.

Table (8)

Numbers of absorption sites, litters and measurements.

For 0.5 Gy subgroup at 12th day

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	0.60	1.20	0.54	0.00	3.00
No. of litters	7.20	2.93	1.31	2.00	11.00
Measurements					
Size ml.	4.04	0.43	0.19	3.60	4.75
Weight gm.	4.09	0.42	0.19	3.66	4.86
Length (Lat)* mm	34.10	0.75	0.33	33.57	35.57
Girth* mm	41.92	0.47	0.21	41.00	42.20
Tail length mm	14.06	2.17	0.97	11.90	16.90
Skull (AP)* mm	15.45	0.74	0.33	14.13	16.00
Skull (BP)* mm	10.24	0.89	0.40	9.47	11.60

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-1 Gy.**

Table (9) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 1.00, SD ± 0.63 and SE ± 0.28. The minimum and maximum values were 0.00 and 2.00.
- The mean **number of litters** was 7.00, SD ± 1.26 and SE ± 0.57. The minimum and maximum values were 5.00 and 9.00.

Measurements of litters.

- The mean **size** was 3.24 ml, SD ± 0.42 and SE ± 0.19. The minimum and maximum values were 2.60 and 3.90 ml.
- The mean **weight** was 3.40 gm, SD ± 0.62 and SE ± 0.28. The minimum and maximum values were 2.76 and 4.46 gm.
- The mean **lateral body length** was 32.51 mm, SD ± 1.61 and SE ± 0.72. The minimum and maximum values were 29.87 and 34.93 mm.
- The mean **girth at umbilicus** was 40.99 mm, SD ± 2.31 and SE ± 1.03. The minimum and maximum values were 38.30 and 44.73 mm.
- The mean **tail length** was 12.56 mm, SD ± 1.06 and SE ± 0.47. The minimum and maximum values were 10.93 and 14.03 mm.
- The mean **antro-posterior dimension of skull** was 15.30 mm, SD ± 0.70 and SE ± 0.31. The minimum and maximum values were 13.97 and 16.07 mm.
- The mean **biparietal dimension of skull** was 9.83 mm, SD ± 0.59 and SE ± 0.26. The minimum and maximum values were 8.93 and 10.60 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show minimal decrease as compared to the control subgroup, and minimal increase in number of absorption sites.

Table (9)

Numbers of absorption sites, litters and measurements.

For 1 Gy subgroup at 12th day

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	1.00	0.63	0.28	0.00	2.00
No. of litters	7.00	1.26	0.57	5.00	9.00
Measurements					
Size ml.	3.24	0.42	0.19	2.60	3.90
Weight gm.	3.40	0.62	0.28	2.76	4.46
Length (Lat)* mm	32.51	1.61	0.72	29.87	34.93
Girth* mm	40.99	2.31	1.03	38.30	44.73
Tail length mm	12.56	1.06	0.47	10.93	14.03
Skull (AP)* mm	15.30	0.70	0.31	13.97	16.07
Skull (BP)* mm	9.83	0.59	0.26	8.93	10.60

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-2 Gy.**

Table (10) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 2.40, SD ± 2.24 and SE ± 1.00. The minimum and maximum values were 0.00 and 6.00.
- The mean **number of litters** was 4.60, SD ± 1.85 and SE ± 0.83. The minimum and maximum values were 2.00 and 7.00.

Measurements of litters.

- The mean **size** was 2.69 ml, SD ± 0.36 and SE ± 0.16. The minimum and maximum values were 2.30 and 3.33 ml.
- The mean **weight** was 2.56 gm, SD ± 0.59 and SE ± 0.27. The minimum and maximum values were 1.83 and 3.60 gm.
- The mean **lateral body length** was 24.44 mm, SD ± 1.33 and SE ± 0.59. The minimum and maximum values were 22.00 and 25.90 mm.
- The mean **girth at umbilicus** was 30.55 mm, SD ± 3.18 and SE ± 1.42. The minimum and maximum values were 24.70 and 33.40 mm.
- The mean **tail length** was 10.80 mm, SD ± 1.37 and SE ± 0.61. The minimum and maximum values were 8.10 and 11.87 mm.
- The mean **antro-posterior dimension of skull** was 11.88 mm, SD ± 1.42 and SE ± 0.64. The minimum and maximum values were 9.60 and 14.00 mm.
- The mean **biparietal dimension of skull** was 8.11 mm, SD ± 1.71 and SE ± 0.76. The minimum and maximum values were 5.10 and 10.40 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show some decrease as compared to the control subgroup, and an increase in number of absorption sites.

Table (10)

Numbers of absorption sites, litters and measurements.

For 2 Gy subgroup at 12th day.

	Mean	SD ±	SE ±	Min	Max
No. of absorption sites	2.40	2.24	1.00	0.00	6.00
No. of litters	4.60	1.85	0.83	2.00	7.00
Measurements					
Size ml.	2.69	0.36	0.16	2.30	3.33
Weight gm.	2.56	0.59	0.27	1.83	3.60
Length (Lat)* mm	24.44	1.33	0.59	22.00	25.90
Girth* mm	30.55	3.18	1.42	24.7	33.40
Tail length mm	10.80	1.37	0.61	8.10	11.87
Skull (AP)* mm	11.88	1.42	0.64	9.60	14.00
Skull (BP)* mm	8.11	1.71	0.76	5.10	10.40

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-3 Gy.**

Table(11) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 6.40, SD ± 2.50 and SE ± 1.12. The minimum and maximum values were 4.00 and 11.00.
- The mean **number of litters** was 1.20, SD ± 1.17 and SE ± 0.52. The minimum and maximum values were 0.00 and 3.00.

Measurements of litters.

- The mean **size** was 1.20 ml, SD ± 1.03 and SE ± 0.46. The minimum and maximum values were 0.00 and 2.50 ml.
- The mean **weight** was 1.02 gm, SD ± 0.89 and SE ± 0.40. The minimum and maximum values were 0.00 and 2.20 gm.
- The mean **lateral body length** was 16.15 mm, SD ± 13.34 and SE ± 5.96. The minimum and maximum values were 0.00 and 29.77 mm.
- The mean **girth at umbilicus** was 22.04 mm, SD ± 17.99 and SE ± 8.05. The minimum and maximum values were 0.00 and 37.00 mm.
- The mean **tail length** was 2.51 mm, SD ± 2.11 and SE ± 0.94. The minimum and maximum values were 0.00 and 4.77 mm.
- The mean **antro-posterior dimension of skull** was 6.42 mm, SD ± 5.25 and SE ± 2.35. The minimum and maximum values were 0.00 and 11.00 mm.
- The mean **biparietal dimension of skull** was 4.87 mm, SD ± 4.01 and SE ± 1.79. The minimum and maximum values were 0.00 and 8.90 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show very significant decrease as compared to the control subgroup, and significant high increase in number of absorption sites.

Table (11)

Numbers of absorption sites, litters and measurements.

For 3 Gy subgroup at 12th day .

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	6.40	2.50	1.12	4.00	11.00
No. of litters	1.20	1.17	0.52	0.00	3.00
Measurements					
Size ml.	1.20	1.03	0.46	0.00	2.50
Weight gm.	1.02	0.89	0.40	0.00	2.20
Length (Lat)* mm	16.15	13.34	5.96	0.00	29.77
Girth* mm	22.04	17.99	8.05	0.00	37.00
Tail length mm	2.51	2.11	0.94	0.00	4.77
Skull (AP)* mm	6.42	5.25	2.35	0.00	11.00
Skull (BP)* mm	4.87	4.01	1.79	0.00	8.90

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

4.2.1.3.RESULTS OF 15th DAY GESTATION GROUP.

➢ Control Subgroup.

Table (12) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 0.60, SD ± 0.49 and SE ± 0.22. The minimum and maximum values were 0.00 and 1.00.
- The mean **number of litters** was 7.80, SD ± 1.60 and SE ± 0.72. The minimum and maximum values were 6.00 and 10.00.

Measurements of litters.

- The mean **size** was 4.56 ml, SD ± 0.35 and SE ± 0.16. The minimum and maximum values were 4.20 and 5.20 ml.
- The mean **weight** was 4.25 gm, SD ± 0.35 and SE ± 0.16. The minimum and maximum values were 3.90 and 4.90 gm.
- The mean **lateral body length** was 35.38 mm, SD ± 2.44 and SE ± 1.09. The minimum and maximum values were 32.30 and 39.60 mm.
- The mean **girth at umbilicus** was 42.78 mm, SD ± 1.95 and SE ± 0.87. The minimum and maximum values were 40.23 and 46.08 mm.
- The mean **tail length** was 14.58 mm, SD ± 0.78 and SE ± 0.35. The minimum and maximum values were 13.50 and 15.50 mm.
- The mean **antro-posterior dimension of skull** was 16.22 mm, SD ± 0.65 and SE ± 0.29. The minimum and maximum values were 15.13 and 16.90 mm.
- The mean **biparietal dimension of skull** was 10.70 mm, SD ± 0.21 and SE ± 0.09. The minimum and maximum values were 10.40 and 10.90 mm.

Table (12)

Numbers of absorption sites, litters and measurements.

For control subgroup at 15th day.

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	0.60	0.49	0.22	0.00	1.00
No. of litters	7.80	1.60	0.72	6.00	10.00
Measurements					
Size ml.	4.56	0.35	0.16	4.20	5.20
Weight gm.	4.25	0.35	0.16	3.90	4.90
Length (Lat)* mm	35.38	2.44	1.09	32.30	39.60
Girth* mm	42.78	1.95	0.87	40.23	46.08
Tail length mm	14.58	0.78	0.35	13.50	15.50
Skull (AP)* mm	16.22	0.65	0.29	15.13	16.90
Skull (BP)* mm	10.70	0.21	0.09	10.40	10.90

(Lat) = Lateral length.*

Girth = Circumference girth at umbilicus.*

(AP) = Antro-posterior dimension of skull.*

(BP) = Biparietal dimension of skull.*

➢ **Irradiated Subgroup-0.5 Gy.**

Table (13) shows the following:

Absorption sites and litters.

- ❑ The mean **number of absorption sites** was 0.40, SD ± 0.80 and SE ± 0.36. The minimum and maximum values were 0.00 and 2.00.
- ❑ The mean **number of litters** was 7.80, SD ± 1.47 and SE ± 0.66. The minimum and maximum values were 5.00 and 9.00.

Measurements of litters.

- ❑ The mean **size** was 4.39 ml, SD ± 0.10 and SE ± 0.05. The minimum and maximum values were 4.20 and 4.50 ml.
- ❑ The mean **weight** was 4.25 gm, SD ± 0.18 and SE ± 0.08. The minimum and maximum values were 4.00 and 4.51 gm.
- ❑ The mean **lateral body length** was 35.19 mm, SD ± 1.37 and SE ± 0.61. The minimum and maximum values were 33.20 and 36.80 mm.
- ❑ The mean **girth at umbilicus** was 42.43 mm, SD ± 0.53 and SE ± 0.24. The minimum and maximum values were 41.70 and 43.00 mm.
- ❑ The mean **tail length** was 14.27 mm, SD ± 1.30 and SE ± 0.58. The minimum and maximum values were 12.50 and 16.20 mm.
- ❑ The mean **antro-posterior dimension of skull** was 16.14 mm, SD ± 0.18 and SE ± 0.08. The minimum and maximum values were 15.80 and 16.30 mm.
- ❑ The mean **biparietal dimension of skull** was 10.60 mm, SD ± 0.17 and SE ± 0.07. The minimum and maximum values were 10.40 and 10.90 mm.

From these results, it is evident that the trend of the affection of this subgroup indicates that the number of litters and their measurements show very minimal decrease as compared to the control subgroup, and very minimal increase in number of absorption sites.

Table (13)

Numbers of absorption sites, litters and measurements.

For 0.5 Gy subgroup at 15th day .

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	0.40	0.80	0.36	0.00	2.00
No. of litters	7.80	1.47	0.66	5.00	9.00
Measurements					
Size ml.	4.39	0.10	0.05	4.20	4.50
Weight gm.	4.25	0.18	0.08	4.00	4.51
Length (Lat)* mm	35.19	1.37	0.61	33.20	36.80
Girth* mm	42.43	0.53	0.24	41.70	43.00
Tail length mm	14.27	1.30	0.58	12.50	16.20
Skull (AP)* mm	16.14	0.18	0.08	15.80	16.30
Skull (BP)* mm	10.60	0.17	0.07	10.40	10.90

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-1 Gy.**

Table (14) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 0.60, SD ± 0.80 and SE ± 0.36. The minimum and maximum values were 0.00 and 2.00.
- The mean **number of litters** was 7.60, SD ± 1.50 and SE ± 0.67. The minimum and maximum values were 5.00 and 9.00.

Measurements of litters.

- The mean **size** was 3.40 ml, SD ± 0.26 and SE ± 0.12. The minimum and maximum values were 3.10 and 3.80 ml.
- The mean **weight** was 3.57 gm, SD ± 0.22 and SE ± 0.10. The minimum and maximum values were 3.30 and 3.88 gm.
- The mean **lateral body length** was 33.67 mm, SD ± 2.19 and SE ± 0.98. The minimum and maximum values were 31.90 and 37.97 mm.
- The mean **girth at umbilicus** was 41.18 mm, SD ± 1.97 and SE ± 0.88. The minimum and maximum values were 38.90 and 44.20 mm.
- The mean **tail length** was 12.93 mm, SD ± 0.69 and SE ± 0.31. The minimum and maximum values were 12.13 and 13.87 mm.
- The mean **antro-posterior dimension of skull** was 15.73 mm, SD ± 0.50 and SE ± 0.22. The minimum and maximum values were 15.00 and 16.37 mm.
- The mean **biparietal dimension of skull** was 9.76 mm, SD ± 0.34 and SE ± 0.15. The minimum and maximum values were 9.20 and 10.20 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show minimal decrease as compared to the control subgroup, and minimal increase in number of absorption sites.

Table (14)

Numbers of absorption sites, litters and measurements.

For 1 Gy subgroup at 15th day .

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	0.60	0.80	0.36	0.00	2.00
No. of litters	7.60	1.50	0.67	5.00	9.00
Measurements					
Size ml.	3.40	0.26	0.12	3.10	3.80
Weight gm.	3.57	0.22	0.10	3.30	3.88
Length (Lat)* mm	33.67	2.19	0.98	31.90	37.97
Girth* mm	41.18	1.97	0.88	38.90	44.20
Tail length mm	12.93	0.69	0.31	12.13	13.87
Skull (AP)* mm	15.73	0.50	0.22	15.00	16.37
Skull (BP)* mm	9.76	0.34	0.15	9.20	10.20

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

➢ **Irradiated Subgroup-2 Gy.**

Table (15) shows the following:

Absorption sites and litters.

- The **number of absorption sites** was 2.20, SD ± 0.75 and SE ± 0.33. The minimum and maximum values were 1.00 and 3.00.
- The mean **number of litters** was 5.40, SD ± 3.14 and SE ± 1.40. The minimum and maximum values were 0.00 and 9.00.

Measurements of litters.

- The mean **size** was 3.02 ml, SD ± 1.53 and SE ± 0.68. The minimum and maximum values were 0.00 and 4.00 ml.
- The mean **weight** was 3.06 gm, SD ± 1.54 and SE ± 0.69. The minimum and maximum values were 0.00 and 4.00 gm.
- The mean **lateral body length** was 26.60 mm, SD ± 13.31 and SE ± 5.95. The minimum and maximum values were 0.00 and 34.00 mm.
- The mean **girth at umbilicus** was 34.06 mm, SD ± 17.04 and SE ± 7.62. The minimum and maximum values were 0.00 and 43.60 mm.
- The mean **tail length** was 11.00 mm, SD ± 5.60 and SE ± 2.51. The minimum and maximum values were 0.00 and 15.80 mm.
- The mean **antro-posterior dimension of skull** was 12.95 mm, SD ± 6.51 and SE ± 2.91. The minimum and maximum values were 0.00 and 17.45 mm.
- The **biparietal dimension of skull** was 8.62 mm, SD ± 4.32 and SE ± 1.93. The minimum and maximum values were 0.00 and 11.10 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show decrease as compared to the control subgroup, and increase in number of absorption sites.

Table (15)

Numbers of absorption sites, litters and measurements.

For 2 Gy subgroup at 15th day .

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	2.20	0.75	0.33	1.00	3.00
No. of litters	5.40	3.14	1.40	0.00	9.00
Measurements					
Size ml.	3.02	1.53	0.68	0.00	4.00
Weight gm.	3.06	1.54	0.69	0.00	4.00
Length (Lat)* mm	26.60	13.31	5.95	0.00	34.00
Girth* mm	34.06	17.04	7.62	0.00	43.60
Tail length mm	11.00	5.60	2.51	0.00	15.80
Skull (AP)* mm	12.95	6.51	2.91	0.00	17.45
Skull (BP)* mm	8.62	4.32	1.93	0.00	11.10

(Lat) = Lateral length.*

Girth = Circumference girth at umbilicus.*

(AP) = Antro-posterior dimension of skull.*

(BP) = Biparietal dimension of skull.*

➢ **Irradiated Subgroup-3 Gy.**

Table (16) shows the following:

Absorption sites and litters.

- The mean **number of absorption sites** was 3.00, SD ± 1.41 and SE ± 0.63. The minimum and maximum values were 1.00 and 5.00.
- The mean **number of litters** was 3.40, SD ± 2.80 and SE ± 1.25. The minimum and maximum values were 0.00 and 6.00.

Measurements of litters.

- The mean **size** was 1.91 ml, SD ± 1.59 and SE ± 0.71. The minimum and maximum values were 0.00 and 3.67 ml.
- The mean **weight** was 2.05 gm, SD ± 1.68 and SE ± 0.75. The minimum and maximum values were 0.00 and 3.64 gm.
- The mean **lateral body length** was 19.89 mm, SD ± 16.26 and SE ± 7.27. The minimum and maximum values were 0.00 and 34.70 mm.
- The mean **girth at umbilicus** was 23.66 mm, SD ± 19.37 and SE ± 8.66. The minimum and maximum values were 0.00 and 40.90 mm.
- The mean **tail length** was 7.17 mm, SD ± 5.92 and SE ± 2.65. The minimum and maximum values were 0.00 and 12.80 mm.
- The mean **antro-posterior dimension of skull** was 9.39 mm, SD ± 7.67 and SE ± 3.43. The minimum and maximum values were 0.00 and 15.93 mm.
- The mean **biparietal dimension of skull** was 5.80 mm, SD ± 4.74 and SE ± 2.12. The minimum and maximum values were 0.00 and 10.07 mm.

From these results, it is evident that the trend of affection of this subgroup indicates that the number of litters and their measurements show very significant decrease as compared to the control subgroup, and evident increase in number of absorption sites.

Table (16)

Numbers of absorption sites, litters and measurements.

For 3 Gy subgroup at 15th day .

	Mean	SD ±	SE ±	Min.	Max.
No. of absorption sites	3.00	1.41	0.63	1.00	5.00
No. of litters	3.40	2.80	1.25	0.00	6.00
Measurements					
Size ml.	1.91	1.59	0.71	0.00	3.67
Weight gm.	2.05	1.68	0.75	0.00	3.64
Length (Lat)* mm	19.89	16.26	7.27	0.00	34.70
Girth* mm	23.66	19.37	8.66	0.00	40.90
Tail length mm	7.17	5.92	2.65	0.00	12.80
Skull (AP)* mm	9.39	7.67	3.43	0.00	15.93
Skull (BP)* mm	5.80	4.74	2.12	0.00	10.07

*(Lat)** = *Lateral length.*

*Girth** = *Circumference girth at umbilicus.*

*(AP)** = *Antro-posterior dimension of skull.*

*(BP)** = *Biparietal dimension of skull.*

4.2.2. Comparative Collective Results.

4.2.2.1.Comparative Collective Results of Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 9th Day of Gestation.

The data in table (17) presents the number of absorption sites (mean ± SE), the number of litters (mean ± SE) for the control and 0.5,1, 2 and 3 Gy subgroups irradiated on 9th day of gestation. It also presents the mean dimensions ± SE, of litters observed of animals irradiated with 0.5, 1 and 2 Gy as compared to control unirradiated subgroup. The subgroup irradiated with 3 Gy developed no fetuses and they presented at full term of pregnancy with uterine absorption sites or early arrest of embryonic development.

The **number of absorption sites** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the number of absorption sites showed very highly significant increase for the 2 and 3 Gy irradiated subgroups as compared to the controls.

The **number of litters** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls, while the it showed highly significant decrease for the 2 Gy irradiated subgroup and very highly significant decrease for the 3 Gy irradiated subgroup compared to the controls.

The mean **fetal size** showed no significant change for the 0.5 and 1 Gy irradiated subgroups compared to controls. On the other hand, the size showed highly significant decrease for the 2 Gy irradiated subgroup as compared to controls.

The mean **fetal weight** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. however, the weight showed highly significant decrease for the 2 Gy irradiated subgroup compared to controls.

The **lateral body length** showed no significant change for the 0.5 and 1 Gy irradiated subgroups compared to controls. On the other hand, the lateral body length was significantly decreased for the 2 Gy irradiated subgroup compared to controls.

The **girth at umbilicus** showed no significant change for the 0.5 and 1 Gy irradiated subgroups compared to controls. On the other hand, the girth at umbilicus was significantly decreased for the 2 Gy irradiated subgroup as compared to controls.

The **tail length** showed no significant change for the 0.5 and 1 Gy irradiated subgroups compared to controls. On the other hand, the tail length was significantly decreased for the 2 Gy irradiated subgroup as compared to controls.

The **antro-posterior dimensions of skull** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the skull (A-P) was significantly decreased for the 2 Gy irradiated subgroup as compared to controls.

The **biparietal dimensions of skull** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the Skull (BP) was significantly decreased for the 2 Gy irradiated subgroup as compared to controls.

Table (17) Shows Mean ± SE of Number of Absorption Sites, Number of Litters and Measurements (recorded at full term) for Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 9th Day of Gestation.

	Control Group	Irradiated Groups			
		0.5 Gy	1 Gy	2 Gy	3 Gy
Number of absorption sites	0.40 ± 0.22	1.00 ± 0.00	1.20 ± 0.44	5.20 ± 0.59***	7.20 ± 0.52***
t – test		non significant	non significant	t=2.02 p<0.001	t=2.02 p<0.0001
Number of litters	6.80 ± 0.44	6.60 ± 0.46	6.40 ± 0.61	1.40 ± 0.88**	No fetuses
t-test		non significant	non significant	t =1.94 p<0.01	
Measurements					
➢ Size (ml)	4.02 ± 0.22	4.00 ± 0.27	3.00 ± 0.05	1.05 ± 0.58**	
t.test		non significant	non significant	t =2.02 p<0.01	
➢ Weight (gm)	4.05 ± 0.23	4.03 ± 0.19	2.96 ± 0.09	0.97 ± 0.53**	
t.test		non significant	non significant	t =2.02 p<0.01	
➢ Lat. body length (mm)	34.36 ± 0.70	33.74 ± 0.46	32.61 ± 0.55	12.39 ± 6.79*	
t.test		non significant	non significant	t =2.13p<0.05	
➢ Girth (circum.) (mm)	41.58 ± 1.09	41.14 ± 1.04	40.42 ± 1.11	14.84 ± 8.14*	
t-test		non significant	non significant	t=2.13 p<0.05	
➢ Tail length (mm)	13.81 ± 0.33	13.12 ± 0.50	11.83 ± 0.39	4.24 ± 2.39*	
t.test		non significant	non significant	t=2.13 p<0.05	
➢ Skull (A-P) (mm)	15.86 ± 0.21	15.39 ± 0.25	15.23 ± 0.38	5.97 ± 3.29*	
t.test		non significant	non significant	t=2.13 p<0.05	
➢ Skull (BP) (mm)	10.48 ± 0.13	10.17 ± 0.29	9.79 ± 0.09	3.58 ± 1.96*	
t.test		non significant	non significant	t=2.13 p<0.05	

p>0.05 non significant *p<0.05 significant **p<0.01 highly significant ***p<0.001 very highly significant

4.2.2.2.Comparative Collective Results of Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 12th Day of Gestation.

The data in table (18) presents the number of absorption sites (mean ± SE) and the number of litters (mean ± SE) for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 12th day of gestation. It also presents the mean dimensions ± SE, of litters observed of animals irradiated with 0.5, 1, 2 and 3 Gy compared to the control unirradiated subgroup.

The **number of absorption sites** showed no significant change for the 0.5, 1 and 2 Gy irradiated subgroups as compared to controls. On the other hand, the number of absorption sites showed highly significant increase for the 3 Gy irradiated subgroup as compared to controls.

The **number of litters** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. While, the number of litters was significantly decreased for the 2 Gy irradiated subgroup and very highly significantly decreased for the 3 Gy irradiated subgroup compared to controls.

The mean **fetal size** showed no significant change for the 0.5 Gy irradiated subgroup compared to controls. On the other hand, the size showed significantly decrease for the 1 Gy irradiated subgroup, very highly significant decrease for the 2 Gy irradiated subgroup and highly significant decrease for the 3 Gy irradiated subgroup compared to controls.

The mean **fetal weight** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. However, the weight showed highly significant decrease for the 2 Gy irradiated subgroup and very highly significant decrease for the 3 Gy irradiated subgroup compared to controls.

The **lateral body length** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the lateral body length showed very highly significant decrease for the 2 Gy irradiated subgroup and significant decrease for the 3 Gy irradiated subgroup as compared to controls.

The **girth at umbilicus** showed no significant change for the 0.5 and 1 Gy irradiated subgroups compared to controls. On the other hand, the girth at umbilicus showed highly significant decrease for the 2 Gy irradiated subgroup and significant decrease for the 3 Gy irradiated subgroup as compared to controls.

The **tail length** showed no significant change for the 0.5 Gy irradiated subgroup as compared to controls. On the other hand, the tail length showed significant decrease for the 1 Gy irradiated subgroup, highly significant decrease for the 2 Gy irradiated subgroup and very highly significant decrease for the 3 Gy irradiated subgroup compared to controls.

The **antro-posterior dimensions of skull** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the skull (A-P) showed highly significant decrease for the 2 Gy irradiated subgroup and significant decrease for the 3 Gy irradiated subgroup compared to controls.

The **biparietal dimensions of skull** showed no significant change for the 0.5 Gy irradiated subgroup as compared to controls. On the other hand, the Skull (BP) was significantly decreased for the 1 Gy, 2 Gy and 3 Gy irradiated subgroups animals as compared to controls.

Table (18) Shows Mean ± SE of Number of Absorption Sites, Number of Litters and Measurements (recorded at full term) for Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 12th Day of Gestation.

	Control Group	Irradiated Groups			
		0.5 Gy	1 Gy	2 Gy	3 Gy
Number of absorption sites	0.40 ± 0.22	0.60 ± 0.54	1.00 ± 0.28	2.40 ± 1.00	6.40 ± 1.12**
t.test		non significant	non significant	non significant	t=2.13 p<0.01
Number of litters	7.40 ± 0.78	7.20 ± 1.31	7.00 ± 0.57	4.60 ± 0.83?	1.20 ± 0.52***
t.test		non significant	non significant	t=1.86 p<0.05	t=1.89 p<0.001
Measurements					
➢ Size (ml)	4.06 ± 0.20	4.04 ± 0.19	3.24 ± 0.19*	2.69 ± 0.16***	1.20 + 0.46**
t.test		non significant	t=1.86 p<0.05	t=1.86 p<0.001	t=2.02 p<0.01
➢ Weight (gm)	4.11 ± 0.24	4.09 ± 0.19	3.40 ± 0.28	2.56 ± 0.27**	1.02 ±0.40***
t.test		non significant	non significant	t=1.86 p<0.01	t=1.89 p<0.001
➢ Lateral body length (mm)	34.37 ± 0.71	34.10 ± 0.33	32.51 ± 0.72	24.44 ± 0.59***	16.15 ± 5.96*
t.test		non significant	non significant	t=1.86 p<0.001	t =2.13 p<0.05
➢ Girth (circum.) (mm)	42.18 ± 1.04	41.92 ± 0.21	40.99 ± 1.03	30.55 ± 1.42**	22.04 ± 8.05*
t-test		non significant	non significant	t=1.89 p<0.001	t =2.13 p<0.05
➢ Tail length (mm)	14.38 ± 0.49	14.06 ± 0.97	12.56 ± 0.47*	10.80 ± 0.61**	2.51 ± 0.94***
t.test		non significant	t =1.86.p<0.05	t=1.86 p<0.01	t=1.94.p<0.001
➢ Skull (A-P) (mm)	16.13 ± 0.27	15.45± 0.33	15.30 ± 0.31	11.88 ± 0.64**	6.42 ± 2.35*
t.test		non significant	non significant	t=2.02 p<0.01	t =2.13 p<0.05
➢ Skull (BP) (mm)	10.61 ± 0.14	10.24±0.40	9.83±0.26*	8.11 ± 0.76*	4.87 ± 1.79*
t.test		non significant	t=1.94 p<0.05	t=2.13 p<0.05	t =2.13 p<0.05

p>0.05 non significant * p<0.05 significant ** p<0.01 highly significant *** p<0.001 very highly significant

4.2.2.3.Comparative Collective Results of Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 15th Day of Gestation.

The data in table (19) presents the number of absorption sites (mean ± SE) and the number of litters (mean ± SE) for the control and 0.5, 1, 2 and 3 Gy irradiated subgroups on 15th day of gestation. It also presents the mean dimensions ± SE of litters observed of animals irradiated with 0.5, 1, 2 and 3 Gy compared to the control unirradiated subgroup.

The **number of absorption sites** showed no significant change for the 0.5 and 1 Gy irradiated subgroups as compared to controls. On the other hand, the number of absorption sites showed highly significant increase for the 2 Gy irradiated subgroup and significant increase for the 3 Gy irradiated subgroup compared to controls.

The **number of litters** showed no significant change for the 0.5, 1 and 2 Gy irradiated subgroups as compared to controls while, the number of litters was significantly decreased for the 3 Gy irradiated subgroup compared to controls.

The mean **fetal size** showed no significant change for the 0.5 and 2 Gy irradiated subgroups compared to controls. On the other hand, the size showed very highly significant decrease for the 1 Gy irradiated subgroup and significant decrease for the 3 Gy irradiated subgroup as compared to controls.

The mean **fetal weight** showed no significant change for the 0.5 and 2 Gy irradiated subgroups as compared to controls. However, the weight showed highly significant decrease for the 1 Gy irradiated subgroup and significant decrease for the 3 Gy irradiated subgroup compared to controls.

The **lateral body length** showed no significant change for the 0.5, 1, 2 and 3 Gy irradiated subgroups as compared to controls.

The **girth at umbilicus** showed no significant change for the 0.5, 1, 2 and 3 Gy irradiated subgroups as compared to controls.

The **tail length** showed no significant change for the 0.5 and 2 Gy irradiated subgroups compared to controls. On the other hand, the tail length showed highly significant decrease for the 1 Gy irradiated subgroup, significant decrease for the 3 Gy irradiated subgroup compared to controls.

The **antro-posterior dimensions of skull** showed no significant change for the 0.5,1, 2 and 3 Gy irradiated subgroups as compared to controls.

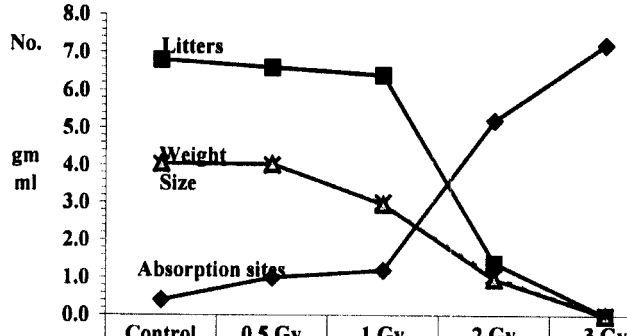
The **biparietal dimensions of skull** showed no significant change for the 0.5, 2 and 3 Gy irradiated subgroups as compared to controls. On the other hand, the skull (BP) showed highly significant decrease for the 1 Gy irradiated subgroup compared to controls.

Table (19) Mean ± SE of Number of Absorption Sites, Number of Litters and Measurements (recorded at full term) for Control and 0.5, 1, 2 and 3 Gy Subgroups Irradiated on 15th Day of Gestation.

	Control Group	Irradiated Groups			
		0.5 Gy	1 Gy	2 Gy	3 Gy
Number of absorption sites	0.60 ± 0.22	0.40 ± 0.36	0.60 ± 0.36	2.20 ± 0.33**	3.00 ± 0.63*
t-test		non significant	non significant	t=1.89 p<0.01	t=2.02 p<0.05
Number of litters	7.80 ± 0.72	7.80 ± 0.66	7.60 ± 0.67	5.40 ± 1.40	3.40 ± 1.25*
t-test		non significant	non significant	non significant	t=1.94 p<0.05
Measurements					
➢ Size (ml)	4.56 ± 0.16	4.39 ± 0.05	3.40 ± 0.12***	3.02 ± 0.68	1.91 ± 0.71*
t.test		non significant	t=1.89 p<0.001	non significant	t=2.13 p<0.05
➢ Weight (gm)	4.25 ± 0.16	4.25 ± 0.08	3.57± 0.10**	3.06 ± 0.69	2.05 ± 0.75*
t.test		non significant	t=1.89 p<0.01	non significant	t=2.13 p<0.05
➢ Lateral body length (mm)	35.38 ± 1.09	35.19 ± 0.61	33.67 ± 0.98	26.60 ± 5.95	19.89 ± 7.27
t.test		non significant	non significant	non significant	non significant
➢ Girth (circum.) (mm)	42.78 ± 0.87	42.43 ± 0.24	41.18 ± 0.88	34.06 ± 7.62	23.66 ± 8.66
t-test		non significant	non significant	non significant	non significant
➢ Tail length (mm)	14.58 ± 0.35	14.27 ± 0.58	12.93±0.31**	11.00 ± 2.51	7.17 ± 2.65*
t.test		non significant	t=1.89 p<0.01	non significant	t=2.13 p<0.05
➢ Skull (A-P) (mm)	16.22 ± 0.29	16.14 ± 0.08	15.73 ± 0.22	12.95 ± 2.91	9.39 ± 3.43
t.test		non significant	non significant	non significant	non significant
➢ Skull (BP) (mm)	10.70 ± 0.09	10.60 ± 0.07	9.76 ± 0.15**	8.62 ± 1.93	5.80 ± 2.12
t.test		non significant	t=1.89 p<0.01	non significant	Non significant

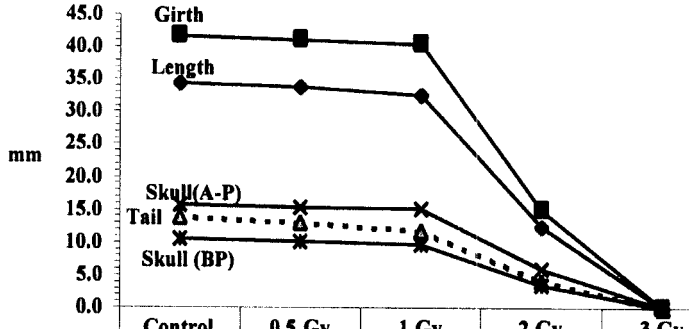
p>0.05 non significant * p<0.05 significant **p<0.01 highly significant *** p<0.001 very highly significant

The following figures (1-6) present curves and tables that illustrate number of absorption sites, number of litters and measurements of size, weight, lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for the litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9^{th} day of gestation (figures 1-2), 12^{th} day of gestation (figures 3-4) and 15^{th} day of gestation (figures 5-6).



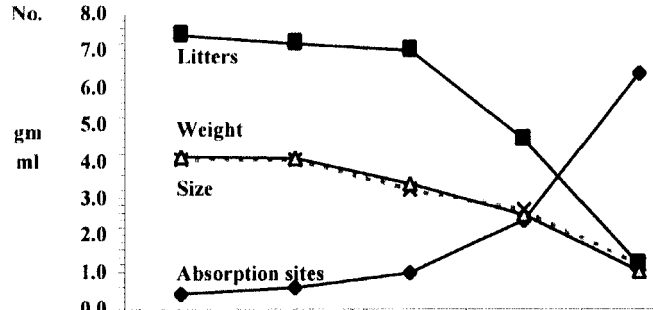
	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Absorption sites	0.40	1.00	1.20	5.20	7.20
No. of litters	6.80	6.60	6.40	1.40	0.00
Size ml	4.02	4.00	3.00	1.05	0.00
Weight gm	4.05	4.03	2.96	0.97	0.00

Figure (1) Shows variations in number of absorption sites, number of litters and measurements of weight and size for litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th day of gestation.



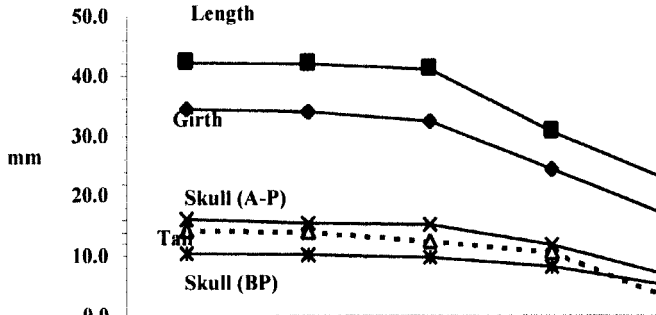
	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Length mm	34.36	33.74	32.61	12.39	0.00
Girth mm	41.58	41.14	40.42	14.84	0.00
Tail length mm	13.81	13.12	11.83	4.24	0.00
Skull(A-P) mm	15.86	15.39	15.23	5.97	0.00
Skull(BP) mm	10.48	10.17	9.79	3.58	0.00

Figure (2) Shows variations in measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of control and o.5, 1, 2 and 3 Gy subgroups irradiated on 9th day of gestation.



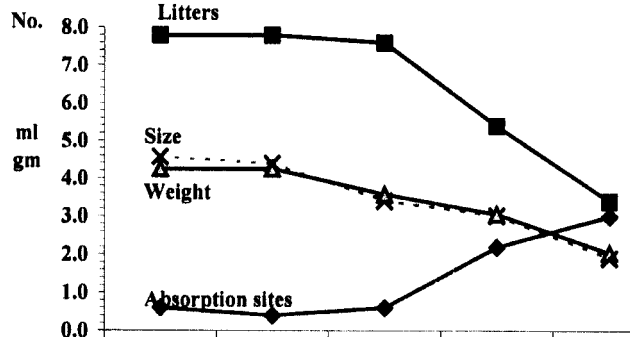
	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Absorption sites	0.40	0.60	1.00	2.40	6.40
No. of litters	7.40	7.20	7.00	4.60	1.20
Size ml	4.06	4.04	3.24	2.69	1.20
Weight gm	4.11	4.09	3.40	2.56	1.02

Figure (3) Shows variations in number of absorption sites, number of litters and measurements of weight and size for litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 12th day of gestation.



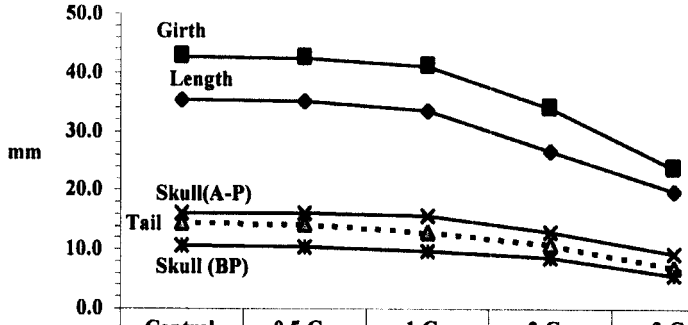
	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Length mm	34.37	34.10	32.51	24.44	16.15
Girth mm	42.18	41.92	40.99	30.55	22.04
Tail length mm	14.38	14.06	12.56	10.80	2.51
Skull(A-P) mm	16.13	15.45	15.30	11.88	6.42
Skull(BP) mm	10.61	10.24	9.83	8.11	4.87

Figure (4) Shows variations in measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 12th day of gestation.



	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Absorption sites	0.60	0.40	0.60	2.20	3.00
No. of litters	7.80	7.80	7.60	5.40	3.40
Size ml	4.56	4.39	3.40	3.02	1.91
Weight gm	4.25	4.25	3.57	3.06	2.05

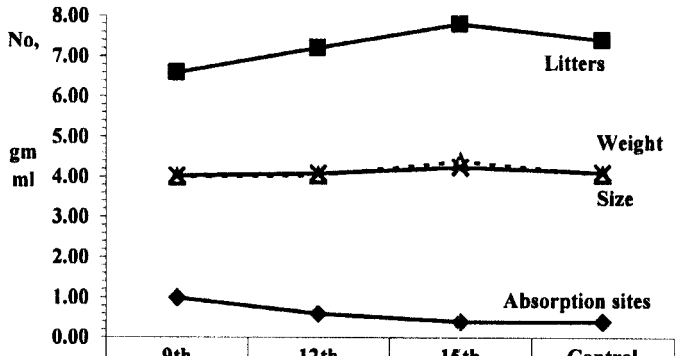
Figure (5) Shows variations in number of absorption sites, number of litters and measurements of weight and size for litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 15h day of gestation.



	Control	0.5 Gy	1 Gy	2 Gy	3 Gy
Length mm	35.38	35.19	33.67	26.60	19.89
Girth mm	42.78	42.43	41.18	34.06	23.66
Tail length mm	14.58	14.27	12.93	11.00	7.17
Skull(A-P) mm	16.22	16.14	15.73	12.95	9.39
Skull(BP) mm	10.70	10.60	9.76	8.62	5.80

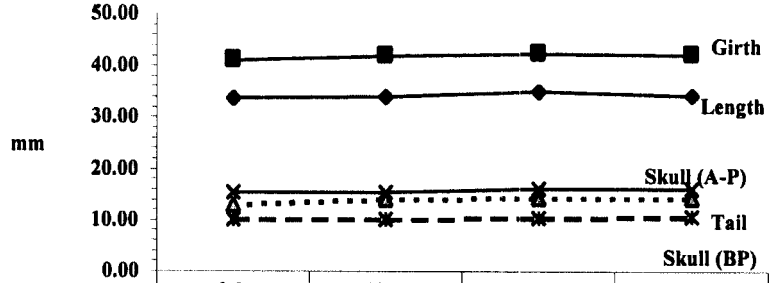
Figure (6) Shows variations in measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 15th day of gestation.

The following figures (7– 14) present curves and tables that illustrate number of absorption sites, number of litters and measurements of size, weight, lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for the litters of animals irradiated on 9th, 12th and 15th days of gestation with individual doses 0.5 Gy (figures7-8), 1 Gy (figures 9-10), 2 Gy (figures 11-12) and 3 Gy (figures 13-14). Data of control subgroups is also indicated.



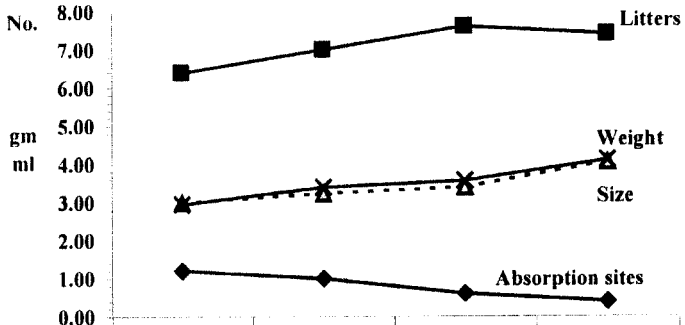
	9th	12th	15th	Control
Absorption sites	1.00	0.60	0.40	0.40
No. of litters	6.60	7.20	7.80	7.40
Size ml	4.00	4.04	4.39	4.06
Weight gm	4.03	4.09	4.25	4.11

Figure (7) shows numbers of absorption sites, litters and measurements of size and weight for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose of 0.5 Gy. Control data is also indicated.



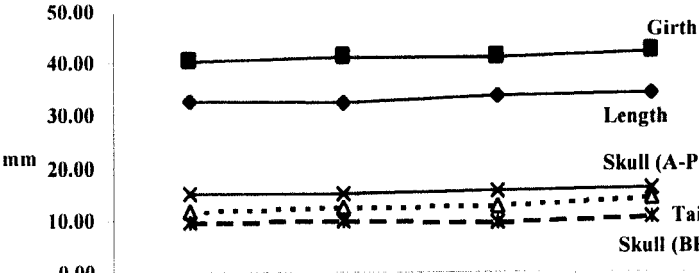
	9th	12th	15th	Control
Length mm	33.74	34.10	35.19	34.37
Girth mm	41.14	41.92	42.43	42.18
Tail length mm	13.12	14.06	14.27	14.38
Skull(A-P) mm	15.39	15.45	16.14	16.13
Skull(BP) mm	10.17	10.24	10.60	10.61

Figure(8) shows measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose 0.5 Gy. Control data is also indicated.



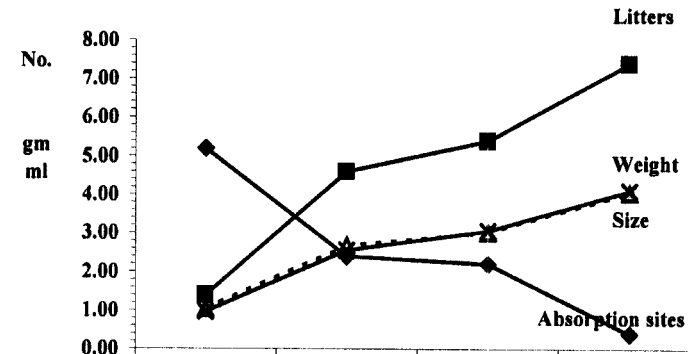
	9th	12th	15th	Control
Absorption sites	1.20	1.00	0.60	0.40
No. of litters	6.40	7.00	7.60	7.40
Size ml	3.00	3.24	3.40	4.06
Weight gm	2.96	3.40	3.57	4.11

Figure (9) shows numbers of absorption sites, litters and measurements of size and weight for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose of 1 Gy. Control data is also indicated.



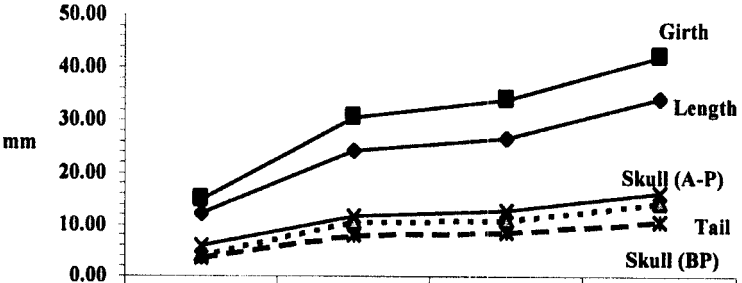
	9th	12th	15th	Control
Length mm	32.61	32.51	33.67	34.37
Girth mm	40.42	40.99	41.18	42.18
Tail length mm	11.83	12.56	12.93	14.38
Skull(A-P) mm	15.23	15.30	15.73	16.13
Skull(BP) mm	9.79	9.83	9.76	10.61

Figure (10) shows measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose 1 Gy. Control data is also indicated.



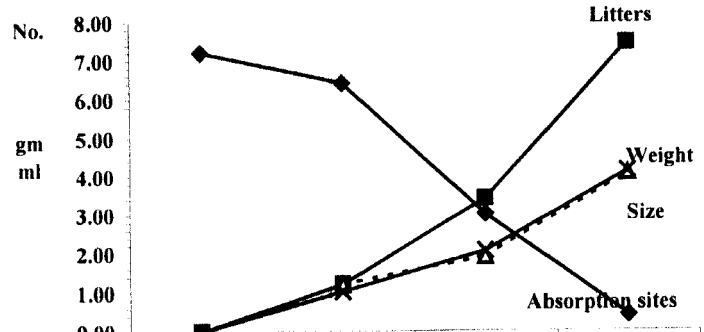
	9th	12th	15th	Control
Absorption sites	5.20	2.40	2.20	0.40
No. of litters	1.40	4.60	5.40	7.40
Size ml	1.05	2.69	3.02	4.06
Weight gm	0.97	2.56	3.06	4.11

Figure (11) shows numbers of absorption sites, litters and measurements of size and weight for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose of 2 Gy. Control data is also indicated.



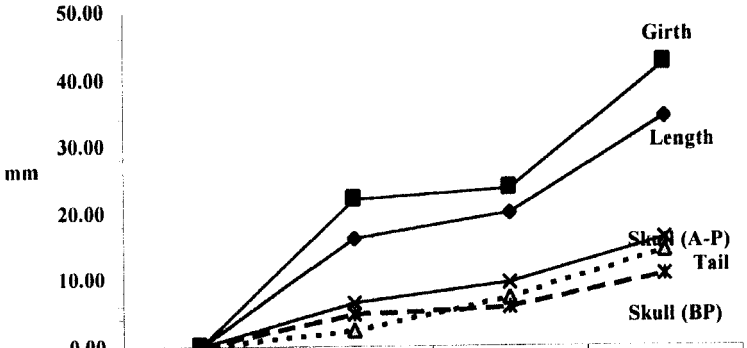
	9th	12th	15th	Control
Length mm	12.39	24.44	26.60	34.37
Girth mm	14.84	30.55	34.06	42.18
Tail length mm	4.24	10.80	11.00	14.38
Skull(A-P) mm	5.97	11.88	12.95	16.13
Skull(BP) mm	3.58	8.11	8.62	10.61

Figure (12) shows measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose 2 Gy. Control data is also indicated.



	9th	12th	15th	Control
Absorption sites	7.20	6.40	3.00	0.40
No. of litters	0.00	1.20	3.40	7.40
Size ml	0.00	1.20	1.91	4.06
Weight gm	0.00	1.02	2.05	4.11

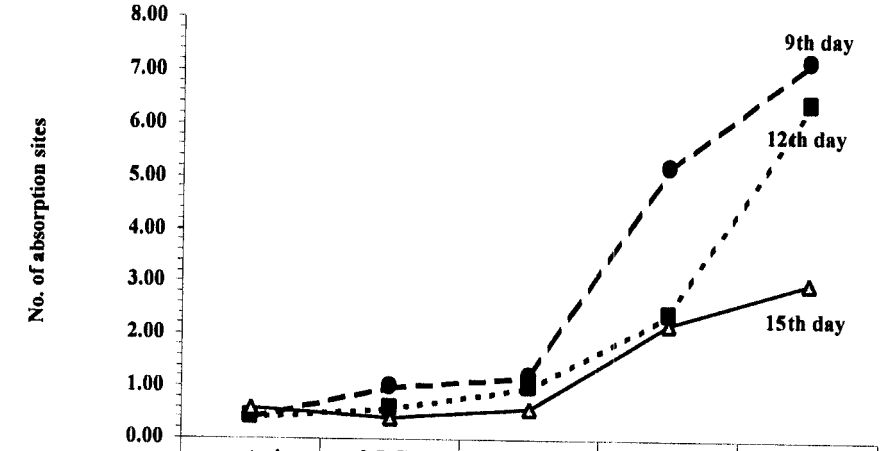
Figure (13) shows numbers of absorption sites, litters and measurements of size and weight for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose of 3 Gy. Control data is also indicated.



	9th	12th	15th	Control
Length mm	0.00	16.15	19.89	34.37
Girth mm	0.00	22.04	23.66	42.18
Tail length mm	0.00	2.51	7.17	14.38
Skull(A-P) mm	0.00	6.42	9.39	16.13
Skull(BP) mm	0.00	4.87	5.80	10.61

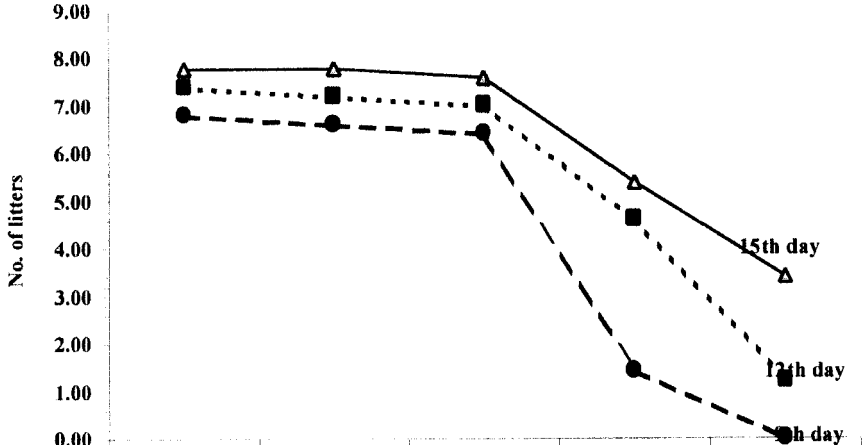
Figure (14) shows measurements of lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull for litters of subgroups irradiated on 9th, 12th and 15th day of gestation for a dose 3 Gy. Control data is also indicated.

The following figures (15-23) show the changes induced in each of the parameters studied (number of absorption sites (figure 15), number of litters (figure 16) and measurements of size (figure 17), weight (figure 18), lateral body length (figure 19), circumference girth at umbilicus (figure 20), tail length (figure 21) and dimensions of skull antro-posterior (figure 22) and biparietal (figure 23); as related to the control and subgroups irradiated with 0.5, 1, 2 and 3 Gy on 9th, 12th and 15th days of gestation.



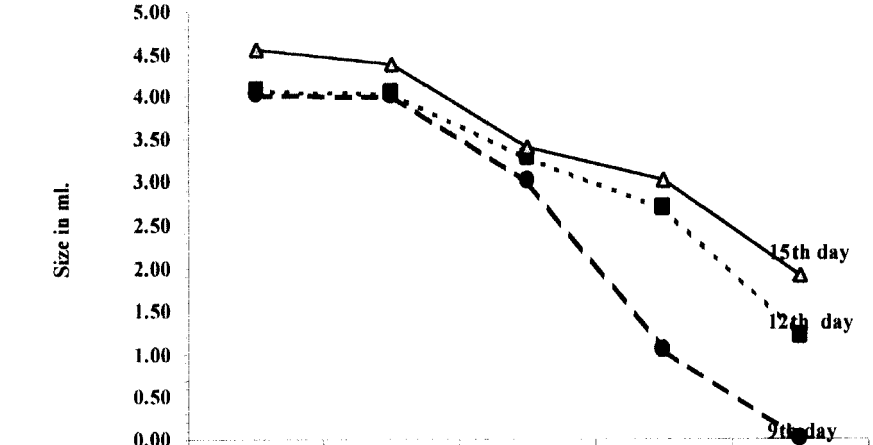
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	0.40	1.00	1.20	5.20	7.20
12th day	0.40	0.60	1.00	2.40	6.40
15th day	0.60	0.40	0.60	2.20	3.00

Figure (15) Shows number of absorption sites for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



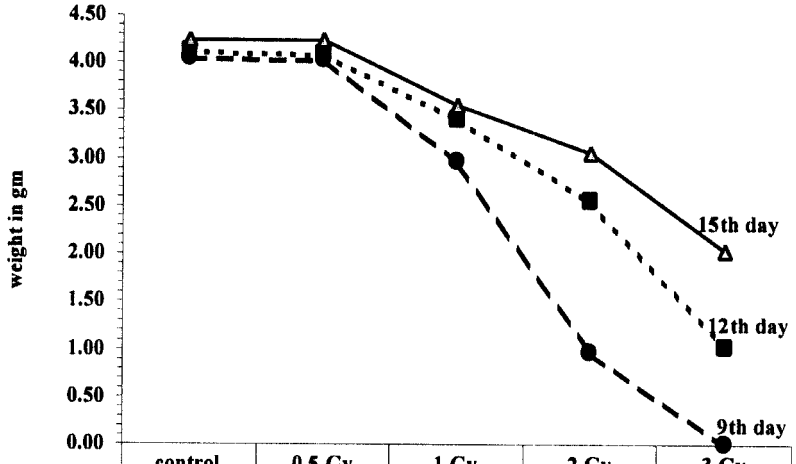
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	6.80	6.60	6.40	1.40	0.00
12th day	7.40	7.20	7.00	4.60	1.20
15th day	7.80	7.80	7.60	5.40	3.40

Figure (16) Shows number of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



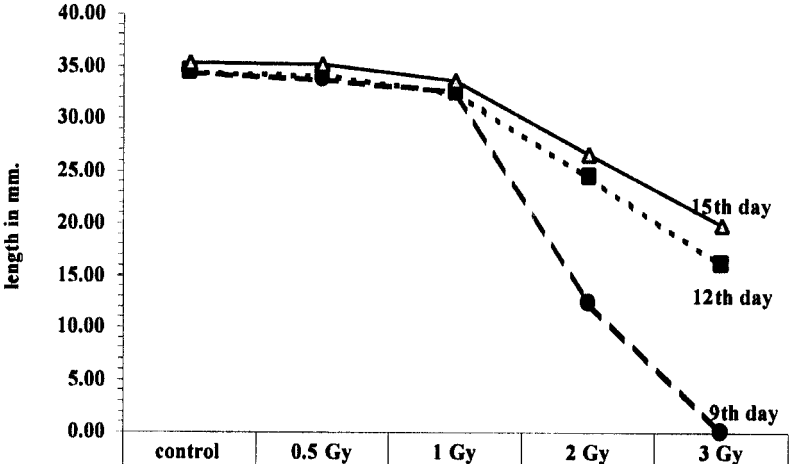
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	4.02	4.00	3.00	1.05	0.00
12th day	4.06	4.04	3.27	2.69	1.20
15th day	4.56	4.39	3.40	3.02	1.91

Figure (17) Shows data for size of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



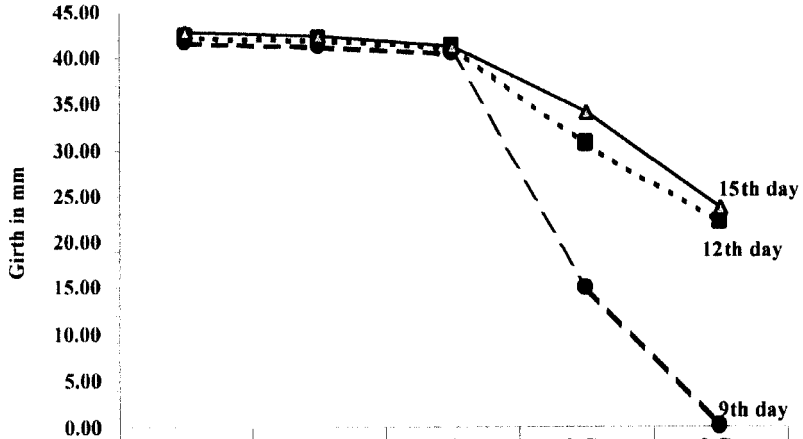
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	4.05	4.03	2.96	0.97	0.00
12th day	4.11	4.09	3.40	2.56	1.02
15th day	4.25	4.25	3.57	3.06	2.05

Figure (18) Shows data for weight of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



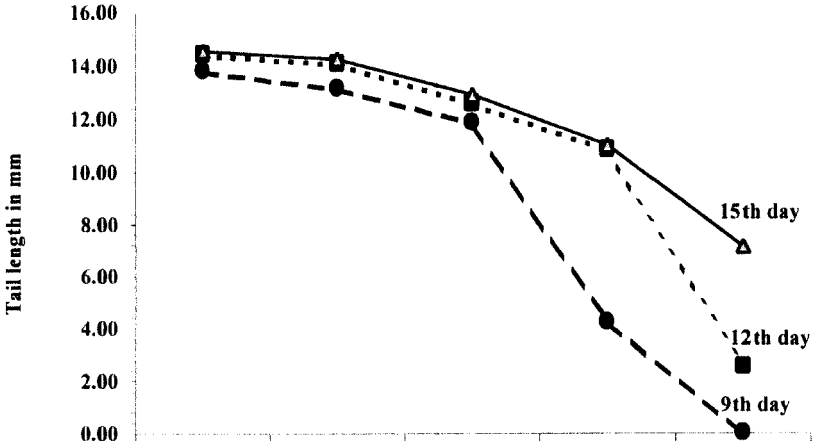
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	34.36	33.74	32.61	12.39	0.00
12th day	34.37	34.10	32.51	24.44	16.15
15th day	35.38	35.19	33.67	26.60	19.89

Figure (19) Shows data for lateral body length of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



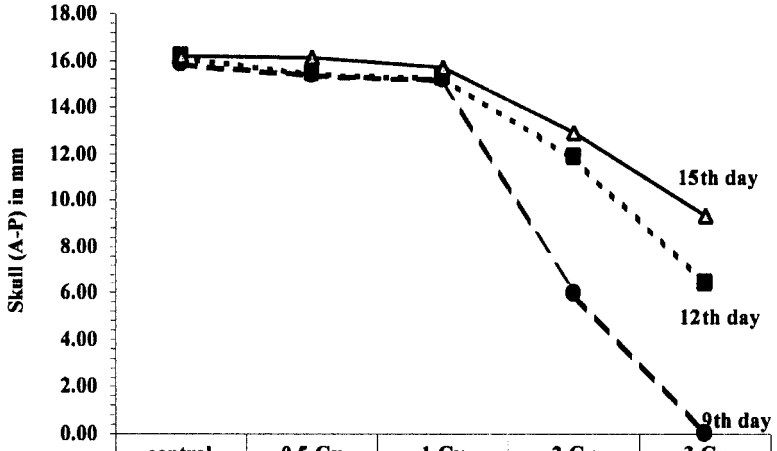
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	41.58	41.14	40.42	14.84	0.00
12th day	42.18	41.92	40.99	30.55	22.04
15th day	42.78	42.43	41.18	34.06	23.66

Figure (20) Shows data for <u>circumference girth at umbilicus</u> of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



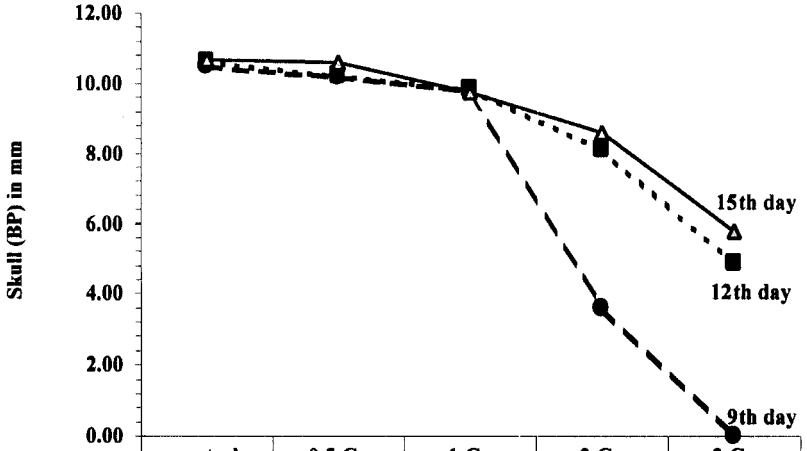
	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	13.81	13.12	11.83	4.24	0.00
12th day	14.38	14.06	12.56	10.80	2.51
15th day	14.58	14.27	12.93	11.00	7.17

Figure (21) Shows data for <u>tail length</u> of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	15.86	15.39	15.23	5.97	0.00
12th day	16.13	15.45	15.30	11.88	6.42
15th day	16.22	16.14	15.73	12.95	9.39

Figure (22) Shows data for antro-posterior dimensions of skull of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.



	control	0.5 Gy	1 Gy	2 Gy	3 Gy
9th day	10.48	10.17	9.79	3.58	0.00
12th day	10.61	10.24	9.83	8.11	4.87
15th day	10.70	10.60	9.76	8.62	5.80

Figure (23) Shows data for biparietal dimensions of skull of litters for the control and 0.5, 1, 2 and 3 Gy subgroups irradiated on 9th, 12th and 15th days of gestation.

The illustrative curves presented in figures (1-23) were modeled for the purpose of portraying distinctly the effect of radiation on each of the various parameters studied as related to the radiation doses used and the different periods of gestation at which irradiation took place.

The data presented in figures (1-6) indicate the changes that occurred in the various parameters according to days of gestation 9, 12 and 15, as related radiation dose.

The data presented in figures (7-14) indicate the changes that occurred in the various parameters according to doses of irradiation 0.5, 1, 2 and 3 Gy, as related to day of gestation.

The data presented in figures (15-23) is the collective data of the changes induced in each parameter studied as related to radiation dose and date of gestation. The data appearing in these figures (15-23) will be used as the ground material for the interpretation and discussion of the results of the morphological studies.

PART 2 OF RESULTS

4.3. Congenital Anomalies.

Special attention was given to the detection of congenital malformations during the observation and recording of data for the litters born to mothers of the irradiated subgroups. All data procured for the malformations observed were compared to litters from control unirradiated mothers. The following plates present some congenital malformations that were detected. These malformations include decrease in length, litters with no tail, no eye fissures, very small litters, haemencephalocele, penguin shaped litters, cranial hemorrhage, very small limbs and tails, very small ears, absorption sites and congested litters.

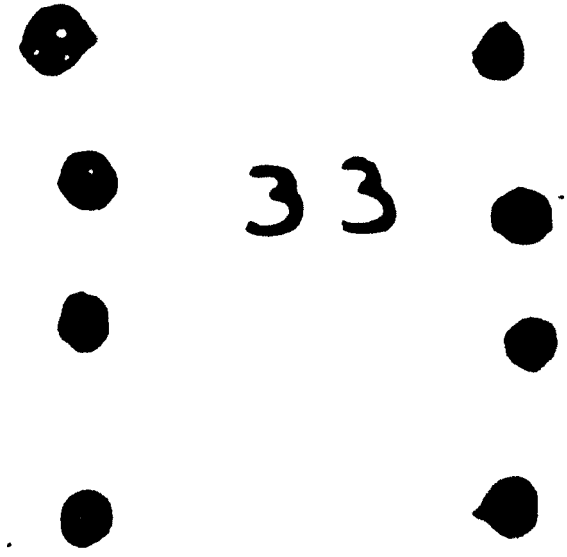


Plate (2) shows 8 of 11 absorption sites from a mother exposed to 3 Gy on 12th day of gestation. (Magnification of 1:1).

Plate (3) shows viable litters from an unirradiated control mother. The average length of a control litter is 35 mm (at birth). (Magnification of 1:1).

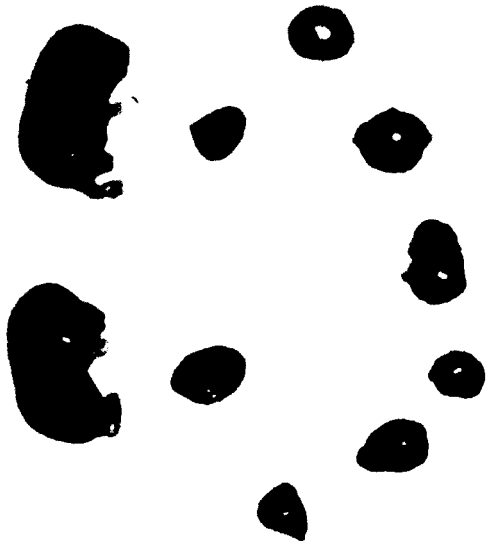


Plate (4) shows two small viable litters, (20 mm length) (at birth) from a mother exposed to 2 Gy on 9th day of gestation. The litters shown have no tail. The uterus included several absorption sites. (Magnification of 1:1).

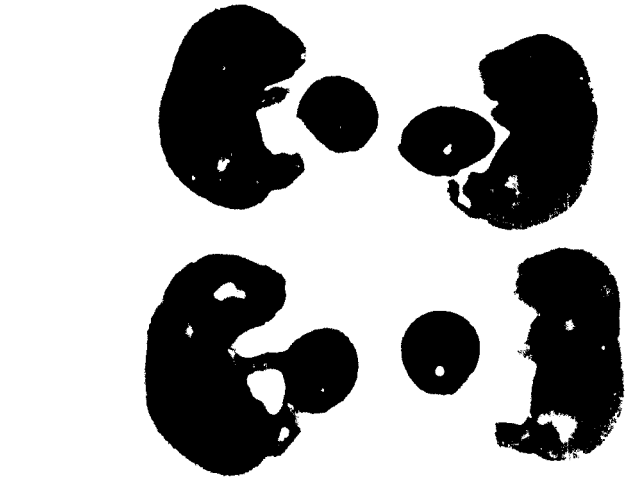


Plate (5) shows four small viable litters (23 mm at birth) from a mother exposed to 2 Gy on 9th day of gestation. The litters have no eye fissures. (Magnification of 1.3:1).

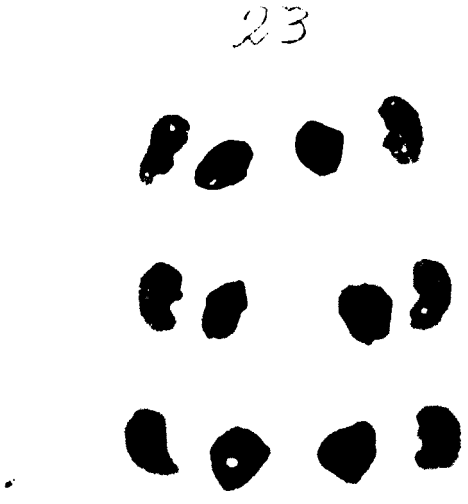


Plate (6) shows six nonviable litters from a mother exposed to 2 Gy on 12th day of gestation. They are nonviable very small litters (about 13 mm length). The litters present no features. (Magnification of 1:1).

Plate (7) 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 (8) 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 (9) 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).

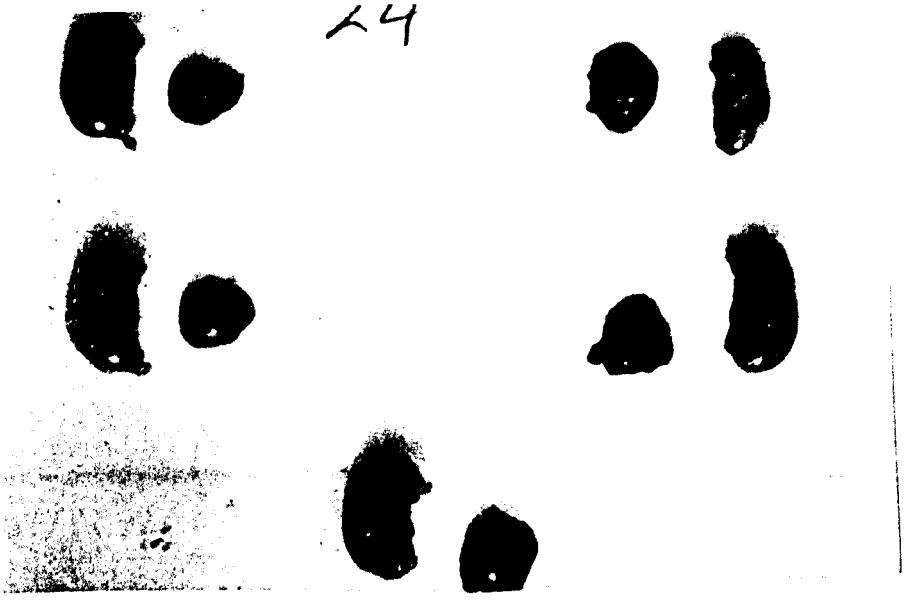


Plate (10) shows five viable litter from a mother exposed to 3 Gy on 12th day of gestation. they are penguin shaped abnormal litters. They have very small limbs, tails and ears. The occipital region of the skull of these litters present dark blood coloration which appears as a blood collection inside the skull. (Magnification of 1: 1).

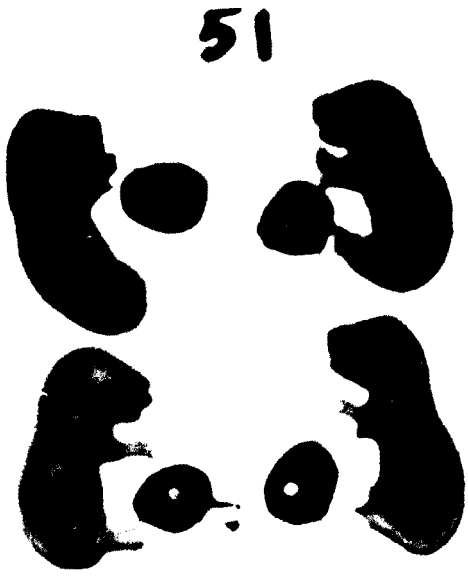


Plate (11) shows 4 of 9 viable litters from a mother exposed to 1 Gy on 15th day of gestation. All the litters have no eye fissures. (Magnification of 1:1.2).

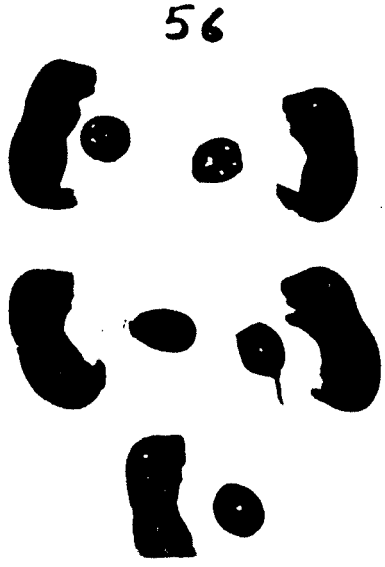


Plate (12) shows 5 of 9 normal viable litters from a mother exposed to 1 Gy on 15th day of gestation. They have no eye fissures. One of the litters has only one eye. (Magnification of 1:1.5).

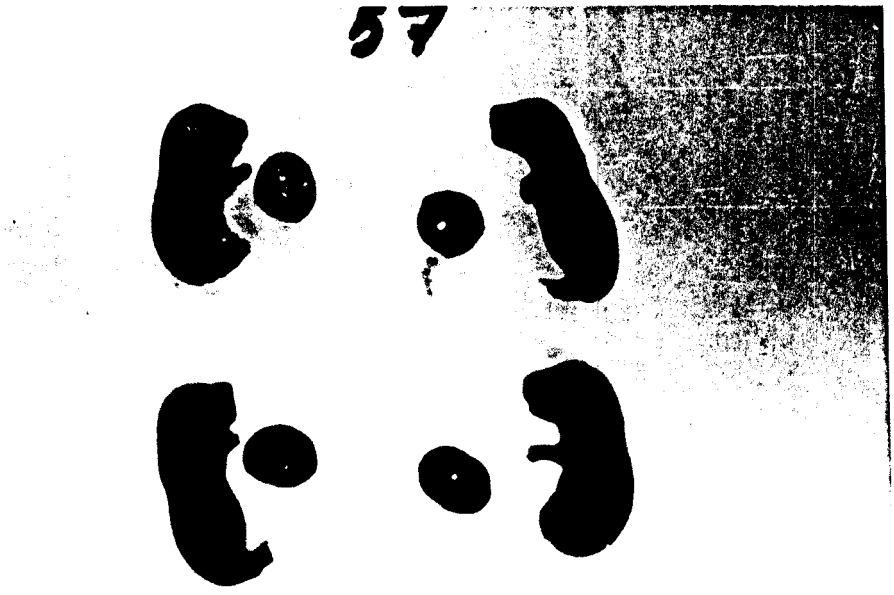


Plate (13) shows 4 of 7 litters from a mother exposed to 1 Gy on 15th day of gestation. They are viable litters have no eye fissures. Three of the litters are congested. (Magnification of 1:1.4).

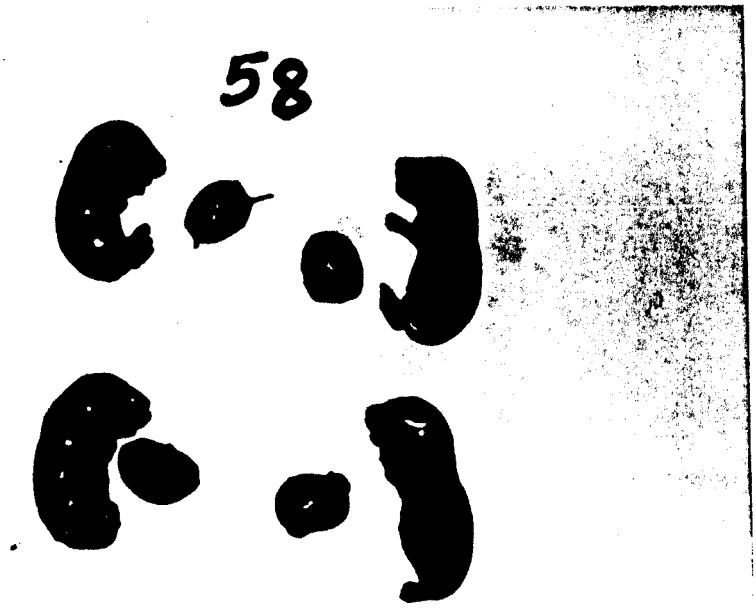


Plate (14) shows 4 of 8 litters from a mother exposed to 1 Gy on 15th day of gestation. They are viable litters have no eye fissures. (Magnification of 1:1.4).

PART 3 OF RESULTS

4.4.Results of Histopathological Studies.

4.4.1.Introductory.

This part deals with the results of histopathological studies of tissues collected from litters of control and irradiated animals. The tissues chosen were the heart, lung, liver, spleen, small and large intestine, thymus, kidney, suprarenal gland, skull, brain and meninges. The histopathological sections of these tissue specimens were examined and results were recorded.

Thirty six litters from irradiated subgroups and three from control subgroups were examined histopathologically in this thesis. The litters were chosen randomly, one from each irradiated mother. The number of litters represents all irradiated subgroups except the subgroup irradiated with 3 Gy on 9^{th} day of gestation which had no litters. Therefore, the percentage plotted for the severity is for a total thirty six.

The data collected from observations on radiation induced histopathological alterations in tissues of litters were essentially based on arbitrary scores given according to the severity of lesions observed. The variations in cellular response of tissues to the same radiation dose and the same period of gestation, is postulated to have multifactorial attributes. Therefore, there was no defined unit used for measurement. In distinction to the data given in part 1 and 2 of the results where actual measurements were performed using defined units of size, weight and length. The tables showed statistical analysis and the curves showed a definite dose effect relationship as related to the various periods of gestation.

The organs that revealed pathological changes were the liver, ileum, kidney, brain, spleen, suprarenal, thymus, lungs, and heart. These tissues

showed variable degrees of radiation induced histopathological tissue changes. For quantifying these changes, arbitrary scores were formulated to differentiate between the type and severity of the changes induced by the various radiation doses used.

The arbitrary scores were designated subject to the pathological findings observed in each tissue examined. In the following presentations, the arbitrary scores for the pathological changes of each tissue are given.

A histogram was constructed to indicate the numbers of specimens presenting with histopathological changes for the various tissues affected with different degrees by irradiation (page 147). Three tissues namely large intestine, pancreas and bone were not affected and therefore excluded from the histogram.

Liver.

- No degeneration scores 0.
- Mild degeneration scores 1.
- Moderate degeneration scores 2.
- Severe degeneration with focal necrosis scores 3.
- Severe degeneration with hepatocellular necrosis scores 4.

Ileum (small intestine).

- No degeneration scores 0.
- Focal mucosal degeneration (part of the circumference) scores 1.
- Mucosal degeneration for whole mucosal circumference scores 2.
- Affection of layers other than mucosa scores 3.
- Necrotic changes whether focally small or extensive scores 4.

Kidney.

- No degeneration scores 0.
- Mild tubular degeneration scores 1.
- Severe tubular degeneration scores 2.
- Tubular and glomerular degeneration scores 3.
- Renal necrosis scores 4.

Brain.

- Absence of gliosis, edema, hydrocephalus scores 0.
- Gliosis, edema, hydrocephalus or congenital anomalies score 1.

Spleen.

- No lymphocytic depletion (normal spleen) scores 0.
- Lymphocytic depletion scores 1.

Suprarenal gland.

- Absence of degeneration, hypoplasia or hyperplasia scores 0.
- Degeneration or hypoplasia scores 1.

Thymus gland.

- No lymphocytic depletion (normal thymus) scores 0.
- Mild lymphocytic depletion scores 1.
- Severe lymphocytic depletion scores 2.

Lungs.

- Normal lung with no inflammation and no prominent alveolar lining cells (i.e. pneumocytes) scores 0.
- Inflammation or prominent alveolar lining cells (i.e. pneumocytes) scores 1.

Heart.

- Absence of swollen mural or valvular endothelium or other abnormalities scores 0.
- Swollen mural or valvular endothelium scores 1.

All the organs of litters demonstrating radiation induced changes after radiation exposure during intrauterine life were studied histopathologically with descriptive recordings and statistical formulations of severity and frequency. This was based on arbitrary formulations of score as indicated which identifies the extent of pathological change that occurred.

The organs that showed no pathological changes and were similar to the control specimens were the meninges, large intestine (plate 15), pancreas (plate 16) and bone (plate 17).

The following presentations provide observations on histological studies performed for tissue from litters of irradiated subgroups at all periods of gestation.

4.4.2.Liver

Table (20) shows the severity and frequency of the histopathological changes of the liver. These changes vary from mild to severe degeneration with added focal necrosis (scoring from 0 to 3). No case with severe degeneration with hepatocellular necrosis was observed. Plates 18-22 illustrate these findings. Degenerative liver changes was represented as vacuolar degeneration of the cytoplasm of different severities. Extra-medullary haemopoitic (EMH) elements are seen, this is a normal finding, the haemopoitic elements included erythroblastic cells, myeloblastic cells and the characteristic small multinucleated giant cells (Megakaryocytes) (plate 20). The severity, frequency and percent of histopathological changes indicate that 4 cases (11.1%) show no change (plates18 and 19), 7 cases (19.4%) show slight changes (plate 20), 13 cases (36.1%) show moderate changes (plate 21) and 12 cases (33.3%) show severe changes with focal necrosis (plate 22). This indicates that the total affected number with various severities was 32 cases (88.9%) and 4 cases (11.1%) were not affected. The collective data for the severity and frequency of the pathological alterations found in the liver are presented as follows.

Table (20) Severity and Frequency of Histopathologic Changes of Liver

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4	11.1%	4	11.1%
1	7	19.4%	32	88.9%
2	13	36.1%		
3	12	33.3%		

4.4.3.Ileum.

Table (21) shows the severity and frequency of the histopathological changes of the ileum. These changes vary from focal mucosal degeneration to extensive necrotic changes affecting all coats of the ileum (scoring from 0 to 4). Plates 23-27 illustrate these findings. The severity, frequency and percent of histopathological changes indicate that 12 cases (33.3%) show no change (plate 23), 7 cases (19.4%) show slight changes (plate 24), 5 cases (13.9%) show moderate changes (plate 25), 9 cases (25%) show severe changes (plate 26) and 3 case (8.3%) show very severe changes (plate 27). This indicates that the total affected number with various severities was 24 cases (66.7%) and 12 cases (33.3%) were not affected. The collective data for the severity and frequency of the pathological alterations found in the ileum are presented as follows.

Table (21) Severity and Frequency of Histopathologic Changes of Ileum.

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	12	33.3%	12	33.3%
1	7	19.4%	24	66.7%
2	5	13.9%		
3	9	25.0%		
4	3	8.3%		

4.4.4.Kidney.

Table (22) shows the severity and frequency of the histopathological changes of the kidney. These changes vary from mild tubular degeneration to severe renal necrosis (scoring from 0 to 4). Plates 28-31 illustrate these findings. Degenerative changes of the kidney are mainly seen in the parenchymal elements (the tubular epithelium), the mesenchymal elements (the glomeruli, interstitium and blood vessels) are affected to a much lesser degree. The severity, frequency and percent of histopathological changes indicate that 27 cases (75%) show no change (plate 28), 3 cases (8.3%) show slight changes (plate 29), 1 case (2.8%) shows moderate changes (plate 30), 4 cases (11.1%) show severe changes, and 1 case (2.8%) shows very severe changes (plate 31). This indicates that the total affected number with various severities was 9 cases (25%) and 27 cases (75%) were not affected. The collective data for the severity and frequency of the pathological alterations found in the kidney are presented as follows.

Table (22) Severity and Frequency of Histopathologic Changes of kidney.

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	27	75.0%	27	75.0%
1	3	8.3%	9	25.0%
2	1	2.8%		
3	4	11.1%		
4	1	2.8%		

4.4.5.Brain.

Table (23) shows the severity and frequency of the histopathological changes of the brain. These changes vary from presence or absence of

gliosis, edema and hydrocephalus (scoring from 0 to 1). Plates 32-35 illustrate these findings. The table indicates that 30 cases (83.3%) show no change (plates 32, 33) and 6 cases (16.7%) show slight changes (plates 34, 35). The collective data for the severity and frequency of the pathological alterations found in the brain are presented as follows.

Table (23) Severity and Frequency of Histopathologic Changes of Brain

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	30	83.3%	30	83.3%
1	6	16.7%	6	16.7%

4.4.6.Spleen.

Table (24) shows the severity and frequency of the histopathological changes of the spleen. These changes vary from presence or absence of lymphatic depletion (scoring from 0 to 1). Plates 36-38 illustrate these findings. Lymphocytic depletion is a prominent effect of radiation that varies in severity from mild to severe, in its severe degree the shadow of necrotic lymphocytic cells remains visible. The table indicates that 30 cases (83.3%) show no change (plate 36) and 6 cases (16.7%) show variable degrees of lymphoid cells depletion (plates 37, 38). The collective data for the severity and frequency of the pathological alterations found in the spleen are presented as follows.

Table (24) Severity and Frequency of Histopathologic Changes of Spleen

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	30	83.3%	30	83.3%
1	6	16.7%	6	16.7%

4.4.7. Suprarenal Gland.

Table (25) shows the severity and frequency of the histopathological changes of the suprarenal gland. These changes vary from presence or absence of degeneration, hyperplasia or hypoplasia (scoring from 0 to 1). Plates 28, 29, 31 and 39 illustrate these findings. The table indicates that, 33 cases (91.7%) have no change (plate 28) and 3 case (8.3%) shows changes (plate 29, 31 and 39). The collective data for the severity and frequency of the pathological alterations found in suprarenal gland presented as follows.

Table (25) Severity and Frequency of Histopathologic Changes of Suprarenal

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	33	91.7%	33	91.7%
1	3	8.3%	3	8.3%

4.4.8. Thymus Gland.

Table (26) shows the severity and frequency of the histopathological changes of thymus gland. These changes vary from mild to severe lymphocytic depletion (scoring from 0 to 2). Plates 40-42 illustrate these findings. Irradiation induced essentially lymphocytic depletion of the gland Lymphoid stroma, depletion varied from mild to severe degrees. The table indicates that 34 cases (94.4%) show no change (plate 40), 1 case (2.8%) shows slight change (plate 41) and 1 case (2.8%) shows severe change (plate 42). This indicates that the total affected number with various severities was 2 cases (5.6%) and 34 cases (94.4%) were not affected. The collective data for the severity and frequency of the pathological alterations found in the thymus gland are presented as follows.

Table (26) Severity and Frequency of Histopathologic Changes of Thymus

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	34	94.4%	34	94.4%
1	1	2.8%	2	5.6%
2	1	2.8%		

4.4.9.Lungs.

Table (27) shows the severity and frequency of the histopathological changes of the lungs. These changes vary from presence or absence of inflammation or pneumocytes (scoring from 0 to 1). Plates 43-45 illustrate these findings. The table indicates that, 34 cases (94.4%) have no change (plate 43) and 2 case (5.6%) shows changes (plates 44, 45), one as interstitial inflammatory reaction reach in lymphocytes and the second as prominent alveolar lining (pneumocytes). The collective data for the severity and frequency of the pathological alterations found in lung presented as follows.

Table (27) Severity and Frequency of Histopathologic Changes of Lungs

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	34	94.4%	34	94.4%
1	2	5.6%	2	5.6%

4.4.10.Heart.

Table (28) shows the severity and frequency of the histopathological changes of the heart. These changes vary from presence to absence of swollen mural or valvular endothelium (scoring from 0 to 1). Plates 46-47 illustrate these findings. indicate that, 35 cases (97.2%) have no change

(plate 46) and 1 cases (2.8%) show changes (plate 47). The collective data for the severity and frequency of the pathological alterations found in heart presented as follows.

Table (28) Severity and Frequency of Histopathologic Changes of Heart

Severity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	35	97.2%	35	97.2%
1	1	2.8%	1	2.8%

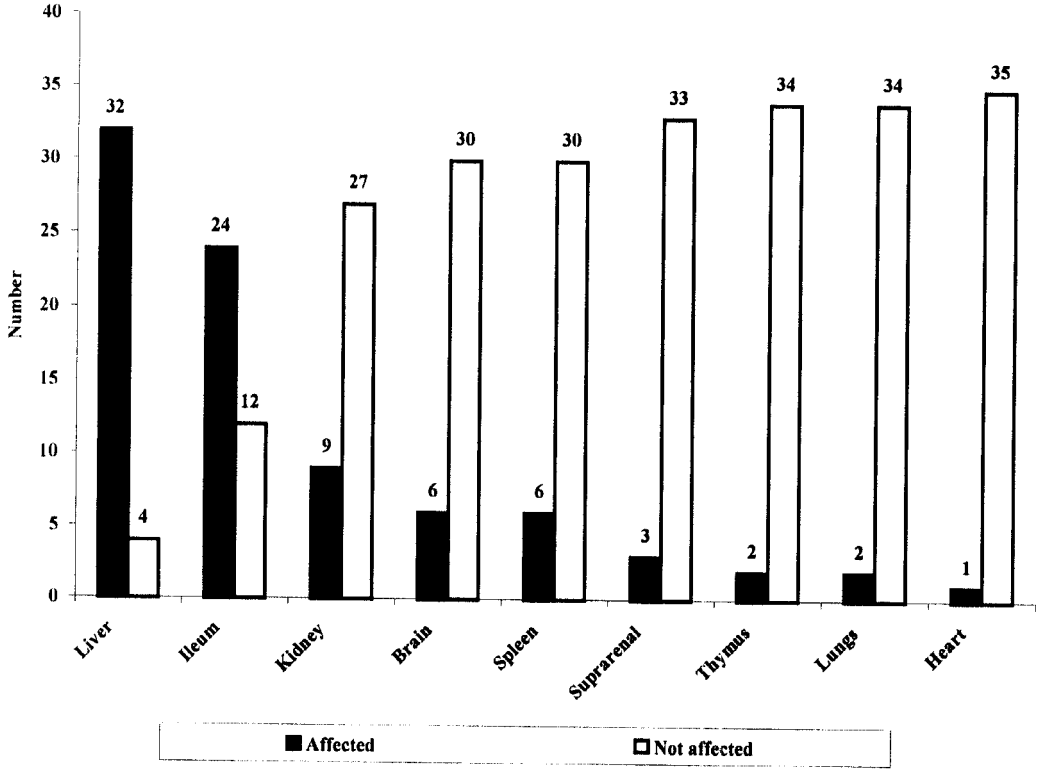
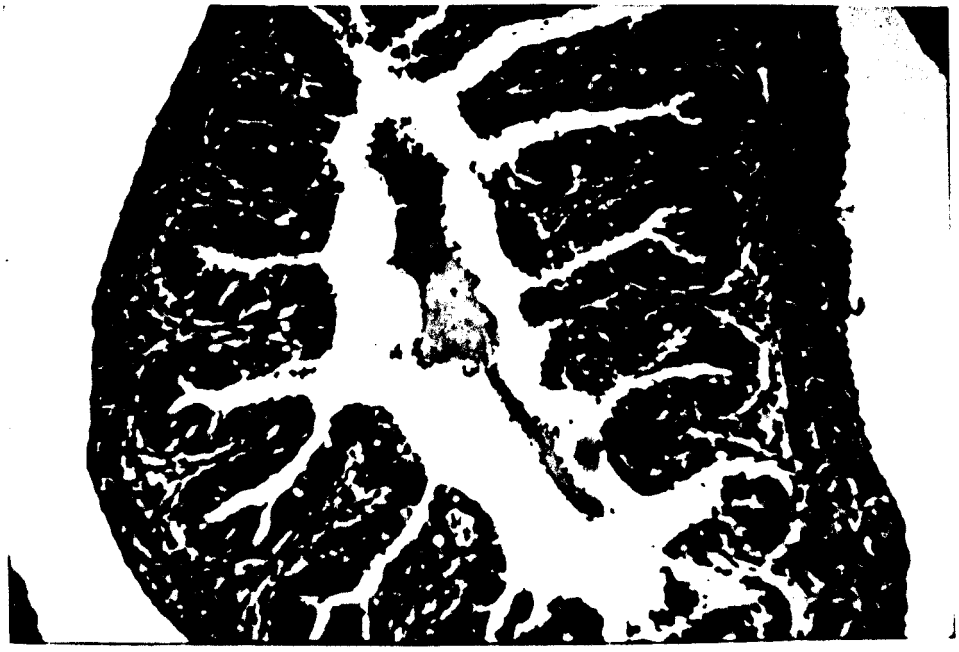
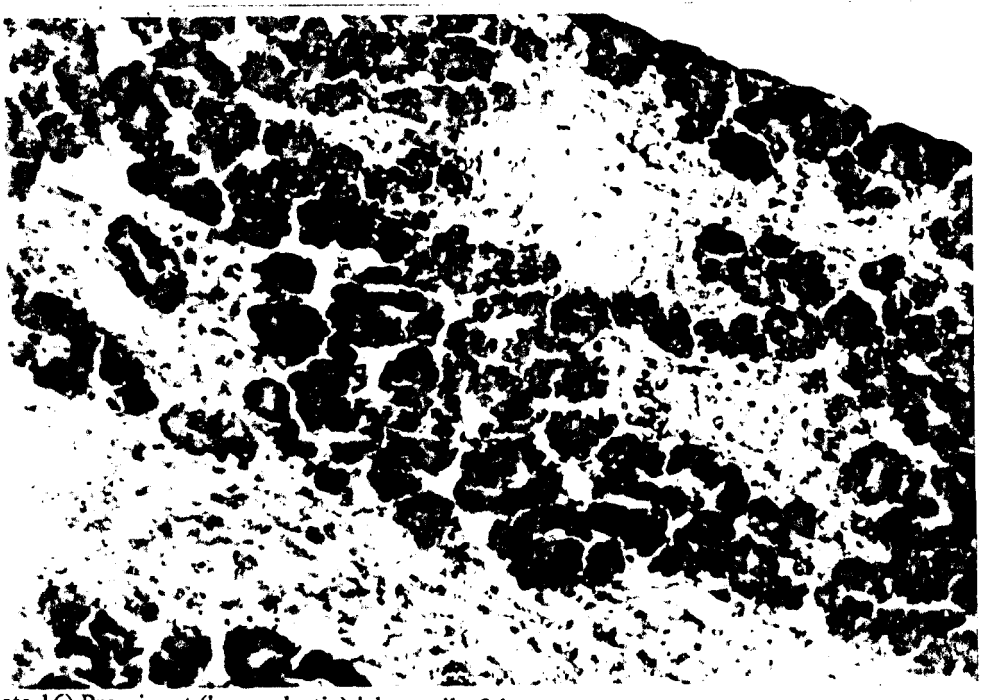


Figure (24) shows a histogram presenting the number of the affected and non affected individual tissues examined histopathologically for litters from irradiated subgroups.

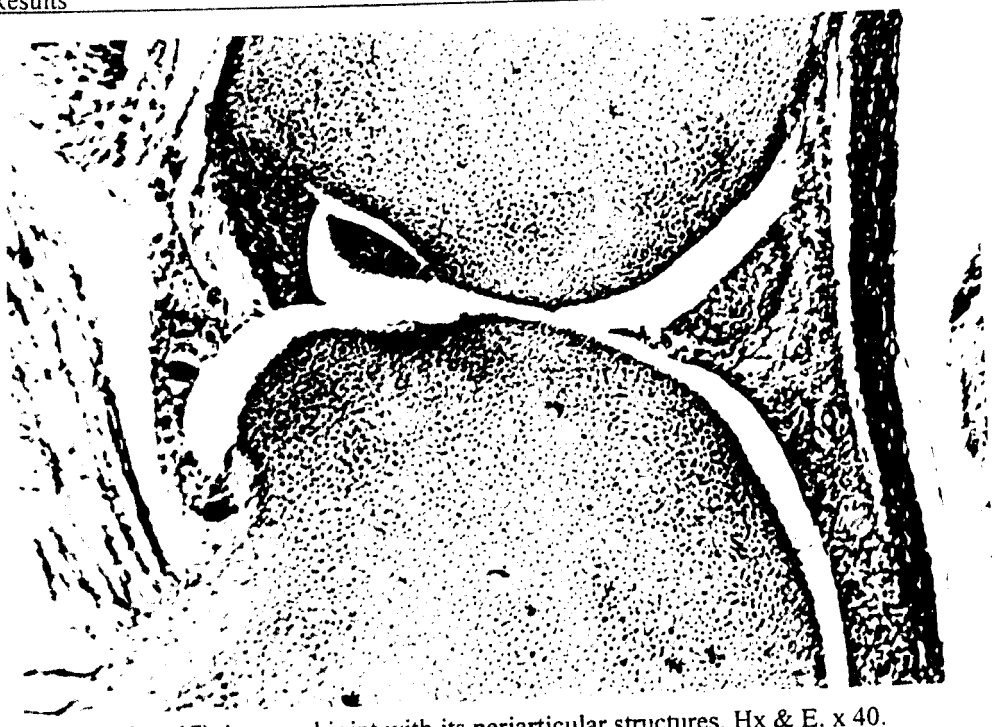
The information obtained from the histopathological studies, reveals that the tissues most affected are the liver, ileum and kidney. The most liver affected was that of the subgroup irradiated on 15^{th} day of gestation, with the dose 1 Gy. The ileum most affected was with the subgroup irradiated on 15^{th} day of gestation, with the dose 1 Gy. The kidney most affected was with the subgroup irradiated on 9^{th} day of gestation, with the dose 0.5 Gy. This observation will be subjected to scientific interpretation in the section of the discussion.



(Plate 15) Normal large intestine. Hx & E. x 100.

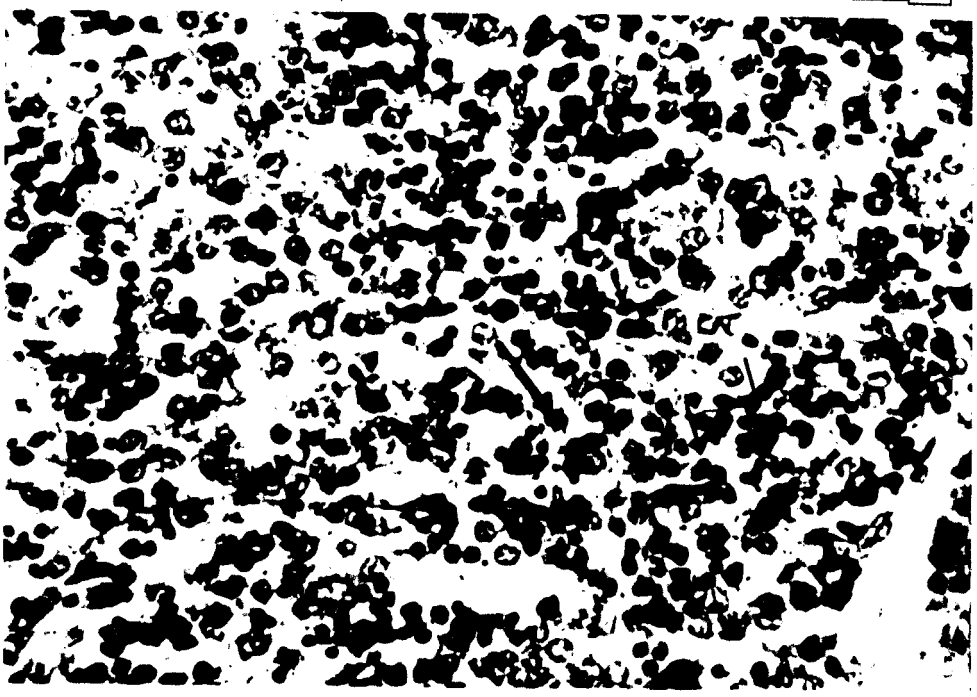


(Plate 16) Prominent (hyperplastic) islets cell of the pancreas. A rather normal finding. Hx & E. x 100.

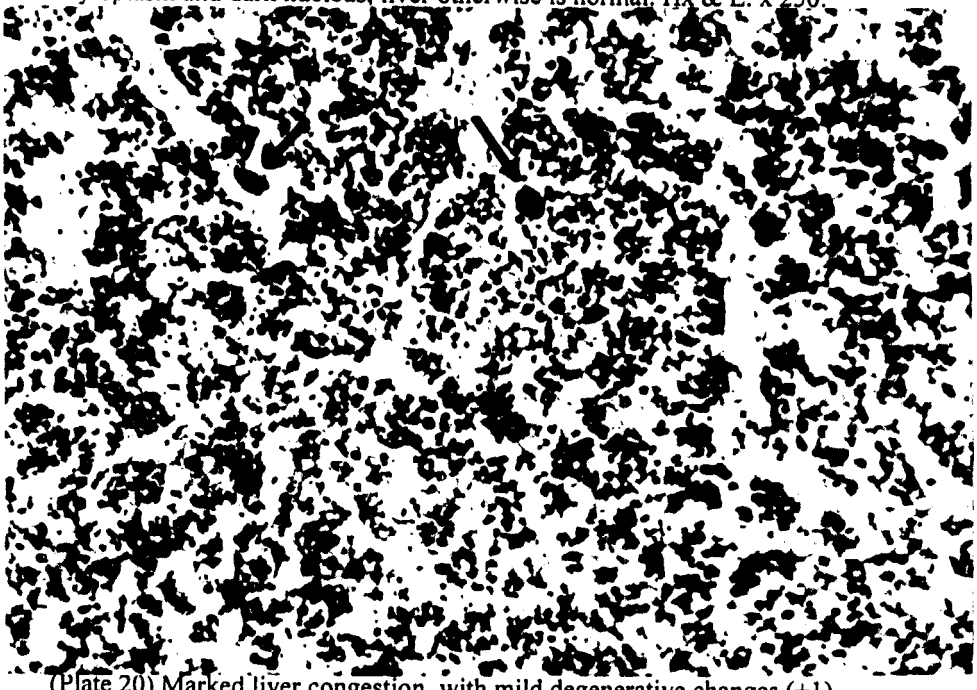


(Plate 17) A normal joint with its periarticular structures. Hx & E. x 40.

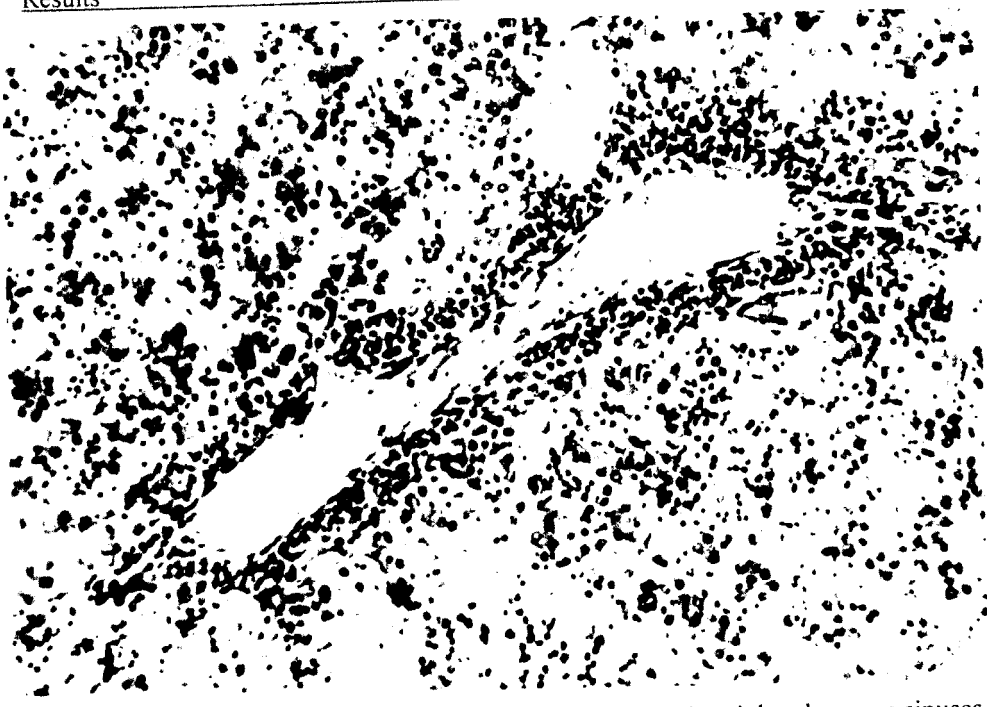
(Plate 18) Normal (control) liver. Hx & E. x 100.



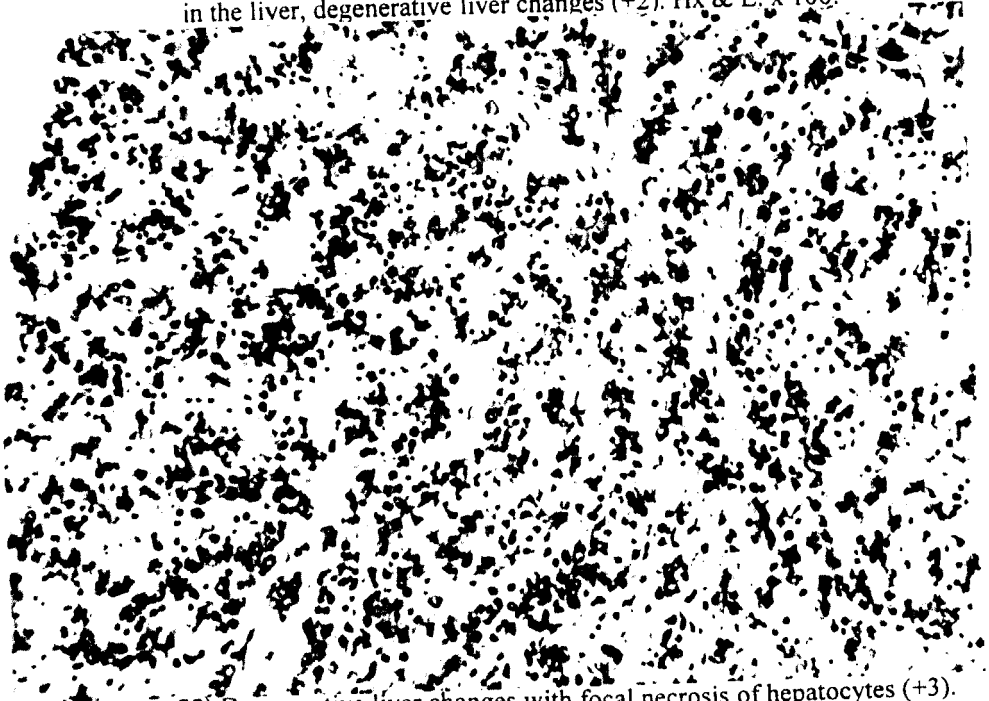
(Plate 19) EMH, prominent erythroblasts (arrows) with bright red cytoplasm and dark nucleus, liver otherwise is normal. Hx & E. x 250.



(Plate 20) Marked liver congestion, with mild degenerative changes (+1), some Megakaryocytes are seen (arrows). Hx & E. x 100.

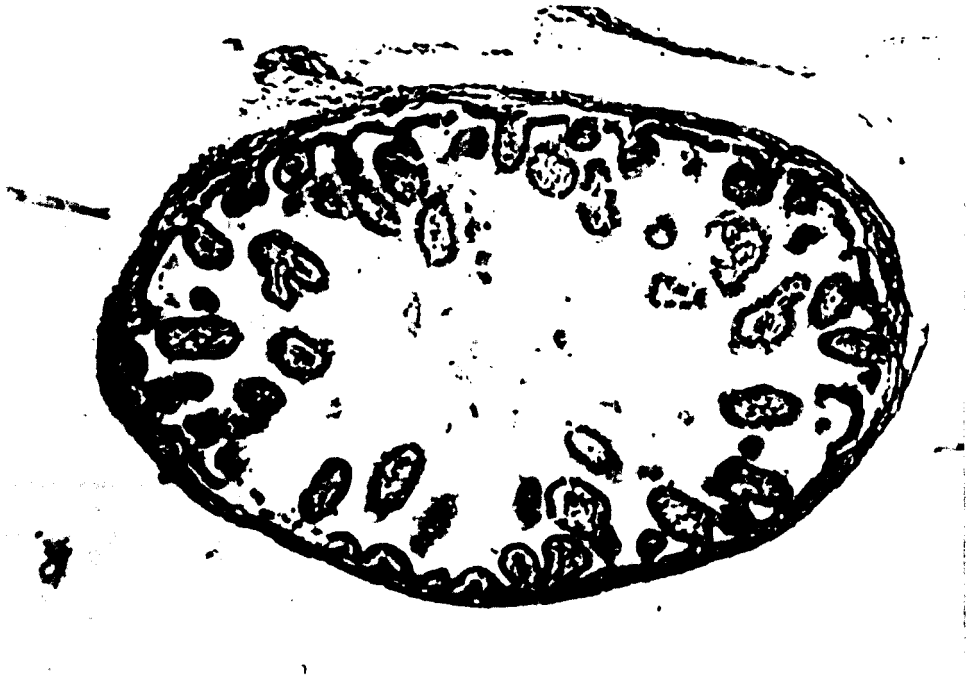


(Plate 21) EMH, Haemopoitic cells concentrated around peripheral venous sinuses in the liver, degenerative liver changes (+2). Hx & E. x 100.



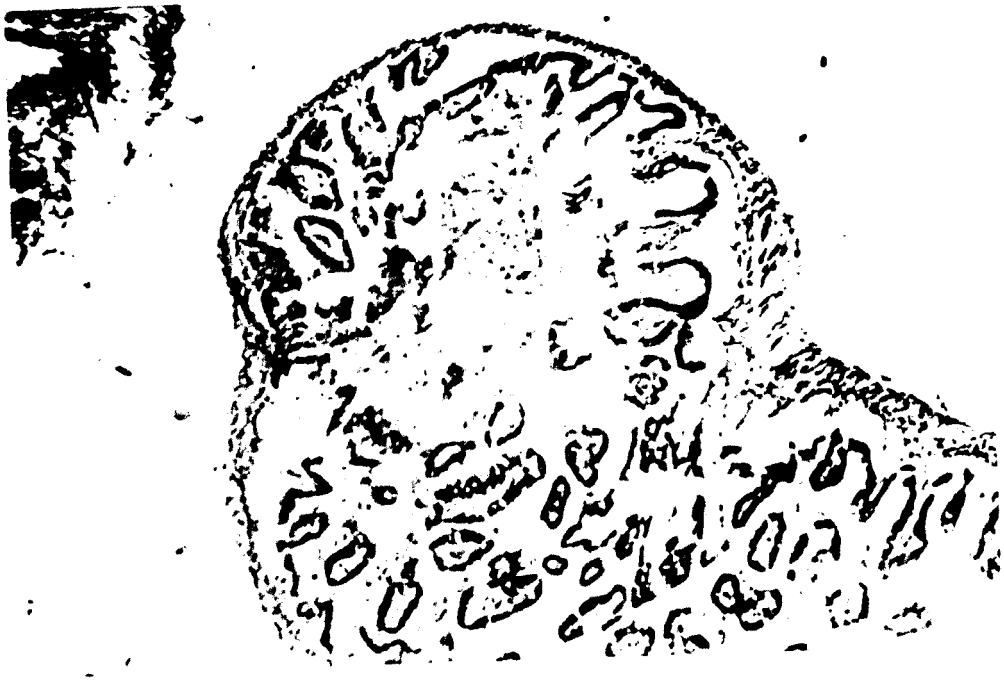
(Plate 22) Degenerative liver changes with focal necrosis of hepatocytes (+3). Hx & E. x 100.

(Plate 23) Normal (control) ileum. Hx & E. x 40.



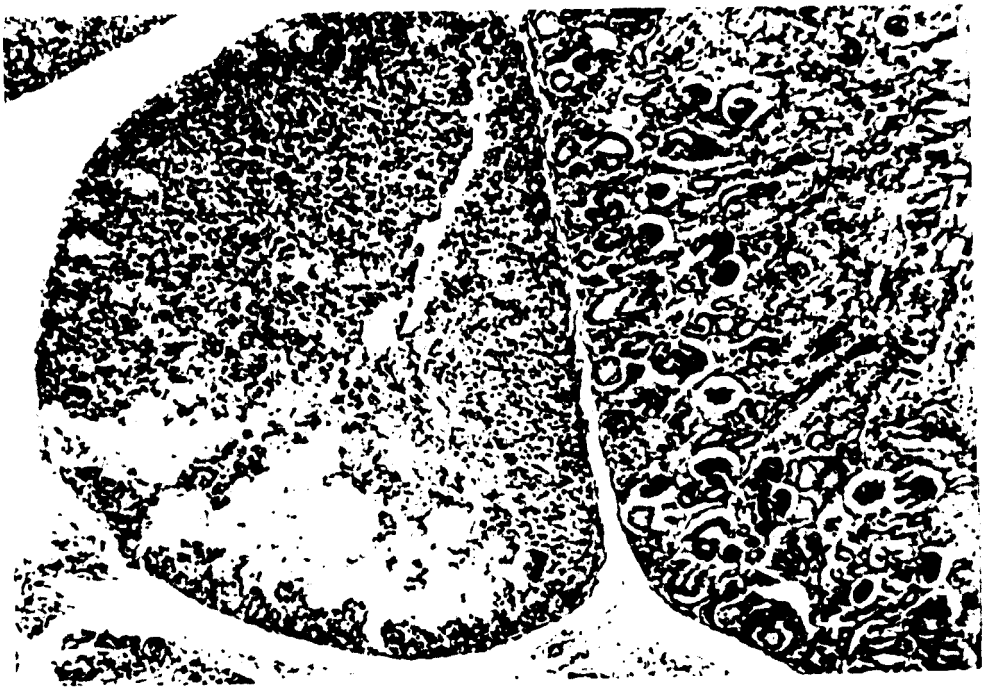
(Plate 24) Mild focal mucosal degeneration of the ileum (+1). Hx & E. x 40.

(Plate 25) Ileal mucosal degeneration, (+2) changes. Hx & E. x 40.

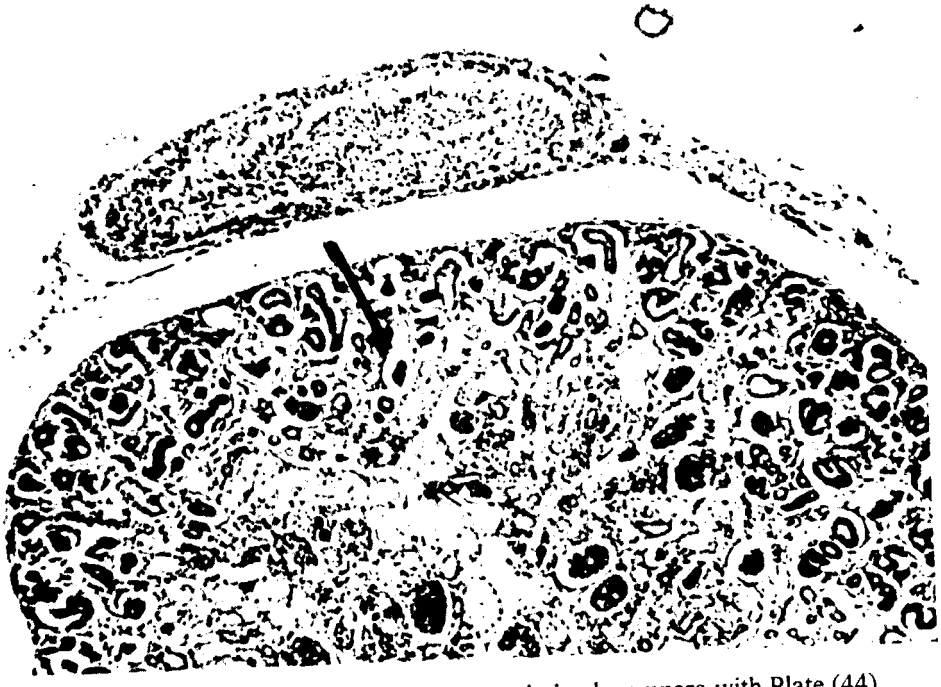


(Plate 26) Severe ileal degenerative changes affecting mucosa and submucosa (+3). Hx & E. x 40.

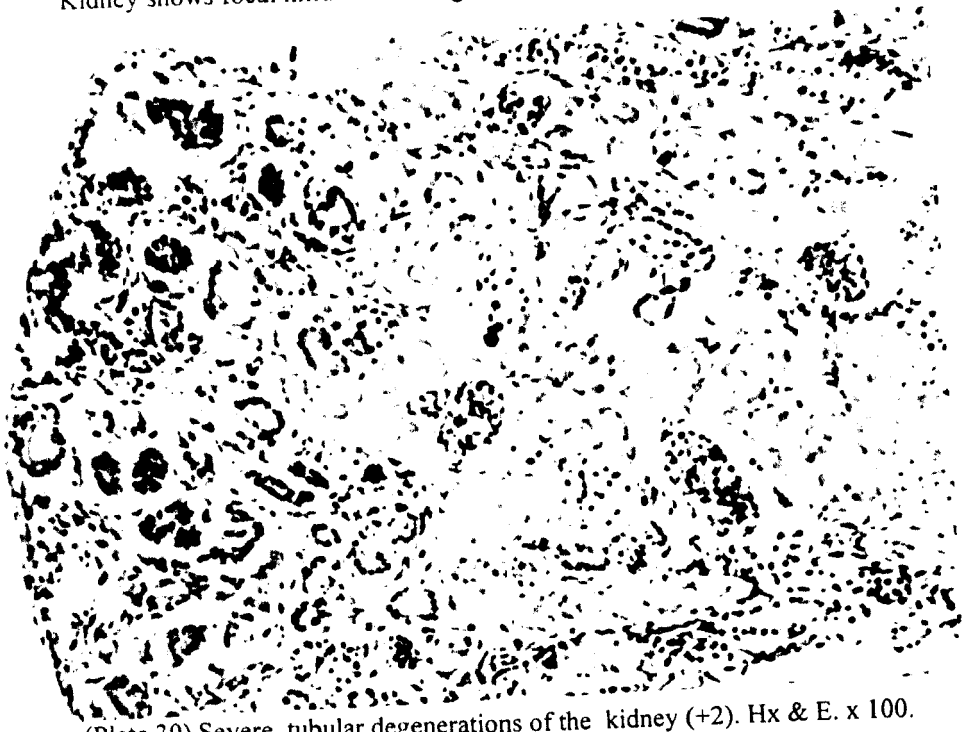
(Plate 27) Small intestine, all layers are necrotic (+4). Hx & E. x 100.



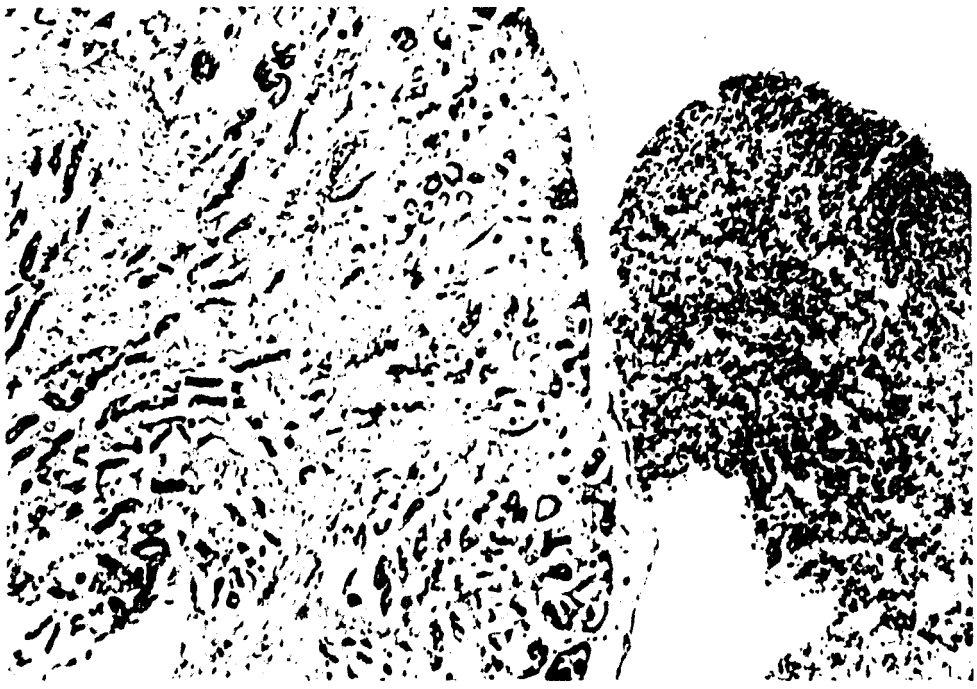
(Plate 28) Normal (control) kidney and suprarenal gland. Hx & E. x 40.



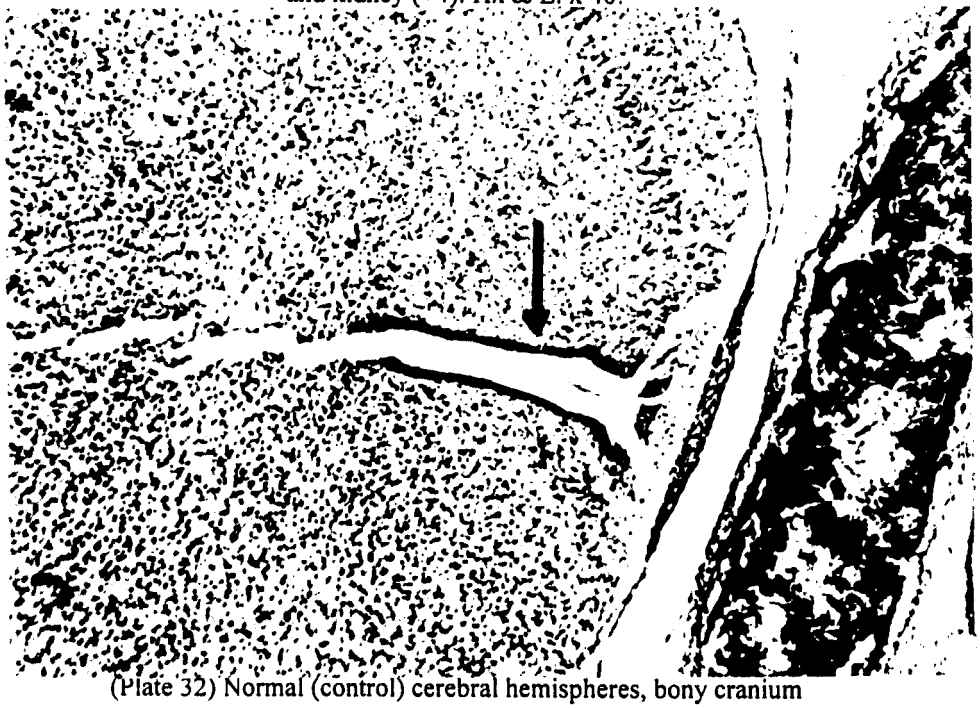
(Plate 29) Hypoplasia of the suprarenal gland, compare with Plate (44). Kidney shows focal mild tubular degeneration (+1) (arrow). Hx & E. x 100.



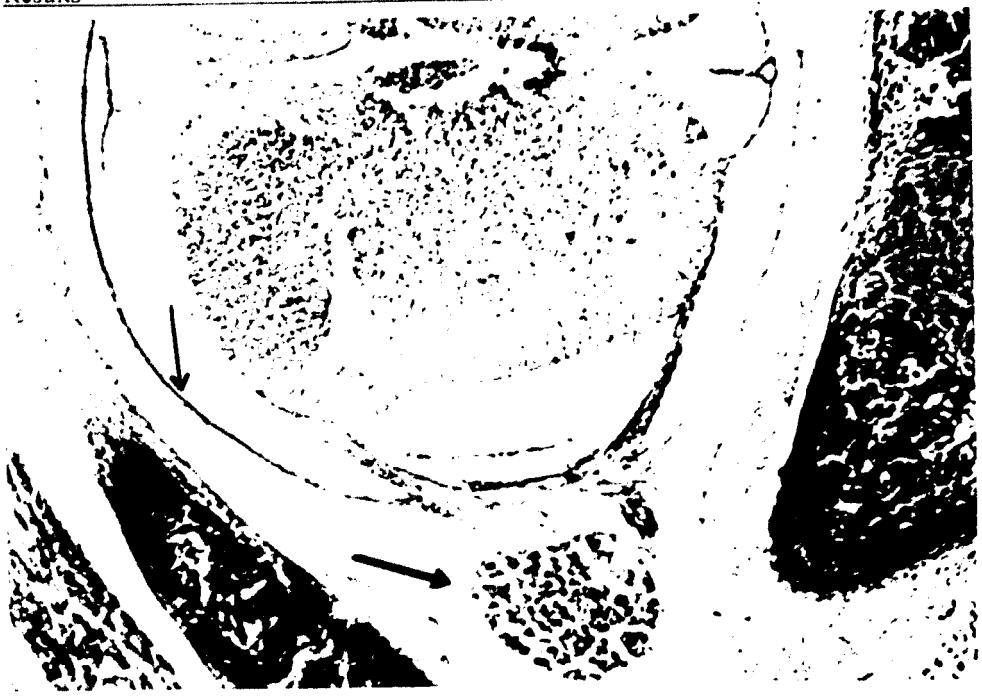
(Plate 30) Severe tubular degenerations of the kidney (+2). Hx & E. x 100.



(Plate 31) Marked degenerative and necrotic changes of the suprarenal glands and kidney (+4). Hx & E. x 40.

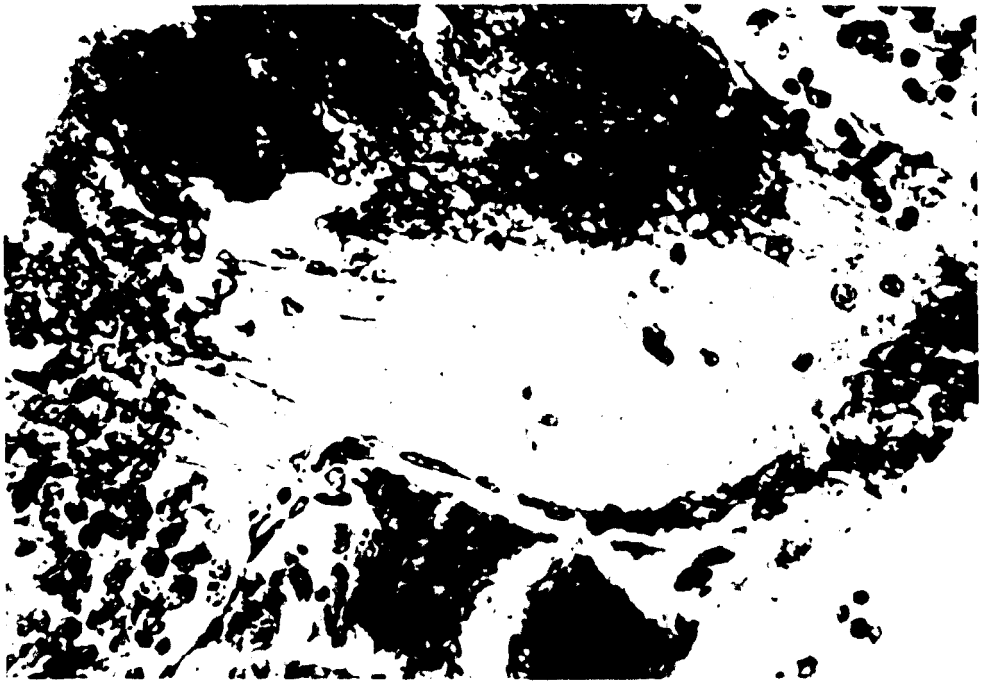


(Plate 32) Normal (control) cerebral hemispheres, bony cranium and part of ventricular septum (arrow) are seen. Hx & E. x 40.

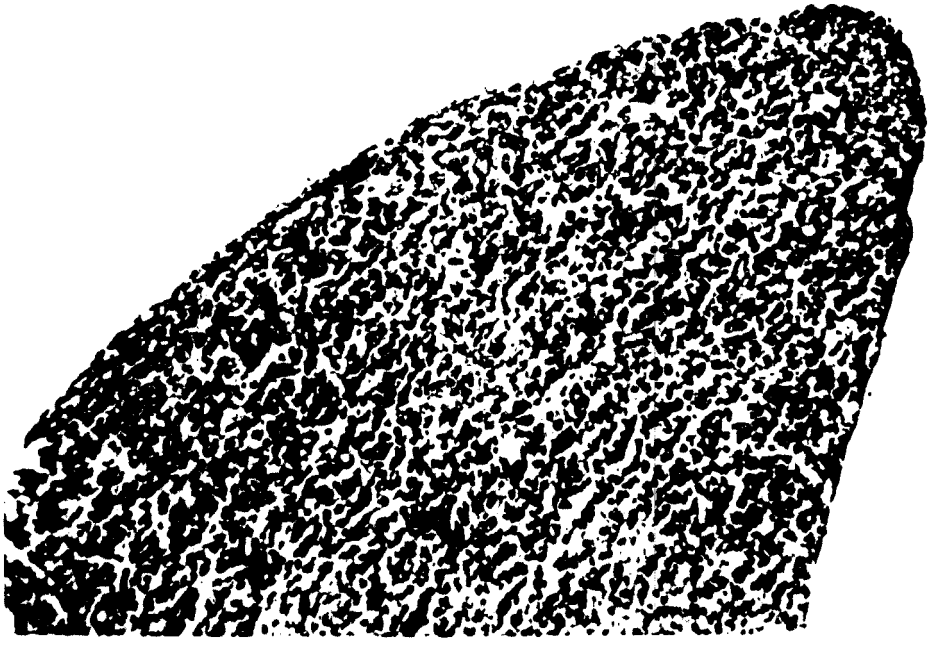


(Plate 33) Normal spinal cord; spinal ganglion (thick arrow) and meninges (thin arrow). Hx & E. x 100.

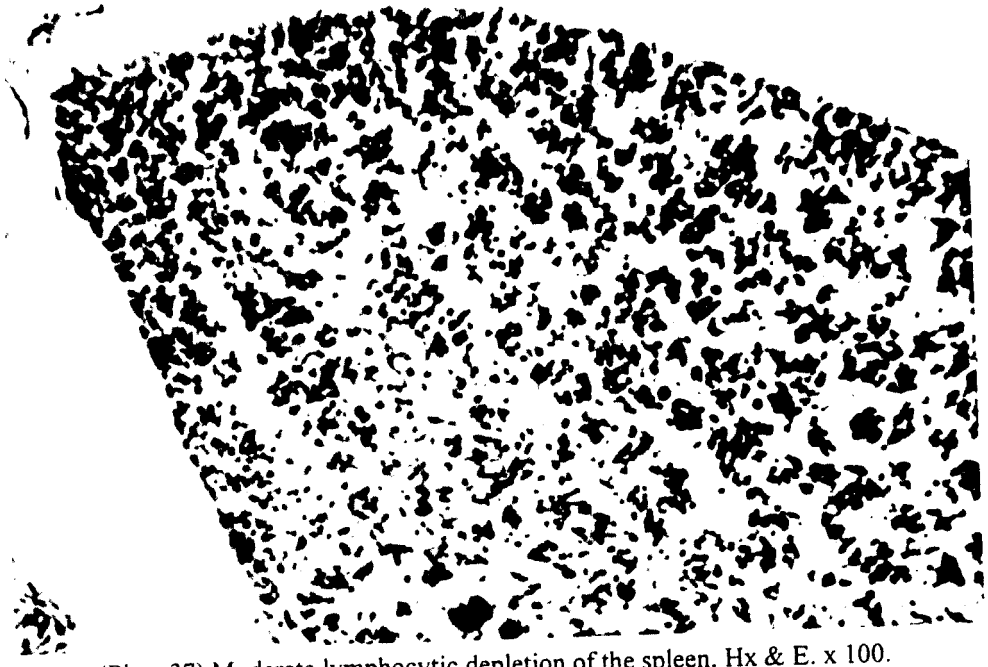
(Plate 34) Focal cerebral gliosis with increased glial fibrils (arrow). Hx & E. x 100.



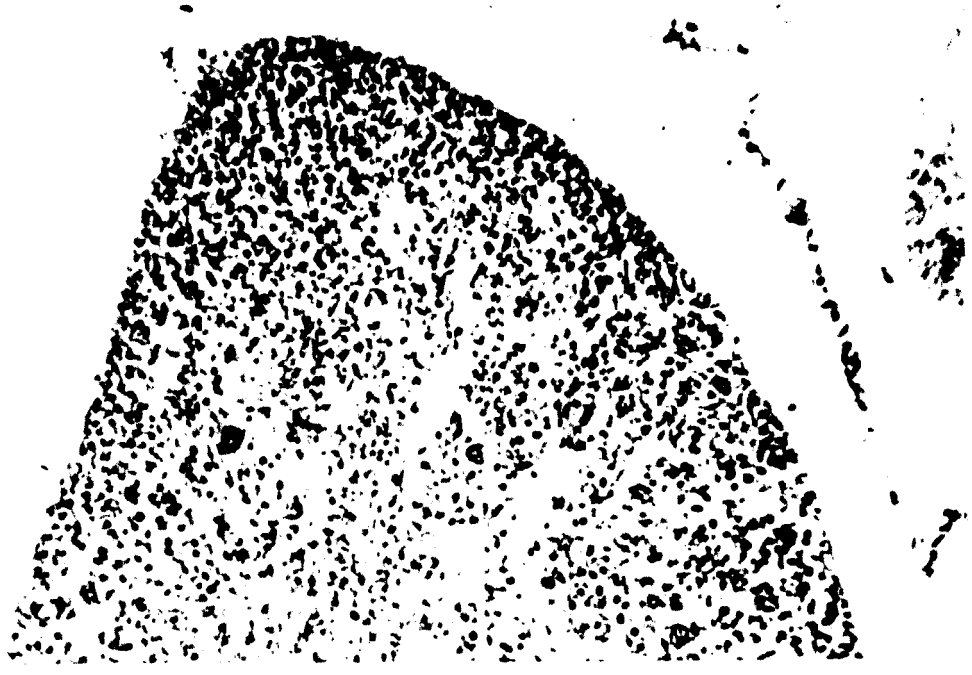
(Plate 35) Focal cerebellar gliosis, excess loose glial fibers with minimal cells and interstitial edema. Hx & E. x 250.



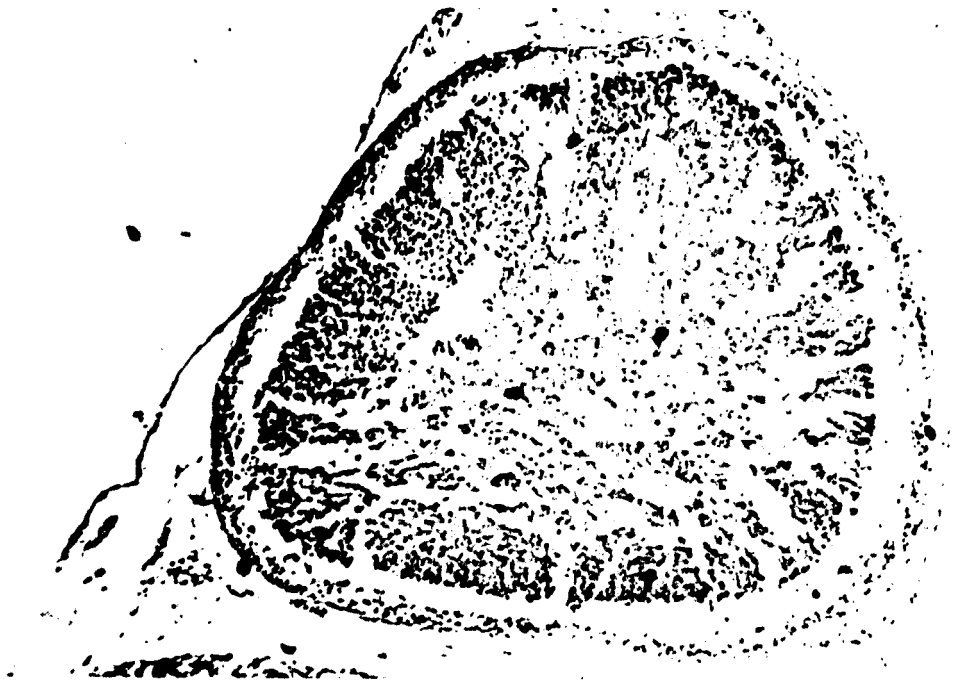
(Plate 36) Normal (control) spleen. Hx & E. x 100.



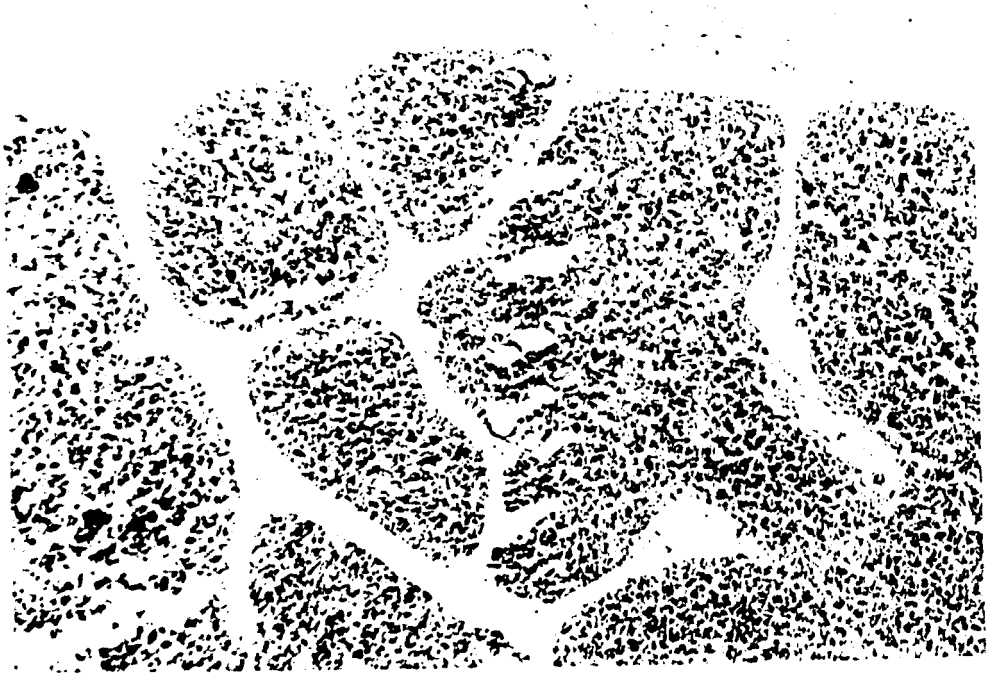
(Plate 37) Moderate lymphocytic depletion of the spleen. Hx & E. x 100.



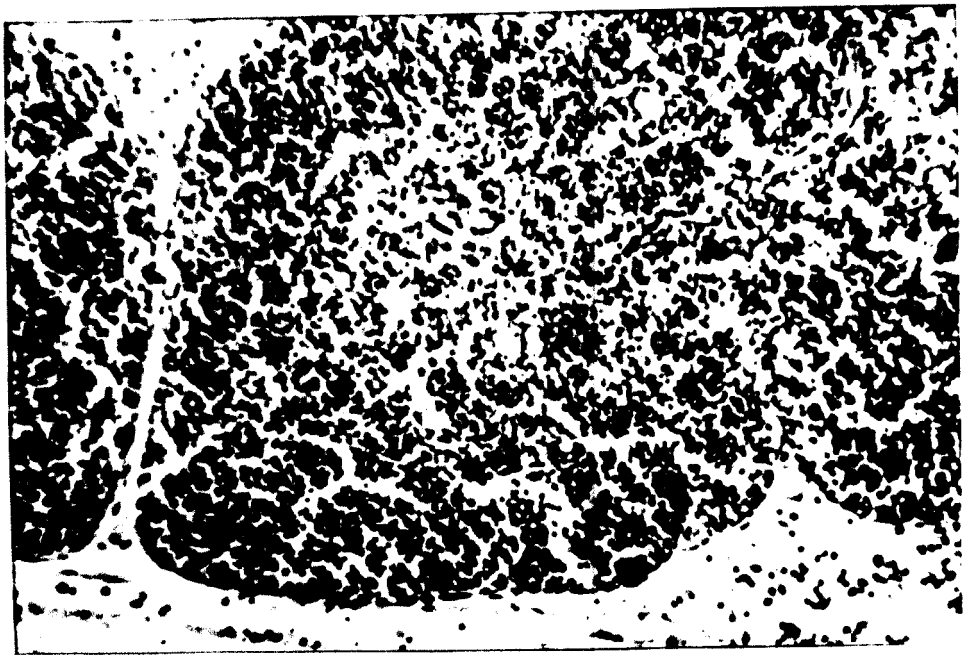
(Plate 38) Marked lymphocytic depletion of the spleen. Hx & E. x 100.



(Plate 39) Moderate degenerative changes of the suprarenal gland. Hx & E. x 40.

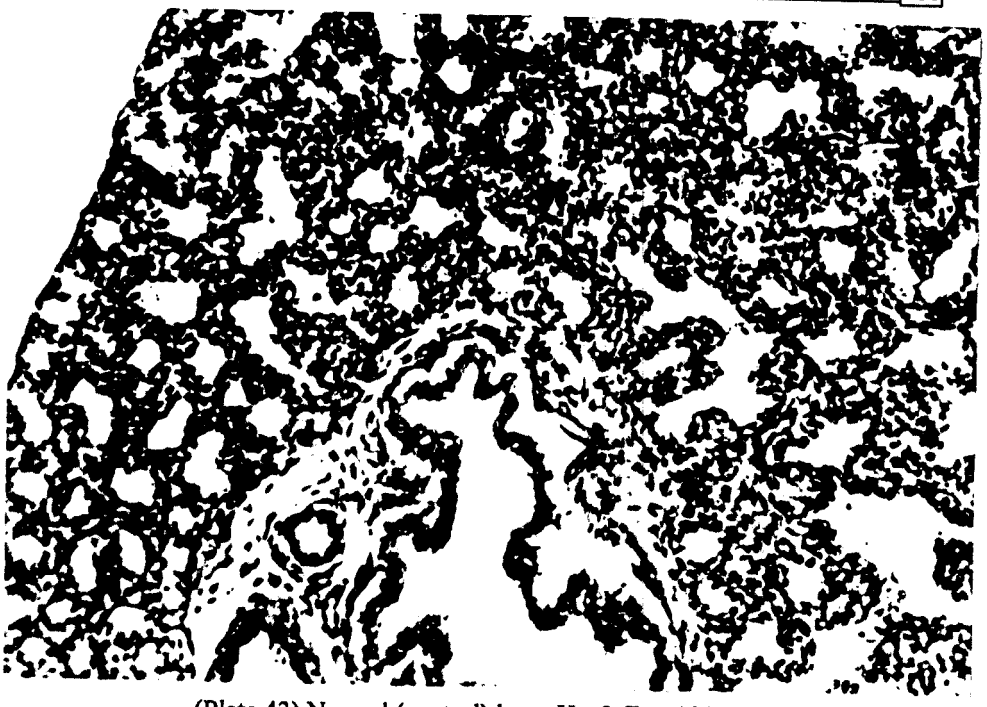


(Plate 40) A normal thymus gland. Hx & E. x 40.

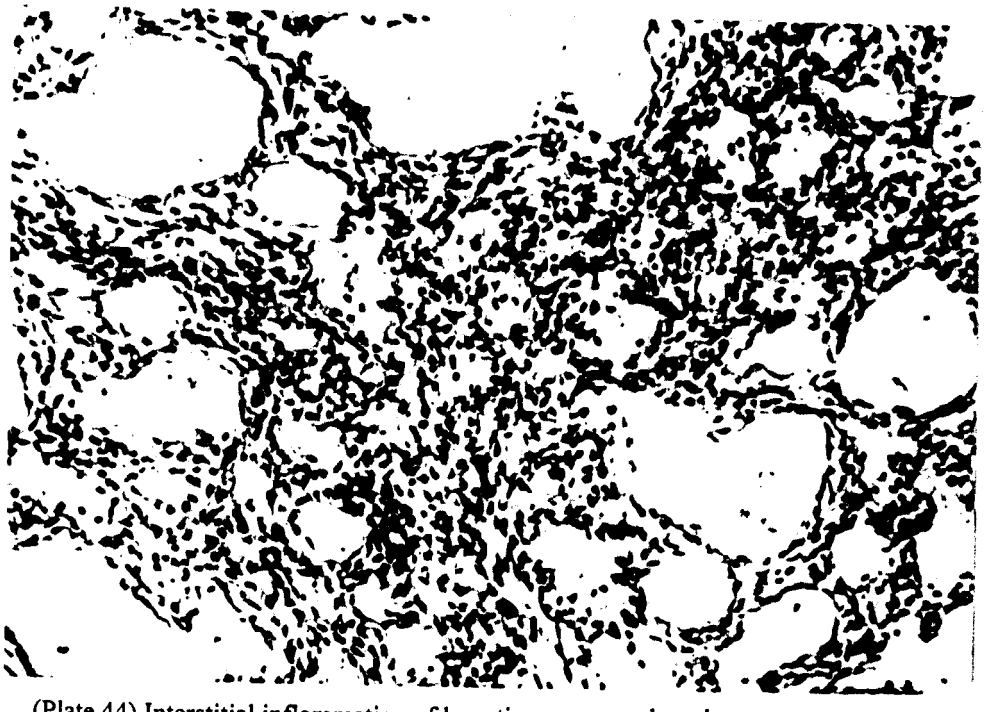


(Plate 41) Thymus gland with mild lymphocytic depletion. Hx & E. x 100.

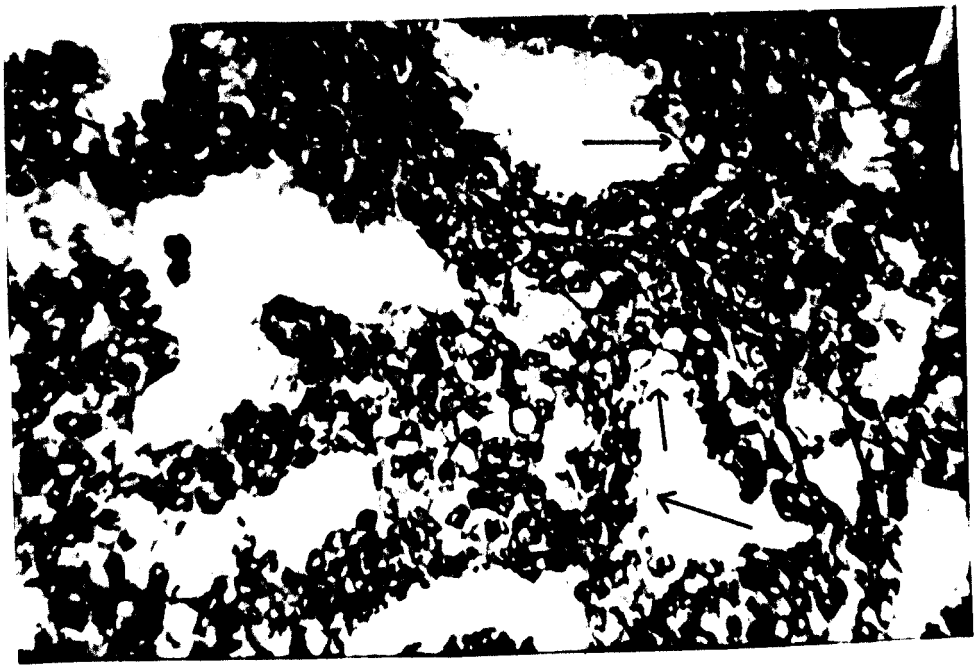
(Plate 42) Thymus gland with severe lymphocytic depletion. Hx & E. x 100.



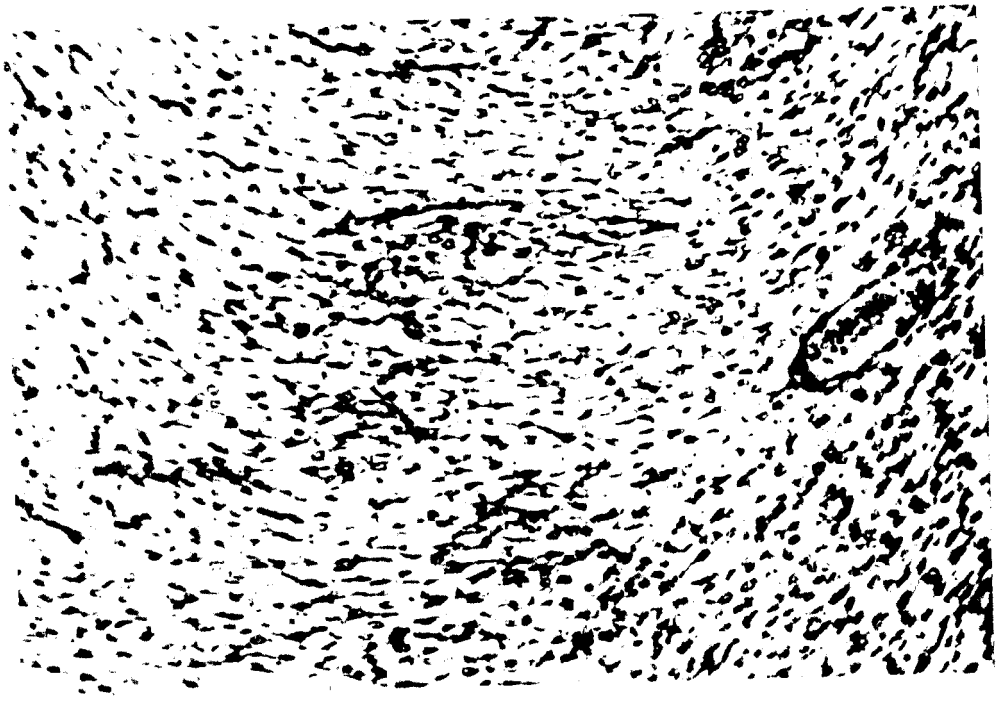
(Plate 43) Normal (control) lung. Hx & E. x 100.



(Plate 44) Interstitial inflammation of lung tissues, many lymphocytes are seen. Hx & E. x 100.



(Plate 45) Prominent pneumocytes, the alveolar spaces (arrows). Hx & E. x 250.



(Plate 46) Normal (control) cardiac muscle. Hx & E. x 100.

(Plate 47) Markedly swollen (vacuolar changes), endocardial cells lining a papillary cardiac muscle. Hx & E. x 250.

DISCUSSION

5.DISCUSSION.

5.1.PREAMBLE.

This thesis is essentially concerned with the study of the effects of ionizing radiation on embryonic development and fetal growth in mammals. Both the physical system of radiation and the biological system of the embryonic development are highly intricate and complex systems. Because of the complexity of the two systems, several parameters have been studied involving different doses of radiation at different periods of gestation. A preface of information is necessary to pave the route for a comprehensive discussion of the data procured from the studies performed in this thesis.

The time period of embryonic development and fetal growth also known as the period of pregnancy or gestation is the most vulnerable phase in the life of man and animals. This vulnerability is also characteristic of the reproductive periods of all living organisms. This period, particularly in mammals, is recognized as being a supreme grand constitution of very highly refined biochemical and biological processes in harmonious orchestration of finitely timed organization entailing multifactorial mechanisms occurring at all molecular, cellular and tissue levels during the whole gestation period. The inherent nature of this intricate complexity renders the constituent ground elements of the developing mammalian embryo and fetus very highly responsive to all extrinsic and intrinsic agents that may interfere or disrupt the normal patterns of embryonic development and growth.

Many agents have been recognized which have disturbing impacts on the highly vulnerable patterns of the biochemical and biological mechanisms occuring during gestation. These include chemical and physical agents, mental stress, physical and psychological trauma and

several other factors. The experimental studies performed in this thesis are intimately concerned with the effects of ionizing radiation as a physical agent affecting and disturbing the normal biological sequential mechanisms of embryonic cellular development and organization of fetal growth during all the stages of gestation. The very rapidly changing cellular modification and kinetics of the developing embryo imposes a definite distinction on the cellular and tissue radiation induced response. This response varies according to type, function and behavior of tissue cellular patterns existing at the specific time periods of gestation at which radiation exposure took place. An added factor that should be considered in the interpretation of the final radiation induced embryonic changes, is the potential for molecular repair of sublethal cellular damage.

The extreme complexity of the numerous factors influencing the final outcome of the effect of ionizing radiation on the embryo and fetus, renders the study of this domain of scientific research a matter coined with a wide bracket of uncertainties and results that are not exactly reproducible. However, because of its extreme importance in its application to human life, this subject has and will remain to have a high priority among the sciences dealing with agents that may affect intrauterine reproductive mechanisms which may with certain probabilities impose abnormalities on future generations of mankind.

The interactions of ionizing radiation with biological systems are a very complex matter indeed. The continuous changing patterns of the nature and kinetics of the biological system, greatly adds to the complexity of the mechanisms of interaction. Fundamental radiobiology teaches that the ultimate effects of ionizing radiation on biological systems are the result of these intricate interactions that take place between the physical system of ionizing radiation and the biological system exposed. Both the physical system of ionizing radiation and the biological system, particularly that during gestation, are highly quantized

systems. The physical system is quantized by the type, energy and dose of radiation; other factors being involved as the dose rate and mode of exposure whether single or protracted. The biological system is quantized by the density, the cellular biomolecular arrangement and the ionization potential of the physicochemical bonds of these biomolecules. Other factors are involved such as the biochemical, biological and environmental patterns of the cellular populations present in the biological system at time of irradiation.

Other physical and biological parameters are involved that dictate the final outcome of the radiation effects on any particular biological system. The exact determining factors in the complicated processes and mechanisms that finally lead to the ultimate biological effects still remain to be issues of concern. The physical process of radiation energy absorption, the physico-chemical processes and the possible repair mechanisms, all occur in a time period from 10^{-13} to 10^{-10} seconds. What happens at the submolecular level in the biological system during this extremely short period of time, precisely determines the ultimate cellular and tissue changes that may appear in due time of hours, days, months or years after radiation exposure.

5.2.APPRAISAL.

In studying the effects of ionizing radiation on biological systems, one may begin with changes incurred in the whole organism and descend along the organizational hierarchy to the tissue, cellular and biomolecular levels attempting to explain and correlate the changes observed. Alternatively, one may begin with the alterations that take place at the biomolecular level and attempt to predict and correlate the changes that might appear at higher levels of organization.

However, it has become evident that the radiation effects on cellular populations are the basis of appreciating the changes produced at the levels of tissues, organs and whole organism. The study of radiation induced cellular changes also serves to understand and interpret the changes that may have occurred at the subcellular level.

An objective discussion of the integrated results obtained in this thesis requires an appraisal of certain important biological parameters related to embryonic development and fetal growth and the inherent radiobiological mechanisms of the various stages. The very major cellular mechanisms of extreme importance that occur during embryonic development and fetal growth are cellular proliferation, differentiation and growth. ***Cell Proliferation*** is an essential process for the continuity of biological life. The rate of this process varies according to cell type and species of organism; it is a unique specific property of the cell. The process of cell proliferation is maintained by cell division. ***Cell Differentiation*** is a major intricate mechanisms in biological systems of which our knowledge is far inferior to our ignorance. The process of differentiation involves a sequence of events that finally terminate in the appearance of highly distinctive cell types, which become integrated to form a functioning tissue. Fully differentiated cells, because of their function are completely distinct with no intermediaries, and there is no situation in which one type changes into another. ***Cell Growth*** implies an increase in size and mass resulting from synthesis of specific tissue components. The transition from single cell to multicellular adult, i.e., the growth of the organism is accomplished by controlled cell growth and cell division processes which in many tissues continue throughout the life of the individual, but is very high during embryonic life. Recent analyses have uncovered a large and growing number of factors that appear to be able to promote growth. The science of radiobiology teaches us that cellular populations during the processes of proliferation, differentiation and growth are highly radiosensitive. However, cells that have become differentiated are relatively radioresistant **(Gardner et al., 1985).**

Since this thesis is related to the effects of ionizing radiation on embryonic development and fetal growth, it is necessary to portray briefly the various major biological mechanisms that take place in the various stages of gestation. These stages are the preimplantation period, the stage of organogenesis and the stage of fetal growth. The principal events of embryonic development and fetal growth are fertilization, cleavage, implantation, placentation, organogenesis, organ differentiation and growth. These occur in all mammals and in humans in approximately the same sequence. It is only the time scale that differs from one species to the other. The corresponding periods of gestation in humans and the biological mechanisms involved should be mentally visualized in order to attain a concept of the radiation effects that may occur to humans during radiation exposure at corresponding gestation periods.

The stage of **preimplantation** includes all the period starting with ovum fertilization, development of morula, cleavage and all the processes of the early embryonic period. The ultimate phase of this period is implantation which is the early stage of placentation that denotes the formation of the placenta by combination of embryonic and maternal tissue to serve as a medium for physiological interchange between mother and conceptus. During that early period of embryonic life, very active and rapid biochemical and biological processes take place within a framework of intensive cellular and tissue organization and specification. The cellular features are essentially those of high proliferation, differentiation and organization. These supremely critical cellular functions, coupled with the minute size of embryonic tissue containing all the cellular elements of the future neonate; are all features that make this stage of early embryonic development very highly sensitive to radiation. Radiation injury at this stage is therefore, expected to be severe with massive cellular injury and a high probability of embryonic death. Remnants of these pathological sequences will appear later as uterine absorption sites. The severity and frequency of occurrence of such effects are dose dependent, the higher the

dose, the higher the severity and frequency of occurrence of these effects at this early phase of gestation.

The term **organogenesis** denotes the time period during which the major embryonic tissue are organized and developed. This stage starts by implantation and placentation and terminates at the stage of transition when cellular and tissue differentiation are all nearly complete. At this stage, the fetus attains the specific characteristics and morphological features of its species. However, it is very important to note that some processes of tissue and cellular organization of the central nervous system, the special senses and species behavioral characteristics continue to undergo development and organization during the period of fetal growth up to the end of pregnancy. This has been reported to be very pronounced in humans **(Moore, 1988)** and also in mammals **(Hendrickx and Houston, 1970).**

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. Two designations for describing growth are used, namely, absolute growth and relative growth. Absolute growth is the increment in dimensions of the fetus in a unit of time. Relative growth is the increment changes in dimension for a unit of time divided by the dimension attained at the time of measurement. Absolute growth increases throughout pregnancy, but relative growth begins to decrease about the middle of 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 **(Macdonald, 1980).** In rat, the period of fetal growth takes place from day 17 to day 21 of gestation. This period registers rapid increase in the linear dimensions and weight of the fetus. The development of different organs of the embryo and fetus is not strictly coordinated in time and therefore, organs may not achieve the exact degree of development at a given time. It must be remembered that some processes of tissue differentiation and organization of brain cellular elements of the central nervous system and other tissues of special senses and musculo-skeletal system continue to take place during the period of fetal growth. The period of fetal growth is considered a radiosensitive stage during intrauterine life, however, the types of radiation induced fetal effects are different to those induced during the previous two periods of preimplantation and organogenesis.

5.3. FUNDAMENTAL RADIOBIOLOGY.

This provides the basic issues for the proper understanding of the sequential temporal mechanisms that terminate into the ultimate effects of ionizing radiation on biological systems. After radiation exposure, the radiation energy is absorbed into the physico-chemical bonds of the molecules of the irradiated biological system. This results into successive

processes of excitation and ionization of the bonds, with the subsequent production of molecular alterations in the irradiated biosystem. These molecular alterations are the precursors of cellular effects which are governed by the number and type of molecule affected, magnitude of molecular affection as the residual radiation injury after repair mechanisms. The interplay of these parameters in the biological medium ultimately impose the type and severity of cellular changes and subsequent tissue impairment.

The target theory postulates that a certain critical volume or molecule of the cell is responsible for the ultimate effect of cellular injury. The DNA molecule is considered the primary site of radiation injury to the cell. The molecules of the cell membrane system may assume secondary importance. Several factors are involved in determining the radiosensitivity of cellular populations. These include cell proliferation, processes of cellular differentiation and other biological mechanisms of organization, growth, migration and other cellular activities. Differentiated cells which have completed the process of differentiation are relatively radioresistant. Based on these considerations, all cellular processes involved in embryonic development and fetal growth during intrauterine life render embryonic and fetal tissues highly sensitive to radiation injury **(Lea, 1946).**

Much has been mentioned regarding the biology of gestation. The consideration of the radiation dose and its impact on the ultimate biological damage incurred is also of fundamental significance. The type, severity, incidence, probability of occurrence of a certain biological end point induced by radiation is always a function of dose. The radiation doses used in this study range from 0.5 to 3 Gy. This range includes a radiation dose scale between the upper scale of low doses (0.5 Gy) and the lower scale of high doses (3 Gy). This was particularly chosen for these experiments to include both the high dose ranges that will induce

deterministic effects and the low dose ranges that may induce stochastic effects with certain probabilities. The differences between both is a fundamental conceptual issue that will further be evidenced and clarified during the final discussion of the data procured for the parameters studied at the various doses and at the different periods of gestation. It should be mentioned in this context that for the proper estimation of stochastic delayed effects and the higher probability of their occurrence, a large number of animals should be exposed. This is in distinction to deterministic effects which are encountered with a high degree of occurrence at high doses. This particular difference between deterministic and probabilistic mechanisms of radiation induced effects on mammalian systems is a basic premise.

5.4. FEATURES AND INTERPRETATION OF RESULTS.

The aim of this study was to assess the effects induced on embryo/fetus by different doses of ionizing radiation at various stages of pregnancy. This was performed to identify the relationship between time of gestation, dose of radiation and type of effect induced. To satisfy the experimental requirements, seventy five pregnant albino rats of species Rattus rattus were chosen for the experimental groups from about 280 animals. The irradiated pregnant animals were divided into three groups, each was further subdivided into control and irradiated subgroups. Each irradiated subgroup was individually exposed to 0.5, 1, 2 or 3 Gy of Cobalt-60 gamma rays. Each group were specified to a certain day of gestation (days 9, 12 and 15), this corresponded to stages of early organogenesis, major organogenesis and fetal growth.

On day twenty one, the pregnant animals were sacrificed, the neonate litters were numbered, examined and absorption sites were detected and recorded. Observations on 403 litters from control and irradiated subgroups included measurements of size, weight, lateral body length,

circumference of girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull. Statistical analysis was done for validation of results. Three aspects of results were addressed namely, number of absorption sites, number of litters and morphological measurements of litters, observations on congenital malformations and histopathological studies of some organs.

The features and interpretation of results will form the substance and core of the discussion.

5.4.1. Morphological Studies.

The First Parameter observed in the morphological studies was the Number of Absorption Sites. Figure 15 shows that the number of absorption sites is maximum for the 3 Gy subgroup irradiated on 9^{th} day of gestation and is least for the 0.5 Gy subgroup irradiated on 15^{th} day of gestation. This indicates that maximum injury occurred during early stages of gestation with 3 Gy, giving evidence that absorption sites have a high incidence of occurrence at a high dose during the early period of gestation.

The Second Parameter was the Number of Litters. Figure 16 shows that the number of litters is maximum for the 0.5 Gy subgroup irradiated on 15^{th} day of gestation and is zero for the 3 Gy subgroup on 9^{th} day of gestation. This indicates that minimal injury occurred during late stages of gestation with 0.5 Gy, giving evidence that the number of litters is maximum at low dose and late period of gestation.

From the results of these two parameters, it is evident that the number of litters reciprocates with the number of absorption sites. The rational interpretation of this fact is that Absorption Sites occur due to radiation induced lethal injury to the developing embryonic cells during the early

stages. High doses will result in maximum injury to the cellular populations of the developing embryo. Maximal cell death will induce arrest of embryonic development, with subsequent embryonic death and absorption of cellular debris. These absorption sites will remain in situ in the uterine compartments to signify a fertilization that failed to proceed to full development due to death of the cellular elements of early embryo by the insult inflected from the high dose. Lower doses will provide a chance for embryonic survival, and this is evidenced by the lower values of absorption sites. Correspondingly, lowest dose (0.5 Gy) on 15^{th} day of gestation (late period of gestation), resulted in the lowest incidence of absorption sites and highest value of litters. During that period of gestation, cellular populations of the fetus would have attained final biological organizational maturity which certainly makes them relatively more tolerant to radiation injury.

The experimental framework of this thesis did not include the follow up of live litters regarding survival, longevity, conditions of morbidity and development of congenital anomalies. However, such aspects should be considered seriously for future work.

The Third Parameter observed was the Size of Litters. Figure 17 shows that measurements of litter size appear to be of highest value for the 0.5 Gy subgroup irradiated on 15^{th} day of gestation and lowest value for the 2 Gy subgroup irradiated on 9^{th} day of gestation. This indicates that maximum radiation induced effect on litter size occurred at the early period of gestation (9^{th} day) and a dose of 2 Gy. The higher dose of 3 Gy was lethal on 9^{th} day and induced less injury at 12^{th} and 15^{th} days than that induced by 2 Gy on 9^{th} day of gestation.

The Fourth Parameter observed was the Weight of Litters. Figure 18 shows that the weight of litters appears to be the highest value for the 0.5 Gy subgroup irradiated on 15th day of gestation; and lowest value for the

2 Gy subgroup irradiated on 9th day of gestation. This also indicates that maximum radiation injury on litter weight occurred at the early period of gestation (9^{th} day) with a dose of 2 Gy. The higher dose of 3 Gy was lethal at 9^{th} day and induced less injury at 12^{th} and 15^{th} days than that induced by 2 Gy on 9^{th} day of gestation.

The features of the results for size and weight of litters take a similar pattern. In the early periods of gestation, cellular populations of the developing embryo are proliferating and radiation injury certainly affects the future size and weight of the litters. At later periods of gestation, the cellular population becomes more developed, mostly differentiated, have attained an appreciable degree of growth and therefore, more radioresistant to radiation injury. However, it is evident that 2 Gy appears to inflict more injury on 9^{th} day of gestation than 3 Gy on 12^{th} and 15^{th} days. This fact establishes the understanding that the time of irradiation during gestation is more critical to the effect produced than radiation dose.

The Fifth Parameter observed was the Lateral Body Length of Litters. Figure 19 shows that the lateral body length of litters shows highest value for the 0.5 Gy subgroup irradiated on 15^{th} day of gestation; and the lowest value for the 2 Gy subgroup irradiated on 9^{th} day of gestation. This provides evidence that the results for the lateral body length of litters is particularly dependent on time of irradiation during gestation.

The Sixth Parameter observed was the Girth at Umbilicus of Litters. Figure 20 shows that the girth at umbilicus appears to be highest value for the 0.5 Gy subgroup irradiated on 15^{th} day of gestation; and lowest value for the 2 Gy subgroup irradiated on 9^{th} day of gestation. This provides evidence that the results for the girth at umbilicus of litters are particularly dependent on time of irradiation during gestation.

The Seventh Parameter observed was the Tail Length of Litters. Figure 21 shows that the tail length appears to be highest value for the 0.5 Gy subgroup irradiated on 15th day of gestation; and lowest value for the 3 Gy subgroup irradiated on 12th day of gestation. This provides evidence that the results for the tail length of litters are particularly dependent on time of irradiation during gestation.

The Eighth Parameter observed was the Skull (A-P) of Litters. Figure 22 shows that the skull (A-P) appears to be highest value for the 0.5 Gy subgroup irradiated on 15th day of gestation; and lowest value for the 2 Gy subgroup irradiated on 9th day of gestation. This provides evidence that the results for the skull (A-P) of litters are particularly dependent on time of irradiation during gestation.

The Ninth Parameter observed was the Skull (B-P) of Litters. Figure 23 shows that the skull (B-P) appears to be highest value for the 0.5 Gy subgroup irradiated on 15th day of gestation; and lowest value for the 2 Gy subgroup irradiated on 9th day of gestation. This provides evidence that the results for the skull (A-P) of litters are particularly dependent on time of irradiation during gestation.

The fifth, sixth, eighth and ninth parameters [lateral body length, girth at umbilicus, skull (A-P) and skull (B-P)] provide evidence that maximum injury occurred with the subgroup irradiated with 2 Gy on 9th day of gestation and the minimal injury occurred to litters of subgroups irradiated with 0.5 Gy on 15th day of gestation. The rational interpretation for these findings is that at early stages of gestation (9th day), the embryonic cellular population is highly active due to the high degree of proliferation, organization and partial differentiation of early embryonic cells. Radiation induced depression of these activities were the result of the 2 Gy exposure, providing decreased measurements. The 3 Gy subgroup on 9th day resulted in cellular death of the embryonic cellular

populations providing total loss of the embryo and formation of absorption sites. Minimal injury as indicated from the results was obtained by the least dose of 0.5 Gy at the late period of gestation (15^{th} day) at a time when fetal cells are relatively well organized, differentiated and in a process of growth. The cellular conditions in this case provide a state of cellular radioresistance. This explanation is the basic radiobiological rationality of these findings.

However, the seventh parameter studied (tail length) presents a somewhat different finding, where, the subgroup irradiated with 3 Gy at 12^{th} day of gestation is the condition which shows maximum injury indicated by the least value for tail length. This finding is attributed to the fact that the rat tail is essentially osseous tissue (bony tissue) whose cells are essentially differentiating during middle phase of gestation. Injury induced by a high (3 Gy) on the 12^{th} day will therefore be more effective than injury induced by 2 Gy on the 9^{th} day.

The general findings of the seven measurements of morphological studies essentially present similar features and same pattern of radiation induced cellular effects on embryonic development. This is briefly concluded by the fact that 3 Gy on 9^{th} day of gestation is lethal resulting in death of the early embryonic cells, with the final formation of absorption sites, or the total resorption and phagocytosis of cellular debris. The dose of 2 Gy at 9^{th} day of gestation appears to cause highest changes in measurements taken, except the tail length which was affected mostly by 3 Gy on 12 day. These observations follow proper dose-effect relationship at the period of gestation considered.

The overall features of the results obtained from the morphological studies carried out on litters indicate that all the parameters measured appear to follow the same trend. The size and weight of litters, the lateral body length, circumference of girth, tail length antroposterior and

biparietal skull dimensions, all appear to follow the same pattern of radiation induced response to the radiation doses used and the days of gestation on which the pregnant animal subgroups were irradiated.

The distinct salient feature observed that is common to all parameters is that maximum radiation induced effect in the values of the parameters occurred in the 2Gy subgroup irradiated on 9^{th}day of gestation. The tail length is the only exception. This, considering the fact that the 3Gy subgroup irradiated on 9^{th}day of gestation resulted in intrauterine embryonic death and no litters developed to full term. This particular observation provides evidence that the early stages of gestation (9^{th} day) are more vulnerable to radiation at a relatively lower dose of (2Gy), than the later stages (12^{th}, 15^{th} day) at a relatively higher dose of (3Gy). This distinct and constant observation in all the parameters studied provides essential criteria in the radiobiology of embryonic and fetal cellular populations. During the early phases of gestation, embryonic primordial cells prevail characterized by being highly radiosensitive because of their extreme activity of biochemical, functional, organizational, proliferating processes and partial differentiation. Therefore lethal injury occurred at 3 Gy, and non lethal but effect inducing injury occurred at 2 Gy and less. During the middle and later phases of gestation, more developed differentiated cells prevail in the cellular populations of the embryo. These differentiated cell systems are less responsive to radiation than the cell systems that exist at the early phases of gestation.

The sequential development of radiation effects on living organism (in this work, the embryo/fetus) starts at the molecular level and is then reflected to the cells of the whole body at all stages of cell development, cellular proliferation, differentiation, growth and organization. This prospect affects the bulk of the cellular population of the growing and developing fetus i.e. size, weight, length, girth and others. This affection does not permit the cells to grow as normal cells (cells of the controls) in

size and function. Radiation energy affects all biological functions of cells and tissues. All the biochemical functions of cells and tissues, that are the essential mechanisms permitting the fetus to reach the normal growth and development are affected by radiation. The findings reported and discussed indicate that radiation effects on embryonic development, apart from lethality induced by high doses at early stages of gestation; will result in a generalized state of growth retardation as indicated by common pattern of decrease in the dimensions measured. The data presented in this work basically conforms with similar findings that are reported by other authors **(Knauss, 1980; Jensh and Brent, 1988; Tomoko and Yasunari, 1993; Sun-Xuezhi et al., 1995).**

5.4.2.Congenital Malformations.

The studies of the appearance of congenital malformation after in utero irradiation during pregnancy in mammals has 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 of congenital malformations were obtained after irradiation during the stage of 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 of 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 consist 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 of eye fissures, penguin shaped litters, very small ear, haemencephalocele and other types. These congenital malformations were observed in live litters removed from uteri of 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 12^{th} day of gestation. Also, penguin shaped litters showed other congenital malformations in the form of very small limbs, small tails, low set ears or no ears. These various malformations were observed in litters from mothers irradiated on 12^{th} 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) and when irradiation takes place at early periods of gestation.

It is very important to mention that congenital malformations in this study were not observed at the radiation doses of 0.5 Gy. This does not means that such dose is without effect. It means that to materialize an observable effect from that dose on embryonic development, a much greater number of animals must be irradiated with that dose to establish a probability of an effect that can be related to the small radiation dose used. This particular aspect involves and underlies the stochastic concepts of radiation induced effects after radiation exposure to low doses and low dose rates. This concept is scientifically fully accepted and formulates the basic criteria for radiation protection of occupational exposure. It also formulates the basic international recommendations that pregnant women should not be exposed to radiation on the abdomen and the exposure limit for pregnant women should not exceed 1 mSv on the skin of the abdomen (which will result in a much lesser dose than 1 mSv to the uterus).

5.4.3. Histopathological Studies.

The literature survey that was performed at the start and during the experimental part of this work revealed that histological studies on embryonic and fetal tissues after irradiation received little attention. The reason for this scarcity can be attributed to the fact that embryonic and fetal cellular populations continuously undergo perpetual dynamic biological changes from one status of organization to the other. These embryonic and fetal cells become representatives of specific organ tissues only at the late stages of gestation. Only at that stage will radiation induced injury to the fetal tissues provide cellular changes that represent histopathological findings that could be quantified with radiation dose.

The histopathological studies performed in the present work, however, were introduced for the purpose of adding an important dimension in the domain of radiation induced effects on embryonic development and fetal growth. In spite of the difficulties encountered during the performance of these studies and non-conformance of some of the findings observed; the studies certainly provided definite evidence of actual cellular and tissue pathology in embryo/fetus induced by radiation.

From the finding of the histopathological studies on the tissue of 12 organs from live litters of animal subgroups irradiated on 9^{th}, 12^{th} and 15^{th} day of gestation, to doses of 0.5, 1, 2 and 3 Gy; only 9 showed histopathological findings of different severities and frequencies in the litters of irradiated subgroups as compared to the controls. This indicates that some fetal tissues are more radiosensitive than others; also that these tissues exhibited various degrees of radiosensitivities at the various stages of gestation.

The outstanding feature of these studies point out to the rational scientific fact that cells undergoing proliferation, differentiation, growth and organization appear to exhibit more pathological findings than other

cells. The findings reported indicate that the liver and ileum showed the highest degree of pathological change as compared to other affected tissues. The least affected organs were the heart and lungs, an observation that indicates that the differentiated property of these tissues at early stages of gestation establishes their radioresistant nature.

During embryonic development and fetal growth, the cellular populations are in a continuous kinetics of organizational processes. The ultimate effect of radiation on the embryonic and fetal cellular populations varies from cell modification, depressed mitosis, mitotic death, disturbed differentiation, programmed cell death (apoptosis), cellular degeneration and necrosis. The occurrence of these various changes and their severity will depend on several factors; the most important of which are the biological status of the cell at time of irradiation, the radiosensitivity, the extent of cellular and tissue organization, the stage of gestation and the radiation dose.

Cellular populations of the developing embryo and growing fetus are characterized by some peculiarity which make them possess a different response to physical agents, different to that of adult tissues. These peculiarities are the extreme variation of the kinetics of individual cells in the same cellular population. This is due to non synchronicity of cells in the same tissue undergoing the same biological process, in the same compartment of cellular population (e.g. If x number of cells are in a dividing cell system, not all the number will synchronously go in and out through stages of the cell cycle). These cellular peculiarities impose a condition of differential response to external agents(e.g. Radiation exposure). This differential response imposes a situation of individual cellular variability, which is postuled to manifest itself clearly in the cellular populations of the developing embryo.

The assessment of histological tissue changes after irradiation of the developing embryo was determined by the designation of arbitrary units;

an evaluation system which is not always consistent and hence the use of "image morphometric studies" was developed which looks to be more appropriate. This system of histological assessment was not used in the present studies due to difficulties encountered. On these grounds, modeling of a dose-effect relationship will stand no ground of a scientific rationality. In this context, it is reasonable to consider that variations in the cellular response of tissues to the same radiation dose and the same period of gestation, a situation which is subject to multifactorial attributes and certainly this would urge us to indulge more deeply into the field of statistics, to choose more advanced statistical tools or even to try to formulate new ones.

In spite of the discrepancy of the observations on the histopathological studies, the findings obtained opened up an important avenue that should be pursued in the study of radiation effects on the developing embryonic tissue.

5.5. CONCLUSIONS AND RECOMMENDATIONS.

The effect of ionizing radiations on the developing embryo and the growing fetus is an issue of great concern to human populations. Essentially, the matter involves any radiation induced injury to the embryo from the start of conception to the time of delivery. During that period, the embryo undergoes profound, extremely delicate, complicated, actively interacting mechanisms and processes of metabolic, biochemical and biologic nature. These precisely programmed mechanisms serve to provide for the necessary cellular manifestation of proliferation, differentiation, organization, growth, migration and cellular kinetics.

All these mechanisms operating during intrauterine life, render the cellular population of the embryo and fetus very vulnerable to radiation injury at any stage of development. However, the ultimate damage incurred is basically dependent on the stage of embryogenesis at time of

irradiation and the magnitude of radiation dose delivered to the uterus and uterine adenexa. Depending on these criteria, the most important radiation induced effects on embryonic development and fetal growth, come under the main headings of Intrauterine Fetal Death [IUFD], Intrauterine Growth and Developmental Retardation [IUGDR], Congenital Malformations [CM] that appear at birth, and late effects that may manifest themselves with various probabilities in the future life of the neonate. These effects are not reproducible for the same mammalian species under similar conditions of radiation dose and period of gestation. This points to the extremely intricate mechanisms of the unique processes of the programmed spatial organization of embryonic histogenesis throughout the whole developmental period of the embryo and fetus.

Several authors have studied the effects of ionizing radiation on embryonic and fetal development both by epidemiological studies on radiation exposed human populations and by animal experiments on mammals. These studies have been comprehensively cited in this thesis in the chapter dealing with literature review. From these studies and from the results of the present work, some significant issues have become very prominent and well established to gain scientific consensus. These issues are formulated in the following statements.

* The whole period of gestation from conception to delivery of the neonate is highly responsive to ionizing radiation and the cellular populations throughout pregnancy are radiosensitive. It must be emphasized that the embryo is a mosaic of innumerable developmental potencies each of which has a period of extreme radiosensitivity during intrauterine life.

* Differences observed in the patterns and severity of the effects induced are essentially related to time of gestation period, radiation dose and the exact status of a particular cell at time of irradiation.

* During the early stages of preimplantation and early organogenesis, the embryonic primordial cells are lethally affected by DNA injury. The cellular debris are phagocytosed and the rest remain as absorption sites. Embryonic death is a prominent feature.

* The stage of major organogenesis is characterized by extensive cellular proliferation, differentiation and tissue histogenesis. These processes are highly radiosensitive, resulting in congenital malformations, decreased developmental patterns and altered morphogenesis. Radiation effects during organogenesis are characteristically teratological.

* The period of fetal growth is responsible for cellular growth, differentiation and organization of the central nervous system specially that dealing with frontal lobe cortical association, neuronal and glial cell migration. Radiation effects induced during intrauterine life appear in post-natal life as functional disabilities of the nervous system, mental retardation, low IQ, abnormalities in behavioral patterns and visual disabilities.

* There is no exact evidence to indicate the existence of recovery processes after radiation induced damage to embryonic cells. The radiation injury is either incompatible with life, or persists to manifest itself according to the future life of the neonate.

* Fetal anomalies are not peculiar to ionizing radiation, but owing to the pervasive nature of radiation, a much greater variety of anomalies can be produced by radiation than by any other inducing agents.

* The course of radiation induced anomalies follow closely the initiation of developmental activity of primordial cellular populations of the various organs. The tissues of CNS, skeleton and growth processes are the most affected.

* The term "Congenital Anomaly" is used by the WHO in the International Classification of Diseases (ICD) to designate structural (or morphological), biochemical and functional disturbances which occur in the conceptus from conception to birth and which may present at birth or later in life. They are not inherited but are induced by extrinsic or intrinsic situations during developmental stages of conceptus. These congenital anomalies include developmental alterations, congenital abnormalities, genetic defects (inborn errors of metabolism, chromosomal abnormalities), fetopathies, growth retardation, immunological diseases, mental retardation, behavioral deviations, defects of the sense organs, congenital hernias and tumor formation.

* It is unlikely that a threshold dose for any human congenital anomaly can ever be established. Therefore, we can only speak of probabilities and possibilities. Dr. Roberts Rugh, an eminent authority on the subject states "It is inconceivable that ionizing radiations at any level of dose is without some effect. There is no developmental stage which is safe, in the sense of being intirely immune to the effects of ionizing radiation".

* A consensus exists that 0.1 Gy (10 rads) or more to the abdomen during the first eight weeks of pregnancy warrants therapeutic abortion to avoid possibility of anomalous neonate. However, the decision of abortion must be given after much deliberation and wisdom.

* Human experience of embryonic and fetal irradiation is the outcome of epidemiological studies performed on pregnant women who received therapeutic irradiation, pregnant females survivors of the Japanese Atomic Bombs and the Marshalles Bekini Islands detonations. Also data obtained from Diagnostic Medical exposures and accidental exposures such as Chernobyl accident. Most of these

studies lacked exact information related to exposure dose, exact outcome of the pregnancy and other important relevant aspects. Such information could prove useful in modeling dose-effect relationship for human in utero irradiation. However, these studies resulted in registering abnormal births, congenital malformations, embryonic deaths and other radiation induced effects.

* It is scientifically justified to consider the embryo and fetus as the most radiosensitive stage of the entire life of any organism. Radiation exposures to pregnant women to the region of the abdominal volume may result in far reaching consequences to future generations.

* International recommendations dictate that the skin of abdomen of pregnant woman should not receive more than 1 mSv during the whole period of pregnancy. Radiation exposures to the abdomen must be avoided during pregnancy.

ENGLISH SUMMARY

SUMMARY

This thesis deals with animal experiments performed to study the effects of ionizing radiation (gamma photons) of different doses on the various stages of embryonic development in rats. Knowledge of the basic premises of these two aspects is essential for the general conceptualization of the experimental framework of the thesis and the results obtained.

Ionizing radiation are forms of energy transmission either photon or particles that are characterized by inducing excitation and ionization within the medium which they traverse. All atomic and nuclear particles are ionizing. Photons that have the property of inducing ionization are X-rays and gamma rays. The energy associated with photons depends on the frequency of wave propagation, the higher the frequency the shorter the wave length, the higher the energy. Particle energy is directly related to particle velocity. The SI unit of radiation energy absorption in matter is the Gray (Gy). This is defined as the radiation energy absorption of one Joule of radiation energy per one kilogram of the biological medium.

The period of embryonic development in mammals extends from conception to delivery of neonate. This period is characterized by the mechanisms of embryonic development involving the very vital processes of cellular proliferation, differentiation, organization and growth. The development of embryonic cellular population and fetal growth are generally categorized into stages of preimplantation, organogenesis and fetal growth. These three main periods of embryonic development are unique in their features and different in respect to the biological processes and mechanisms which take place during each period. Although the basic developmental and organizational features of these stages are essentially similar in all mammals (including mankind); however they are different in duration and organizational detail. In higher mammals (e.g. mankind),

the organizational detail is most supreme. The embryonic tissue has the highest rate of proliferation of embryonic cellular elements, and undergoes major transformation patterns of differentiation and growth. Such highly organized and complex cellular mechanisms render embryonic cells during all stages of gestation highly vulnerable to intrinsic and extrinsic factors.

The current work was conducted to study the effects induced by different doses (0.5, 1, 2 and 3 Gy) of Cobalt-60 gamma radiation on the embryo of rats at the stages of early organogenesis, major organogenesis and fetal growth, corresponding to days 9, 12 and 15 of gestation respectively

Seventy five pregnant female rats were used in this study after verification of successful mating by microscopical vaginal smear. The animals were randomly assigned to control and irradiated groups. Group1: comprised 5 unirradiated control animals and 20 animals divided into four subgroups irradiated on 9^{th} day of gestation, to doses of 0.5, 1, 2 and 3 Gy. These makes a total of five subgroups each of 5 animals. Group2: comprised 5 unirradiated control animals and 20 animals divided into four subgroups irradiated on 12^{th} day of gestation, to doses of 0.5, 1, 2 and 3 Gy. These make a total of five subgroups each of 5 animals. Group3: comprised 5 unirradiated control animals and 20 animals divided into four subgroups irradiated on 15^{th} day of gestation, to doses of 0.5, 1, 2 and 3 Gy. These makes a total of five subgroups each of 5 animals.

All animals of both control and irradiated subgroups were sacrificed by quick decapitation on day 21 of gestation. The uteri were opened and the number of absorption sites and litters were recorded. The morphological studies include measurements of several parameters for litters, namely, size, weight, lateral body length, circumference girth at umbilicus, tail length, antro-posterior and biparietal dimensions of skull.

All measures in millimeters were carried out by vernier caliper. Congenital malformations observed on live litters were recorded and photographed. Histopathological sections of internal organs of live litters, namely, liver, intestine, kidney, brain, spleen, suprarenal gland, thymus, lung, heart, pancreas and bone were examined. The three studies included a total of 403 litters. The total number of measures carried out were 2821 measurements.

The results obtained from these experiments indicated the following salient features for the three studies performed

1. MORPHOLOGICAL STUDIES.

For absorption sites, results indicate that maximum incidence occurred in animal subgroups irradiated with 3 Gy on 9^{th}, 12^{th} and 15^{th} days of gestation and 2 Gy on 9^{th} day of gestation. lower incidence occurred in subgroups irradiated with 2 Gy on days 12^{th} and 15^{th}. Lowest incidence occurred in subgroups irradiated with 0.5 Gy at 9^{th}, 12^{th} and 15^{th} days of gestation.

For Number of Litters, results indicate that maximum numbers occurred in animal subgroups irradiated with 0.5 and 1 Gy on 12^{th} and 15^{th} days of gestation. Lower numbers were observed for subgroups irradiated with 0.5 and 1Gy on 9^{th} day and 2 Gy on 12^{th} and 15^{th} days of gestation. Lowest numbers of litters were observed for subgroups irradiated with 2 Gy at 9^{th} day and with 3 Gy on 9^{th}, 12^{th} and 15^{th} days of gestation.

Observations recorded for the measurements of the parameters taken showed a generalized pattern of maximum decrease in measurements of all parameters appearing in all the 2 Gy subgroup irradiated on 9^{th} day of gestation. This indicates that early phases of gestation are most radiosensitive and that in a generalized phenomena of decrease growth

dimensions. The detailed results of these observations are clearly indicated in the curves and tables shown in figures (15-23). The salient features of these observations on the morphological studies point to the fact that the effect of in utero irradiation on the morphological changes observed on litters indicates a consistent pattern of change that is a function of radiation dose and significantly depends in its magnitude on the time of gestation at which irradiation took place. The text includes 18 tables (table 2-19) and 23 figures (figure 1-23) presenting data of morphological studies of the various parameters.

2. CONGENITAL MALFORMATIONS.

Several congenital malformations were detected in some live litters of different irradiated subgroups. These malformations include growth retardation, absence of tail, absence of eye fissures, haemencephalocele, penguin shaped litters, small limbs and tails, small ears, no ears and congested litters.

Studies on congenital malformations reveal that highest incidence of malformations appeared in litters of subgroups irradiated with 2 and 3 Gy on 12^{th} days of gestation. However, some malformations appeared in litters of other irradiated subgroups specially 2 Gy on 9^{th} day of gestation. The text includes 13 plates (plates 2-14) showing some congenital malformations of litters.

3. HISTOPATHOLOGICAL STUDIES.

The results of Histopathological Studies indicate that some organs showed histopathological changes of different severities and frequencies in the tissues of litters of irradiated subgroups. The tissues that showed the highest histopathological changes are the liver and ileum and to a lesser extent the kidney, brain and spleen. Other tissues as the suprarenal,

thymus, lungs and heart showed lesser degrees of affection regarding severity and frequency. It was observed that the constant pathological findings occurred in the liver and ileum of litters of subgroups irradiated with 2 and 3 Gy at 12^{th} and 15^{th} days of gestation. However, pathological findings observed in other tissues were inconsistent regarding dose and time of irradiation. This inconsistency is very clearly interpreted in the discussion as being attributed essentially to the individual variability in response of cells to radiation injury and also to the fact that the cellular populations undergoing developmental and organizational processes in the embryo and fetus are not synchronous. However, the results reported for the histopathological studies clearly add a new dimension to the effects of ionizing radiation to embryonic development and fetal growth. The text includes 9 tables (tables 20-28), a histogram (figure 24) and 33 plates (plates 15-47) showing normal and histopathological changes of the various organs.

The chapter on discussion is formulated in its detail to provide an overview of ground information in the preamble and appraisal sections. This is followed by a section on the features and interpretation of the results of the three studies performed, morphological studies, studies on congenital malformations and histopathological studies. The features of these studies were outlined and discussion on data was provided. The last part of chapter of discussion provides concluding statements that are very relevant to the subject of the thesis and that integrates the scientific informations that is gained from the results of the thesis to be conceptualized of the effects on radiation on human in utero irradiation; an issue of great importance and significance and is of national and international concern. The international recommendations regarding the subject of in utero irradiation in human population is also indicated.

REFERENCES

REFERENCES

Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K. and Watson, J. (1994):
"Molecular Biology of the Cell." 3rd ed. Garland, New York.

Aldeen, K.A.M. and Konermann G.(1978):
"Effects of Acute X-Irradiation on the Pre-implantation Embryos and on Implantation reaction in the Mouse."
Radiat. Environm. Biophys., 15:47.

Allderice, P.W.; Browne, N. and Murphy, D.P. (1975):
Chromosome 3 Duplication q21- qter Deletion p25- pter Syndrome in Children of Carriers of a Pericentric Inversion inv (3) (p25 q21)"
Am. J. Hum. Genet., 27:699.

Ashby, J.P. and Baird, J.d. (1982):
Differential Changes in Body Composition During Growth and Progesterone Treatment in Intact Female Rats."
J. Endocrinology, 93:391.

Atherton, J.C.; Dark, J.M.; Garland, H.O.; Morgan, M.R.A.; Pedgeon, J. and Soni, S. (1982):
Changes in Water and Electrolyte Balance, Plasma Volume and Composition During Pregnancy in the Rat."
J. Physiology, 330:81.

Auerbach, B.A.; Slowikowska, M.G.; Lenarczyk, M. and Gajewski, A.K. (1986):
"Teratogenic Effects in Exposed to Single Dose of X-rays and Prolonged Administration of Caffeine During Pregnancy."

Ball, J. and Moore, A.D. (1997):

"Interaction of X-rays and Gamma Rays with Matter."
In: Essential Physics for Radiography. 13th ed., 17:252. Blackwell Science.

Balsam, D. and Weiss, R.R. (1981):

"Amniography in Prenatal Diagnosis."
Pediatr. Radiol., 141:379.

Bancroft, J.D. and Stevens, A. (1990):

"The Haematoxylins"
In: Theory and Practice of Histological Techniques, 7:112.

Bannister, L.H. (1995):

"Cell and Tissues"
In: The Anatomical Basis of Medicine and Surgery (Gray's Anatomy) 38th ed. 2:17. ELBS with Churcill Livingstone.

Bannister, L.H.; Berry, M.M.; Collins, P.; Dyson, M.; Dussek, J.E. and Ferguson, M.W.J. (1995):

"Production of Cells"
In: The Anatomical Basis of Medicine and Surgery (Gray's Anatomy) 38th ed. 2:56. ELBS with Churcill Livingstone.

Barron, W.M.; Stamoutsos, B.A. and Liudeheimer, M.D. (1984):

"Role of Blood Volume in the Regulation of Vasopressin Secretion During Pregnancy in Rat."
J. Clinical Investigation, 73:923

Beck, F.; Moffat, D.B. and Davies, D.P. (1985):

Human Embryology" 2nd ed. Blackwell Scientific Publications. Oxford.

Behrman, R.E.; Kliegman, R.M. and Arvin, A.M. (1996):

"Fetal Growth and Development."

In: Nelson Text Book of Pediatrics. 15th ed., 9:33. W.B. Saunders Co. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

Behrman, R.E. and Vaughan, V.C. (1987):

"Developmental Pediatrics."

In: Nelson Text Book of Pediatrics. 13th ed., 2:7. W.B. Saunders Co. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

Bennet, J.P. and Vickery, B.H. (1970):

"Rats and Mice."

In: Reproduction and Breeding techniques for Laboratory animals. Hafez, E.S.E. (ed.), Lea and Fabiger, Philadelphia, P.299.

Brackett, B.G.; Seitz, H.M.; Rocha, G. and Mastroianni, L. (1972):

"The Mammalian Fertilization Process."

In: Biology of Mammalian Fertilization and Implantation. Moghissi, K.S. and Hafez, E.S.E. (ed.), Springfield, Charles C. Thomas, Publisher, P.165.

Breg, W.R. (1975):

"Autosomal Abnormalities."

In: Endocrine and Genetic Diseases of Childhood and Adolescence. Gardner, L.L. (ed.) 2nd ed. W.B. Saunders Co. Philadelphia.

Brent, R.L. (1986):

"Radiation Teratogenesis."

In: Teratogen Update: Environmentally Induced Birth Defect Risks. Sever, J.L. and Brent, R.L. (ed.) Alan R. Liss Inc. New York.

Brent, R.L. and Bolden, B.T. (1967):

"The Indirect Effect of Irradiation on Embryonic Development. The Contribution of Ovarian Irradiation, Uterine Irradiation, Oviduct Irradiation and Zygote Irradiation to Fetal Mortality and Growth Retardation in the Rat."
Radiation research, 30:759.

Carr, D.H.; Law, E.M. and Ekins, J.G. (1972):

"Chromosome Studies in Selected Spontaneous Abortions. Unusual Cytogenetic Disorders."
Teratology, 5:49.

Cember, H. (1985):

"Biological Effects of Radiation."
In: Introduction to Health Physics, 2nd ed. 7:197. Pergamon Press.

Connor, J.M. and Ferguson-Smith, M.A. (1984):

"Essential Medical Genetics." Oxford, Blackwell Scientific Publications.

Cotran, R.S.; Kumar, V. and Robbins, S.L. (1994):

"Environmental and Nutritional Diseases"
In: Robbins Pathological Basis of Disease. 5th ed. W.B. Saunders Co. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo. P.402.

Crooke, A.C. (1970):

"Human Gonadotropins."
In: Scientific Foundations of Obstetrics and Gynecology. Philipp, E.E., Barnes, J. and Newton, M. ed. William Heinemann, Ltd., London.

Devi, P.V.; Baskar, R. and Hande, M. P. (1994):

"Effect of Low dose Gamma Radiation During Late Organogenesis in the mouse Fetus."
Radiation Research, 138(1):133.

Devi, U. P.; and Hande, P. M. (1990):

Effect of Low Dose of 70KVP X-rays on Intrauterine Development of Mice. Experientia, 46:511.

Diengdoh, J. V. and Booth, A. E. (1976):

"Postirradiation Necrosis of the Temporal Lobe Presenting as a Glioma" Jr. Neurosurgery 44:732.

El-Naggar, A.M. (1990):

Postgraduate Radiation Biology Lectures, Ain Shams University, Faculty of Medicine, Radiology Department.

El-Naggar, A.M. (1996):

"Health Hazards of Low Doses of Ionizing Radiation."

In: Proceedings the 6th Conference of Nuclear Sciences and Applications. Published in Arab Journal of Nucl. Sc. Applications 1:264.

El-Naggar, A.M. (1999):

Personal communication.

Enders, A.C. (1970):

"Fertilization, Cleavage and Implantation."

In: Reproduction and Breeding Techniques for Laboratory Animals. Hafez, E.S.E. ed. Lea and Fabiger, Philadelphia Chap. 7:137.

Finch, S. C. (1979).

"The Study of Atomic Bomb Survivors in Japan." Am. J. Med. 66:899.

Fox, R.R. and Laird, C.W. (1970):

"Sexual Cycles."

In: Reproduction and Breeding Techniques for Laboratory Animals. Hafez,E.S.E. ed. Lea and Fabiger, Philadelphia Chap. 5:107.

Gardner, E.J.; Simmons, M.J. and Snustad, D.P. (1985):

"Radiation Induced Mutation."

In: Principles of Genetics. 8th ed. P.301. John Wiley and Sons, Inc. New York, Singapore.

Golbus, M.S. (1980):

"Teratology for the Obstetrician: Current Status."

Obstet. Gynecol., 55:269.

Green, E.L. (1966):

"Biology of Laboratory Mouse." New York, McGraw-Hill.

Greening, J.R. (1985):

"Introduction of Ionizing Radiation."

In: Fundamentals of Radiation Dosimetry. 2nd ed. Chap. 2:6. Institute of Physics Publishing. Bristol and Philadelphia.

Gurdon, J.B. (1973):

"Gene Expression in Early Animal Development." The Study of Its Control by the Microinjection of Amphibian Eggs. Harvey Lectures 69:49-69.

Hall, J.G. (1996):

"Chromosomal Clinical Abnormalities."

In: Nelson Text Book of Pediatrics. 15th ed., 67:312. W.B. Saunders Co. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

Hendrickx, A.G. and Houston, M.L. (1970):

"Gestation and Prenatal Development."

In: Reproduction and Breeding techniques for Laboratory animals. Hafez, E.S.E. (ed.), Lea and Fabiger, Philadelphia, P.157.

Hollander, W.F. and Strong, L.C. (1950):

"Intrauterine Mortality and Placental Fusion in the Mouse."
J. Exp. Zool., 115:131.

Henson, R.A. and Urich, H. (1982):

"Cancer and the Nervous System."
In: The Neurological Manifestations of Systemic Malignant Disease. Blackwell Scientific, Oxford.

Hong,A.I.C.; Kusama, T. Gu,Y. and Aoki, Y. (1993):

"The Combined Effects of Radiation and Ultrasound on ICR Mouse Embryos." China Society of Radiation Protection, BJ (China); Japan Health Physics Society, Tokyo (Japan). Proceedings of Asia Congress on Radiation Protection, 751:184.

Huuskonen, H.; Juutilainen, J. and Komulainen,H., (1993):

"Effects of Low-Frequency Magnetic Fields on Fetal Development in Rats"
Bioelectromagnetics, 14:205.

Iman I. Abdel Gawad, (1995):

"Assessment of Morphological and Biochemical Changes During Pregnancy in Rats Under the Effect of Radiation and Progesterone" Ph.D. Thesis, Department of zoology, Faculty of Science, Cairo University.

ICRP, (1977):

International Commission on Radiological Protection,
Publication Number 55, 1977.

ICRP (1991):

International Commission on Radiological Protection,
Publication Number 60, 1991.

Jensh, R.P. and Brent, R.L. (1986):

"Effects of 0.6 Gray Prenatal X-irradiation on Postnatal Neurophysiologic Development in the Wister Rat."
Proceeding of the society for Experimental Biology and Medicine, 181"611.

Jensh, R.P. and Brent, R.L. (a) (1988):

"Effects of Prenatal X-irradiation on the 14^{th}-18^{th} Day of Gestation on Postnatal Growth and Development in the Rat."
Teratology, 38:431.

Jensh, R.P. and Brent, R.L. (b) (1988):

"Effects of Prenatal X-irradiation on the appearance of reflexes and physiologic markers in the neonatal rat.
Radiation research, 116:416.

Karp, G. (1979):

"Cell Growth and Replication."
In: Cell Biology. Chap. 14:639. Mc Graw-Hill Book Co. New York.

Knauss, G. (1980):

"Dose Response Relationships of Embryonary Radiation Damage for Example in the Mouse Skeleton after Antenatal Exposure to X-radiation". Thesis, University of Freiburg, Medical Faculty.

Lala, P.K.; Kearns, M. and Colavincezo, V. (1984):

"Cell of the Fetomaternal Interface: Their Role in the Maintenance of Viviparous Pregnancy."
Am. J. Anat., 170:501.

Lazjuk, G.I.; Kirillova,I.A; Nikolaev, D.L. and Novikova, I.V. (1993):
"Monitoring of Congenital Malformations in Belarus After Chernobyl Accident" Merwin, S.E. and Balonov, M.I. ed. The Chernobyl Papers. Vol.I. Doses to the Soviet Population and Early Health Effects Studies. Richland, W.A. (united States). Research Enterprises, 455:385.

Lazjuk, G.I.; Kirillova,I.A; Nikolaev, D.L. and Novikova, I.V. (1994):
"Incidence of Developmental Abnormalities Among Human Fetuses in Different Regions of Belarus After the Chernobyl Accident." Russian J. Genetics, 30(9): 1102. Cited in INIS 1/93-1/96.

Lea, D.E., (1946):
"Action of Radiation on Living Cells" Cambridge University press.

Lillien, L.E. and Claude, P. (1981):
"Nerve Growth Factor is a Mitogen for Cultured Chromaffin Cells." Nature, 317:632.

Macdonald, L.E. (1980):
"Pregnancy and Parturition."
In: Veterinary Endocrinology and Reproduction. 3rd ed. P. 453.

Manz, H.J.; Woolley, P.V. III and Ornitz, R.D. (1979):
"Delayed Radiation Necrosis of Brainstem Related to Fast Neutron Beam Irradiation." Case reported and literature review. Cancer, 44:473.

Mazur, L. (1984):
"Intrauterine Development of Mice Embryos After Exposure to X-rays During the Preimplantation Period." Biol. 32:71.

McClure, T.J. (1966):
"Infertility in Mice Caused by Fasting at About the Time of Mating. I. Mating and Behavior and Littering Rats." J. Repord. Fertil. 12:243.

Mettler, F.A. and Moseley, R.D. (1985):

"Medical Effects of Ionizing Radiation." Orlando, Grune and Stratton. P. 18.

Miller, R.W. and Merke, D.P. (1996):

"Radiation Injury."

In: Nelson Text Book of Pediatrics. 15th ed., 662:2002. W.B. Saunders Co. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

Minoru, I. (1995):

"Radiation Induced Apoptosis and Developmental Disturbance of the Brain."

Congenital Anomalies, 35(1):1.

Mole, R.H. (1982):

"Consequences of Prenatal Radiation Exposure for Postnatal Development." Int. J. Radiol. Biol. 42:1.

Moore, K.L. (1988):

"The Developing Human. Clinically Oriented Embryology." 4th ed. W.B. Saunders Co. Harcourt Brace Jovanovich, Inc. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

NCRP, (1985):

National Council on Radiation Protection, (USA) "Medical Radiation Exposure of Pregnant and Potentially Pregnant Women." Report Number 53.

Neu, R.L. and Gardner, L.I. (1975):

"Abnormalities of the Sex Chromosomes."

In: Endocrine and Genetic Diseases of Childhood and Adolescence. Gardner, L.L. ed., 2nd ed. . W.B. Saunders Co., Philadelphia.

Nishimura,H.; Tanimura, T.; Semb, R. and Uwabe, C. (1974):
"Normal Development Of early Human Embryos : Observation of 90 Specimens at Carnegie Stages 7 to 13."
Teratology, 10:1.

Ohzu, E. (1965):
"Effects of Low Dose X-irradiation on Early Mouse Embryos."
Radiation Research, 26:107.

O'Rahilly, R. (1973):
"Developmental Stages in Human Embryos."
In: Embryos of the First Three Weeks (stages 1 to 9). Carnegie Institution of Washington, Washington.

Page, E.W.; Villee, C.A. and Villee, D.B. (1981):
"Human Reproduction."
In: Essentials of Reproduction and Perinatal Medicine. 3rd ed. . W.B. Saunders Co., Philadelphia.

Park, K. (1995):
"Radiation."
In: Park's Text Book of Preventive and Social Medicine. M/S Banarsidas Bhanot Publishers. India.

Persaud, T.V.N. (1979):
"Teratogenesis. Experimental Aspects and Clinical Implications."
Gena, Gustav Fischer Verlag.

Persaud, T.V.N.; Chudley, A.E. and Skalko, R.G. (1985):
"Basic Concepts in Teratology." Alan R. Liss, Inc. New York.

Philippe, J.V. (1975):

"Influence of Ionizing Radiation on Fetoplacental Growth in Mice." Radiation Research, 123(6):640.

Philip Rubins and George W. Casarette (1968):

"Radiopathologic basis of the clinical course"
In: Clinical Radiation Pathology, vol. I:308; W. B. Saunders Company.

Ratcliffe, J.M.; McElhatton, P.R. and Sullivan, F.M. (1993):

"Reproductive Toxicity."
In: General and Applied Toxicology. Bryan Ballantyne; Timothy Marrs and Paul Turner ed. Stockton Press. 2 P898.

Robin, P. and Casarett, G. W. (1968):

"Radiation pathology of the Urinary Tract". In: Clinical Radiation Pathology. Vol. 1, W.B. Saunders Company. Philadelphia, London and Toronto. P. 308.

Roux, C.H.; Eliphant, E.; Gaborlaud, G.; Jaullery, C.H.; Gardette, J.; Dupuis, R. and Lambert, D. (1986):

"Association of Microwaves and Ionizing Radiation: Potentiation of Teratogenic Effects in the Rats."
Radiation Research, 108:317.

Rugh, R. and Wohlfromm, M. (1965):

"Prenatal X-irradiation and Postnatal Mortality."
Radiation Research, 26:493.

Rugh, R.; Wohlfromm, M. and Varma, A. (1969):

"Low Dose X-ray Effects on the Precleavage Mammalian Zygote." Radiation Research, 37:401.

Russell, D.S. and Rubinstein, L.J., (1989):

"Effects of Radiotherapy and Chemotherapy on Cranial and Spinal Tumors and their Surrounding Tissues". In: Pathology of Tumors of the Nervous System, 5th Edition, Edward Arnold, a division of Hodder and Stoughton, London, Melbourne and Auckland.

Russell, L.B. and Russell, W.L. (1954):

"An Analysis of the Changing Radiation Response of the Developing Mouse Embryo."
J. Cellular Comp. Physiol., 43, Suppl. 1:103.

Smith, D.W. and Gong, B.T. (1973):

"Scalp Hair Patterning as a Clue to Early Fetal Brain Development."
Pediat., 83:379.

Stevens, A. and Lowe, J.S. (1997):

"Histology: Don't Switch Off!"
In: Human Histology, 2nd ed. 1:1. Mosby. London, Baltimore, Toronto, Tokyo.

Streffer, C. (1995):

"Radiation Effects After Exposure During Prenatal Development."
Radiology, 35(5):141.

Sun-Xuezhi; Inouye, M.; Hayasaka, S.; Takagish, Y. and Yamamura, H. (1995):

"Effects of Different Doses of Gamma-Radiation on the Developing Brain of Mice."
Environmental Medicine, 39(2):113.

Tedeschi, H. (1993):

"Multifacted Roles of the Cell Surface."
In: Cell Physiology, P.67. Wm. C. Brown Publishers Oxford England.

Thompson, M.V. (1986):

"Genetics in Medicine" 4th ed. W.B. Saunders Co. Philadelphia.

Tofani, S.; Agnesod, G. and Ossola, P. (1986):

"Effects of Low Level Exposure to Radiofrequency Radiation on Intrauterine Development in Rats."
Health Physics, 51(5):489.

Tomoko, K. and Yasunari, H. (1993):

"Stage Differences in Developmental Disorder in ICR Mouse Embryos Irradiated with Gamma-rays."
Congenital Anomalies, 33(2):115.

Tubiana, M.; Dutreix, J. and Wambersie, A. (1990):

"Effect of Irradiation on the Human Body."
In: Introduction to Radiology. P.307. Translated by Bewley, D.K. Taylor and Francis, London, New York, Philadelphia.

UNSCEAR, (1986).

United Nations Scientific Committee on Effects of Atomic Radiation.

UNSCEAR, (1993).

United Nations Scientific Committee on Effects of Atomic Radiation.

Upton, A.C., (1982):

"Radiation Injury: Past, Present and Future." In: Hill, R.B. and Terzian, J.A. (eds.): Environmental Pathology, An Evolving Field. New York, Alan R. Liss, P.9.

Wessels, N.K. (1977):

"Tissue Interactions in Development." W.B. Benjamin Inc., Milano Park, California.

Wilson, W. B. and Kleinschmidt-DeMasters B. K. (1987):

"Sudden Onset of Blindness in patients Treated with Oral CCNU and Low Dose Cranial irradiation." Cancer 59:901.

Yarmonenko, S.P. (1988):

"Radiology of Human and Animals." Translated from Russian by Leib, G. Mir Publishers Moscow.

Zhous, J. and Wang, J. (1982):

"Studies of Radiation Effects on Mouse Embryos in the Pre-implantation Stage."

Chin. J. Radiol. Med. Prot., 2:18.

APPENDIX

Appendix

Detailed data of number of absorption sites, litters and measurements for the litters of the control and the irradiated subgroups to 0.5, 1, 2 and 3 Gy on 9th, 12th and 15th days of gestation.

control 9						Mean	SE	SD	Variance	Minimum	Maximum
No. of absorption sites	01.00	00.00	00.00	00.00	01.00	00.40	00.22	00.49	00.24	00.00	01.00
No. of litters	06.00	08.00	06.00	08.00	06.00	06.80	00.44	00.98	00.96	06.00	08.00
Size ml.	04.70	03.40	04.30	04.20	03.50	04.02	00.22	00.50	00.25	03.40	04.70
weight gm.	04.90	03.90	04.10	04.04	03.30	04.05	00.23	00.51	00.26	03.30	04.90
Length (lat.) mm	36.60	33.30	35.70	33.90	32.30	34.36	00.70	01.57	02.48	32.30	36.60
Girth (circum.) mm	46.08	39.23	41.60	41.33	39.67	41.58	01.09	02.43	05.90	39.23	46.08
Tail length mm	14.70	13.57	13.90	14.33	12.53	13.81	00.33	00.74	00.55	12.53	14.70
Skull (AP) mm	16.50	16.00	15.70	16.00	15.10	15.86	00.21	00.46	00.21	15.10	16.50
Skull (BP) mm	10.80	10.80	10.40	10.40	10.00	10.48	00.13	00.30	00.09	10.00	10.80

control 12						Mean	SE	SD	Variance	Minimum	Maximum
No. of absorption sites	01.00	00.00	00.00	00.00	01.00	00.40	00.22	00.49	00.24	00.00	01.00
No. of litters	06.00	08.00	05.00	08.00	10.00	07.40	00.78	01.74	03.04	05.00	10.00
Size ml.	04.70	03.60	04.30	04.20	03.50	04.06	00.20	00.45	00.20	03.50	04.70
weight gm.	04.90	03.90	04.40	04.04	03.30	04.11	00.24	00.53	00.28	03.30	04.90
Length (lat.) mm	36.60	33.30	35.75	33.90	32.30	34.37	00.71	01.58	02.51	32.30	36.60
Girth (circum.) mm	46.08	40.23	41.60	43.33	39.67	42.18	01.04	02.32	05.39	39.67	46.08
Tail length mm	14.70	14.50	15.90	14.30	12.50	14.38	00.49	01.09	01.19	12.50	15.90
Skull (AP) mm	16.58	16.37	15.77	16.80	15.13	16.13	00.27	00.61	00.37	15.13	16.80
Skull (BP) mm	10.80	10.83	10.43	10.90	10.07	10.61	00.14	00.31	00.10	10.07	10.90

control 15						Mean	SE	SD	Variance	Minimum	Maximum
No. of absorption sites	01.00	00.00	01.00	00.00	01.00	00.60	00.22	00.49	00.24	00.00	01.00
No. of litters	06.00	09.00	06.00	08.00	10.00	07.80	00.72	01.60	02.56	06.00	10.00
Size ml.	05.20	04.20	04.30	04.60	04.50	04.56	00.16	00.35	00.12	04.20	05.20
weight gm.	04.90	03.90	04.10	04.04	04.30	04.25	00.16	00.35	00.12	03.90	04.90
Length (lat.) mm	39.60	35.30	35.80	33.90	32.30	35.38	01.09	02.44	05.93	32.30	39.60
Girth (circum.) mm	46.08	40.23	41.60	43.33	42.67	42.78	00.87	01.95	03.82	40.23	46.08
Tail length mm	14.70	15.50	13.90	15.30	13.50	14.58	00.35	00.78	00.60	13.50	15.50
Skull (AP) mm	16.90	16.37	15.90	16.80	15.13	16.22	00.29	00.65	00.42	15.13	16.90
Skull (BP) mm	10.80	10.90	10.40	10.90	10.50	10.70	00.09	00.21	00.04	10.40	10.90

9th day of gestation

0.5 Gy 9th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	1	1	1	1	1	1.00	0.00	0.00	0.00	1	1	0.03524
No. of litters	6	8	7	7	5	6.60	0.46	1.02	1.04	5	8	0.39224
Size ml.	5	4.1	3.1	3.8	4	4.00	0.27	0.61	0.37	3.1	5	0.48035
weight gm.	4.78	4.05	3.5	3.76	4.07	4.03	0.19	0.43	0.18	3.5	4.78	0.48149
Length (lat.) mm	35.5	34.23	33.27	33	32.7	33.74	0.46	1.02	1.04	32.7	35.5	0.26501
Girth (circum.) mm	44	43.25	38.27	41.5	38.7	41.14	1.04	2.32	5.39	38.27	44	0.40044
Tail length mm	12.3	12.58	11.8	14.4	14.5	13.12	0.50	1.12	1.25	11.8	14.5	0.16924
Skull (AP) mm	16.27	15.7	14.6	15.3	15.1	15.39	0.25	0.56	0.32	14.6	16.27	0.11843
Skull (BP) mm	11.03	10.78	9.33	10.1	9.6	10.17	0.29	0.66	0.43	9.33	11.03	0.21098

1 Gy 9th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	0.00	2.00	2.00	2.00	0.00	1.20	0.44	0.98	0.96	0	2	0.09769
No. of litters	7.00	4.00	7.00	6.00	8.00	6.40	0.61	1.36	1.84	4	8	0.3233
Size ml.	3.11	3.10	3.00	2.80	3.00	3.00	0.05	0.11	0.01	2.8	3.11	0.00662
weight gm.	2.80	3.26	3.01	2.70	3.02	2.96	0.09	0.19	0.04	2.7	3.26	0.00499
Length (lat.) mm	31.82	32.03	31.47	34.93	32.80	32.61	0.55	1.24	1.54	31.47	34.93	0.06043
Girth (circum.) mm	38.80	38.77	41.80	44.65	38.10	40.42	1.11	2.47	6.11	38.1	44.65	0.26131
Tail length mm	12.42	11.80	10.73	11.08	13.10	11.83	0.39	0.86	0.75	10.73	13.1	0.00435
Skull (AP) mm	14.50	15.53	15.83	16.28	14.00	15.23	0.38	0.85	0.72	14	16.28	0.11838
Skull (BP) mm	9.76	9.90	10.00	9.90	9.40	9.79	0.09	0.21	0.04	9.4	10	0.00338

2 Gy 9th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	5.00	3.00	6.00	7.00	5.00	5.20	0.59	1.33	1.76	3	7	0.0005
No. of litters	0.00	5.00	2.00	0.00	0.00	1.40	0.88	1.96	3.84	0	5	0.00139
Size ml.	0.00	3.00	2.25	0.00	0.00	1.05	0.58	1.31	1.71	0	3	0.00384
weight gm.	0.00	2.42	2.45	0.00	0.00	0.97	0.53	1.19	1.42	0	2.45	0.00209
Length (lat.) mm	0.00	32.10	29.85	0.00	0.00	12.39	6.79	15.19	230.77	0	32.1	0.02201
Girth (circum.) mm	0.00	38.77	35.45	0.00	0.00	14.84	8.14	18.21	331.62	0	38.77	0.02092
Tail length mm	0.00	12.63	8.55	0.00	0.00	4.24	2.39	5.35	28.58	0	12.63	0.01121
Skull (AP) mm	0.00	16.20	13.65	0.00	0.00	5.97	3.29	7.36	54.11	0	16.2	0.02728
Skull (BP) mm	0.00	9.33	8.55	0.00	0.00	3.58	1.96	4.39	19.24	0	9.33	0.0172

3 Gy 9th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	9.00	8.00	6.00	6.00	7.00	7.20	0.52	1.17	1.36	6	9	3.9E-05
No. of litters	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	7.8E-05
Size ml.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	4.2E-05
weight gm.	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	4.7E-05
Length (lat.) mm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	8.2E-07
Girth (circum.) mm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	2.2E-06
Tail length mm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	1.6E-06
Skull (AP) mm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	1.3E-07
Skull (BP) mm	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0	1.2E-07

12th day of gestation

0.5 Gy 12th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	0	0	0	0	3	0.6	0.54	1.20	1.44	0	3	0.3847
No. of litters	8	7	11	8	2	7.2	1.31	2.93	8.56	2	11	0.45502
Size ml.	3.75	3.8	3.6	4.75	4.3	4.04	0.19	0.43	0.18	3.6	4.75	0.47505
weight gm.	3.86	3.86	3.66	4.86	4.2	4.088	0.19	0.42	0.18	3.66	4.86	0.47729
Length (lat.) mm	33.57	33.9	33.9	33.57	35.57	34.102	0.33	0.75	0.56	33.57	35.57	0.38519
Girth (circum.) mm	42.2	42	41	42.2	42.2	41.92	0.21	0.47	0.22	41	42.2	0.4175
Tail length mm	16.5	16.9	11.9	12.5	12.5	14.06	0.97	2.17	4.71	11.9	16.9	0.4006
Skull (AP) mm	16	15.13	14.13	16	16	15.452	0.33	0.74	0.55	14.13	16	0.0981
Skull (BP) mm	11.6	9.47	9.47	11	9.67	10.242	0.40	0.89	0.79	9.47	11.6	0.23718

1 Gy 12th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	0.00	1.00	1.00	2.00	1.00	1.00	0.28	0.63	0.40	0	2	0.08716
No. of litters	9.00	7.00	7.00	5.00	7.00	7.00	0.57	1.26	1.60	5	9	0.36045
Size ml.	3.20	3.10	3.90	2.60	3.40	3.24	0.19	0.42	0.18	2.6	3.9	0.01451
weight gm.	3.59	3.38	4.46	2.82	2.76	3.40	0.28	0.62	0.38	2.76	4.46	0.06108
Length (lat.) mm	32.23	32.80	34.93	29.87	32.70	32.51	0.72	1.61	2.60	29.87	34.93	0.06888
Girth (circum.) mm	41.00	42.03	44.73	38.30	38.90	40.99	1.03	2.31	5.33	38.3	44.73	0.24409
Tail length mm	13.27	12.07	14.03	10.93	12.50	12.56	0.47	1.06	1.11	10.93	14.03	0.02172
Skull (AP) mm	15.47	15.50	16.07	13.97	15.50	15.30	0.31	0.70	0.49	13.97	16.07	0.05655
Skull (BP) mm	10.00	10.20	10.60	8.93	9.40	9.83	0.26	0.59	0.35	8.93	10.6	0.02913

2 Gy 12th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	4.00	1.00	6.00	1.00	0.00	2.40	1.00	2.24	5.04	0	6	0.07522
No. of litters	3.00	6.00	2.00	5.00	7.00	4.60	0.83	1.85	3.44	2	7	0.02957
Size ml.	3.33	2.50	2.50	2.80	2.30	2.69	0.16	0.36	0.13	2.3	3.33	0.0008
weight gm.	3.60	2.40	2.25	2.74	1.83	2.56	0.27	0.59	0.35	1.83	3.6	0.00242
Length (lat.) mm	25.23	24.37	25.90	24.70	22.00	24.44	0.59	1.33	1.76	22	25.9	7E-06
Girth (circum.) mm	33.33	33.40	30.10	31.20	24.70	30.55	1.42	3.18	10.14	24.7	33.4	0.00025
Tail length mm	11.57	11.87	11.25	11.20	8.10	10.80	0.61	1.37	1.88	8.1	11.87	0.00194
Skull (AP) mm	14.00	12.10	12.30	11.40	9.60	11.88	0.64	1.42	2.03	9.6	14	0.00107
Skull (BP) mm	10.40	8.53	8.15	8.35	5.10	8.11	0.76	1.71	2.91	5.1	10.4	0.02074

3 Gy 12th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	5.00	4.00	5.00	11.00	7.00	6.40	1.12	2.50	6.24	4	11	0.00384
No. of litters	2.00	3.00	1.00	0.00	0.00	1.20	0.52	1.17	1.36	0	3	0.0003
Size ml.	1.50	2.00	2.50	0.00	0.00	1.20	0.46	1.03	1.06	0	2.5	0.00147
weight gm.	1.15	1.73	2.20	0.00	0.00	1.02	0.40	0.89	0.80	0	2.2	0.00037
Length (lat.) mm	23.46	29.77	27.50	0.00	0.00	16.15	5.96	13.34	177.88	0	29.77	0.02588
Girth (circum.) mm	36.95	36.23	37.00	0.00	0.00	22.04	8.05	17.99	323.80	0	37	0.04418
Tail length mm	3.30	4.77	4.50	0.00	0.00	2.51	0.94	2.11	4.46	0	4.77	2.9E-05
Skull (AP) mm	10.30	10.80	11.00	0.00	0.00	6.42	2.35	5.25	27.53	0	11	0.01015
Skull (BP) mm	7.25	8.90	8.20	0.00	0.00	4.87	1.79	4.01	16.09	0	8.9	0.02283

15th day of gestation

0.5 Gy 15th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	0.00	0.00	0.00	2.00	0.00	0.40	0.36	0.80	0.64	0.00	2.00	0.3417
No. of litters	8.00	9.00	8.00	5.00	9.00	7.80	0.66	1.47	2.16	5.00	9.00	0.5000
Size ml.	4.50	4.44	4.20	4.35	4.44	4.39	0.05	0.10	0.01	4.20	4.50	0.1934
weight gm.	4.35	4.00	4.10	4.30	4.51	4.25	0.08	0.18	0.03	4.00	4.51	0.4922
Length (lat.) mm	34.00	35.63	36.30	36.80	33.20	35.19	0.61	1.37	1.88	33.20	36.80	0.4470
Girth (circum.) mm	43.00	42.67	41.70	41.90	42.90	42.43	0.24	0.53	0.28	41.70	43.00	0.3732
Tail length mm	16.20	15.10	13.30	12.50	14.25	14.27	0.58	1.30	1.70	12.50	16.20	0.3479
Skull (AP) mm	16.30	16.10	15.80	16.25	16.25	16.14	0.08	0.18	0.03	15.80	16.30	0.4114
Skull (BP) mm	10.90	10.57	10.40	10.60	10.53	10.60	0.07	0.17	0.03	10.40	10.90	0.2361

1 Gy 15th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	0.00	2.00	0.00	1.00	0.00	0.60	0.36	0.80	0.64	0.00	2.00	0.5000
No. of litters	9.00	5.00	9.00	7.00	8.00	7.60	0.67	1.50	2.24	5.00	9.00	0.4298
Size ml.	3.60	3.80	3.10	3.25	3.25	3.40	0.12	0.26	0.07	3.10	3.80	0.0005
weight gm.	3.76	3.88	3.39	3.51	3.30	3.57	0.10	0.22	0.05	3.30	3.88	0.0071
Length (lat.) mm	31.90	37.97	32.40	33.03	33.03	33.67	0.98	2.19	4.81	31.90	37.97	0.1633
Girth (circum.) mm	40.17	44.20	38.90	42.73	39.90	41.18	0.88	1.97	3.88	38.90	44.20	0.1407
Tail length mm	13.30	13.23	12.13	12.13	13.87	12.93	0.31	0.69	0.48	12.13	13.87	0.0067
Skull (AP) mm	15.00	16.37	16.03	15.33	15.93	15.73	0.22	0.50	0.25	15.00	16.37	0.1346
Skull (BP) mm	9.20	10.20	9.80	9.97	9.63	9.76	0.15	0.34	0.11	9.20	10.20	0.0012

2 Gy 15th day						Mean	SE	SD	variance	minimum	Maximum	t-test
No. of absorption sites	3.00	2.00	1.00	3.00	2.00	2.20	0.33	0.75	0.56	1.00	3.00	0.0046
No. of litters	0.00	7.00	7.00	4.00	9.00	5.40	1.40	3.14	9.84	0.00	9.00	0.1111
Size ml.	0.00	3.90	3.30	4.00	3.90	3.02	0.68	1.53	2.34	0.00	4.00	0.0573
weight gm.	0.00	4.00	3.40	3.88	4.00	3.06	0.69	1.54	2.38	0.00	4.00	0.1000
Length (lat.) mm	0.00	33.00	33.00	34.00	33.00	26.60	5.95	13.31	177.04	0.00	34.00	0.1300
Girth (circum.) mm	0.00	42.23	42.23	43.60	42.23	34.06	7.62	17.04	290.27	0.00	43.60	0.1826
Tail length mm	0.00	13.07	13.07	15.80	13.07	11.00	2.51	5.60	31.38	0.00	15.80	0.1360
Skull (AP) mm	0.00	15.77	15.77	17.45	15.77	12.95	2.91	6.51	42.36	0.00	17.45	0.1866
Skull (BP) mm	0.00	10.70	10.40	11.10	10.90	8.62	1.93	4.32	18.63	0.00	11.10	0.1950

3 Gy 15th day						Mean	SE	SD	variance	Minimum	Maximum	t-test
No. of absorption sites	4.00	1.00	5.00	2.00	3.00	3.00	0.63	1.41	2.00	1.00	5.00	0.0121
No. of litters	6.00	6.00	0.00	5.00	0.00	3.40	1.25	2.80	7.84	0.00	6.00	0.0161
Size ml.	3.67	3.00	0.00	2.90	0.00	1.91	0.71	1.59	2.51	0.00	3.67	0.0136
weight gm.	3.53	3.64	0.00	3.06	0.00	2.05	0.75	1.68	2.83	0.00	3.64	0.0288
Length (lat.) mm	34.70	33.00	0.00	31.73	0.00	19.89	7.27	16.26	264.52	0.00	34.70	0.0648
Girth (circum.) mm	40.60	40.90	0.00	36.80	0.00	23.66	8.66	19.37	375.29	0.00	40.90	0.0598
Tail length mm	12.80	12.70	0.00	10.37	0.00	7.17	2.65	5.92	35.07	0.00	12.80	0.0331
Skull (AP) mm	15.93	15.93	0.00	15.07	0.00	9.39	3.43	7.67	58.83	0.00	15.93	0.0747
Skull (BP) mm	9.57	10.07	0.00	9.37	0.00	5.80	2.12	4.74	22.49	0.00	10.07	0.0539

ARABIC SUMMARY

الملخص العربى

الملخص العربي

المقدمة:

إن كلمة إشعاع تعني إنتقال الطاقة. ويأخذ الإشعاع بضعة أشكال تعتمد على طبيعته. فالإشعاع المؤين هو الذى يحدث إثارة وتأين للوسط الذي يمر خلاله. و أنواع الإشعاعات المؤينة إما فوتونات أو جسيمات. و الفرق بين هذين النوعين يعتمد على نمط توليد وإرسال الطاقة، وعلى غياب أو وجود الكتلة. فالفوتونات التي لها خاصية التأين هى الأشعة السينية وأشعة جاما. والطاقة المتولدة عن الإشعاع تعتمد على تردده الموجى، فكلما زاد التردد ونقص طوله الموجى قلت طاقته. ووحدة إمتصاص الطاقة الإشعاعية هى الجراى. وتعرف بأنها إمتصاص واحد جول من الطاقة في كيلوجرام واحد من الوسط الحى.

تعتبر الفترة الكاملة للحمل (من الإخصاب حتى الولادة) هي الفترة الأشد حساسية للتشوهات من العوامل الداخلية والخارجية. إن الجنين هو أكثر الأنسجة حساسية للأشعة من أى كائن حى آخر. هذا بسبب كثرة العمليات الحيوية من التكاثر والتميز للنسيج الخلوي الجنيني خلال الحياة الجنينية . والنسيج الجنيني هو النسيج الأكثر تكاثرا وذلك خلال الإنقسام الميتوزى والذي يكون سريعا جدا فى الخلايا الجنينية. مثل هذا الأمر يجعل الجنين (خلال كل مراحل الحمل) هو الأكثر عرضة للإصابة بالمؤثرات الخارجية والداخلية. وتنقسم مراحل تطور الجنين إلى ثلاث مراحل هى: ما قبل الإزدراع، تكوين الأعضاء ونمو الجنين. ورغم أن مراحل النمو الجنينى

متماثلة لمعظم الثدييات ومنهم بالطبع الجنس البشرى، إلا أنها تختلف فى طول كل مرحلة منهم. ومدى الضرر يتعلق بالمسبب كالإشعاع. والمؤثر فى هذه الدراسة هو الإشعاع المؤين. وهناك عدة تأثيرات مختلفة للإشعاع تحدث للجنين خلال فترة الحياة الرحمية. وهذه الإختلافات في التأثير تتوقف بشكل رئيسي على جرعة الإشعاع، ومرحلة الحمل. وهذا الشذوذ فى التطور الذي يحدث خلال الفترة الكاملة للحمل يكون بسبب النسبة العالية من الخلايا الحساسة للأشعة والتى لها نشاط شديد خلال فترة الحياة الجنينية. والتغييرات التي تحدث خلال تطور الجنين تتضمن عملية التكسير التى تحدث للخلايا كنتيجة للموت الخلوي، الذى يسبب تشوه جنيني يكون له أثر على عملية التطور.

الهدف من البحث:

أجريت هذه الدراسة لمعرفة تأثير الجرعات المختلفة لأشعة جاما على الجنين في المراحل المختلفة للحمل.

العينة و الطرق المستخدمة:

خمسة وسبعون جرذ تجارب حبلى بعد التأكد من حدوث الحمل (بالفحص المجهرى لمسحة مهبلية).

اشتملت هذه الدراسة على أربع جرعات من أشعة جاما (٠,٥، ١، ٢ و٣ جراي). وقد عرضت مجموعات من الجرذان الحبلى لأشعة جاما في

الأوقات المحددة من الحمل (مرحلة تكون الأعضاء المبكر، مرحلة تكون الأعضاء الرئيسية ومرحلة نمو الأعضاء). و قد كان الغرض أن يدرس تأثير الإشعاع فى التغييرات التى تطرأ في كل مرحلة على إنفراد وأيضا التغييرات اللاحقة التى تحدث للجنين خلال تطوره أثناء الفترة الكاملة للحمل.

و قد قسمت الحيوانات بشكل عشوائي إلى المجموعات التالية:

المجموعة الأولى: شملت ٢٥ جرذا،٥ حيوانات لم يتم تعريضهم للإشعاع و إعتبارهم المجموعة الضابطة. ٢٠ حيوانا تم تعريضهم لأشعة جاما فى اليوم التاسع من الحمل و التى تقابل مرحلة تكون الأعضاء المبكر هذه المجموعة قد رتبت في أربعة مجموعات فرعية كل منها ٥ حيوانات، طبقا لجرعات الإشعاع ٠,٥، ١، ٢ و٣ جراي.

المجموعة الثانية: شملت ٢٥ جرذا، ٥ حيوانات لم يتم تعريضهم للإشعاع و إعتبارهم المجموعة الضابطة. ٢٠ حيوانا تم تعريضهم لأشعة جاما فى اليوم الثانى عشر من الحمل و التى تقابل مرحلة تكون الأعضاء الرئيسية هذه المجموعة قد رتبت في أربعة مجموعات فرعية كل منها ٥ حيوانات، طبقا لجرعات الإشعاع ٠,٥، ١، ٢ و٣ جراي.

المجموعة الثالثة: شملت ٢٥ جرذا، ٥ حيوانات لم يتم تعريضهم للإشعاع و إعتبارهم المجموعة الضابطة. ٢٠ حيوانا تم تعريضهم لأشعة جاما فى اليوم الخامس عشر من الحمل و التى تقابل مرحلة نمو الأعضاء هذه

المجموعة قد رتبت في أربعة مجموعات فرعية كل منها ٥ حيوانات، طبقا لجرعات الإشعاع ٠,٥، ١، ٢ و٣ جراي.

تم الفصل السريع للرأس لكل المجموعات فى اليوم الواحد والعشرين من الحمل. شرحت الجرذان وأخذ الرحم. حدد عدد الأجنة الكاملة وكذلك مواقع الامتصاص. تم أخذ المقاييس (حجم الوليد، وزنه، طوله الجانبي، محيط البطن عند منطقة السرة، طول الذيل و أبعاد الجمجمة (أمامى خلفى و جانبى)). صور للأجنة الحية وللأرحام بمواقع الإمتصاص قد اخذت فورا بعد التضحية بالحيوانات. لوحظت التشوهات الخلقية وسجلت وصورت. كما تمت دراسة ميكروسكوبية لأنسجة الأعضاء الداخلية (القلب، الرئة، الكبد، الطحال، المعدة، الأمعاء، الغدة الصعترية، الكلي، الغدة الكظرية ، جمجمة، دماغ، وعظم الفخذ مع المفصل).

النتائج

أوضحت النتائج الآتى:

١- الدراسة الوصفية

بالنسبة لمواقع الامتصاص كان أعلى تواجد لها فى المجموعات التى تعرضت لجرعة ٣ جراى فى اليوم التاسع و الثانى عشر و الخامس عشر من الحمل، و كذلك فى المجموعة التى عرضت لاثنين جراى فى اليوم التاسع من الحمل. و كان عدد مواقع الامتصاص قليل فى المجموعات التى تعرضت لجرعة ٢ جراى فى اليوم الثانى عشر و الخامس عشر. وكان

أقل عدد فى المجموعات التى تعرضت لنصف جراى فى اليوم التاسع و الثانى عشر من الحمل.

بالنسبة لعدد المواليد كان أعلى تواجد فى المجموعات التى تعرضت لنصف و واحد جراى فى اليوم الثانى عشر و الخامس عشر من الحمل. و كان عدد المواليد قليل فى المجموعات التى تعرضت لنصف و واحد جراى فى اليوم التاسع و المجموعات التى تعرضت لاثنين جراى فى اليوم الثانى عشر و الخامس عشر من الحمل. و كان أقل تواجد للمواليد فى المجموعات التى تعرضت لاثنين جراى فى اليوم التاسع و ثلاثة جراى فى اليوم التاسع و الخامس عشر من الحمل.

لوحظ أن كل المقاسات التى اخذت اظهرت اشد تأثرا فى المجموعة التى تعرضت لاثنين جراى فى اليوم التاسع من الحمل. و هذا يثبت أن الفترات المبكرة من الحمل هى الأشد حساسية للاشعاع. و هذا مبسوط بالتفصيل مع جداول و منحنيات فى الجزء الخاص بالنتائج.و هذه الملامح للنتائج تثبت أ ن تأثر الجنين يعتمد بشكل اساسى على جرعة الاشعاع و زمن التعريض. تحتوى الرسالة على ٢٨ جدول و ٢٣ منحنى.

٢- التشوهات الخلقية

عدد من هذه التشوهات قد لوحظت فى بعض المواليد تضمنت نقص النمو، غياب الذيل، غياب فتحة العين، مواليد تشبه طائر البطريق، قصر الاطراف و الذيل، غياب و صغر الآذان و مواليد محتقنة. و كانت أكثر

هذه التشوهات حدوثا فى المواليد التى تعرضت لجرعات اثنين و ثلاثة جراى فى اليوم الثانى عشر و كذلك لاثنين جراى فى اليوم التاسع من الحمل.و تحتوى الرسالة على ١٣ صورة تبين هذه التشوهات.

٣- التأثيرات الخلوية المرضية (هستوباثولوجى)

أظهرت الدراسة الميكروسكوبية للأنسجة أن كل نسيج يتأثر بشكل مختلف عن غيره فكان الكبد و الأمعاء الدقيقة هما الأكثر تأثرا و إلى مدى أقل كانت الكلية، المخ و الطحال. و كانت بعض الأنسجة مثل الغدة الكظرية، الغدة الصعترية الرئة و القلب قد أظهرت تغيرات بدرجة قليلة بالنسبة لشدة الاصابة و عدد الحالات. و قد كانت أكثر الحالات التى تأثر فيها الكبد و الأمعاء الدقيقة فى المجموعات التى تعرضت لاثنين و ثلاثة جراى فى اليوم الثانى عشر و الخامس عشر من الحمل. تحوى الرسالة على ٩ جداول و هستوجرام و ٣٣ صورة أظهرت أنسجة طبيعية و أخرى متأثرة.

و فصل المناقشة قد تناول معلومات اساسية عن الموضوع بشكل عام من مقدمة و مدخل ثم ملامح و تفسير للنتائج بكل دراساتها الثلاثة وصفية و تشوهات خلقية و دراسة الأنسجة. و اعطى آخر جزء من المناقشة محصلة فى مجموعة جمل هى حصيلة هذه الدراسة و التوصيات الدولية.

المستخلص

عنوان الرسالة: **التشوهات الخلقية الناتجة من تعرض الجنين للإشعاع (دراسة تجريبية).**
المؤلف: **محمود حسن محمود محمد**
العنوان: جامعة عين شمس معهد الدراسات العليا للطفولة ، قسم الدراسات الطبية، القاهرة، مصر.
التأريخ: نوفمبر ١٩٩٩.
البريد الإليكترونى: shabon .m .h. @ usa.net

هَدَفُ الدّراسةِ

إيجاد العلاقة بين الجرعة الإشعاعية، وزمن التعرض الرحمى، والتأثيرات الخلقية الناتجة.

الطرق التجريبية المستخدمة

خمسة وسبعون جرذ أبيض حبلى قُسّمتَ في ثلاث مجموعاتِ طبقا ليوم التشعيع. المجموعة الأولى تم تشعيعها فى اليوم التاسع من الحمل، والذى يناظر فترة تكوين الأعضاء المبكرة. المجموعة الثانية تم تشعيعها في اليوم الثانى عشر للحمل الذى يواكب فترة تكوين الأعضاء الرئيسية. المجموعة الثالثة قدْ شُععت فى اليوم الخامس عشر للحمل والذى يوازى فترة النمو الجنيني. كل مجموعةٍ قدْ قُسّمَت إلى مجموعة ضابطة وأربعة مجموعات تم تشعيعها بالجُرعات ٠,٥ و ١ و٢ و٣ جراي من أشعة جاما الناتجة من كوبالت-٦٠ المشع.

النَتائِج

الدراسات الوصفيةِ

تم حصر عددِ مواقع الإمتصاص الرحمية، عدد المواليد. وقيس الحجم، ووزن الجسم وأطوال الذيول ومقدار حزام البطن عند السرة، وأبعاد الجمجمةِ. هذه الدّراساتِ أوضحت أنَ هناك تأخر فى النمو عند جرعة ٢ جراى فى اليوم الثانى عشر من الحمل. جرعة ٣ جراى فى اليوم التاسع للحمل كانتْ قاتلة لكل الأجنة.

التشوّهاتِ الخلقيةِ

غياب العيون والدّيولِ فى بعض المواليـد، وفـى البعـض الأخـر كـان لـها أطـراف صغـيرة وآذان منخفضةِ. هذه التشوّهاتِ ظَهرتْ في الغالب في الحيواناتِ التى تعرضـت لجُرَعـات ١ و٢ جـراي خلال فترة تكوين الأعضاء الرئيسيّة.

الدِراسات الخلوية

أجريت هذه الدراسة على ثلاثة عشرَ نسيج أخذَ من المواليدِ. كَشفَت أنّ الأمعاء الغليظـةِ و العظـام و البنكرياس و الأغشية السحائية لما تتـأثّرُ. كـان أقـل الأعضـاء تـأثرا الغـدة الصعتريـة والرئـات والقلب. وقد تأثر المخ والطحال و الغدة الكظرية بدرجة متوسطة. أما الكبد واللفـائفى والكلـي فقـدْ كانت أكثر الأعضاء تأثرا. كان الأثر الباثولوجي الأكثر تواجدا هو الانحلال الخلويَ.

كل البياناتِ السابقة قدْ قُيّمَت بشكل إحصائي.

المحصلة

- اشارتْ النَتائِج أنّ الجنين خلال الفترةَ الكاملة للحمل عرضة لأخطار الإشعاع المؤين. ذلك نتيجة النشاطاتَ الخلوية والعملياتَ البيولوجية للجنين.
- جُرَعة النصف جراى لم تؤدى إلى تأثيرات حادة حتمية ولكن هذا لا ينفى وجود تـأثيرات احتمالية متأخرة.
- أشارت النَتائِجُ أنّ المرأة الحبلىَ لا يَجِبُ أنْ تتعرض للإشعاع خلال الفترة الكاملة للحمل.

الكلمات الدليلية:

الإشعاع، وصفى، تناسلى، خلوى .

جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

شكـــــر

اشكر السادة الأساتذة الذين قاموا بالاشراف و هم :
١- ا.د. أنس مصطفى النجار
٢- ا.د. أمير أحمد فؤاد صدقى
٣- ا.د. عمر السيد الشوربجى
٤- د. مايسة نصر فريد

ثم الأشخاص الذين تعاونوا معى فى البحث و هم :
١- د. إيمان إسماعيل عبد الجواد
٢- ا.د. عبد الرازق زكى حسين
٣- ا.د. فاطمة جابر عبد المجيد

و كذلك الهيئات الآتية :
١- هيئة الطاقة الذرية
٢- المركز الإقليمى للنظائر المشعة

جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطب

رسالة **دكتوراه**

اســم الطالــب: **محمود حسن محمود محمد**
عنوان الرسالة: **التشوهات الخلقية الناتجة من تعرض الجنين للإشعاع (دراسة تجريبية)**

اســم الدرجــة: **دكتوراه**

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٢ - الاسم/ **ا.د. أمير أحمد فؤاد صدقى** الوظيفة/ استاذ علم الأمراض ـ كلية الطب ـ جامعة عين شمس.

٣- الاسم/ **ا.م.د. عمر السيد الشوربجى** الوظيفة/ استاذ مساعد بقسم الدراسات الطبية ـ معهد الدراسات العليا للطفولة - جامعة عين شمس.

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تاريخ البحث / /

الدراسات العليا
ختم الإجازة: أجيزت الرسالة بتاريخ / /١٩٩٩

موافقة مجلس الكلية
/ /

موافقة مجلس الجامعة
/ /

جامعة عين شمس
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قسم الدراسات الطبية

صفحة العنوان

اســم الطالــب: **محمود حسن محمود محمد**

اســم الدرجــة: **دكتوراه**

القسم التابع له: قسم الدراسات الطبية

اسم المعهد: **معهد الدراسات العليا للطفولة**

الجـامعـــة : **جامعة عين شمس**

سنة التخرج: **١٩٩٩**

سنة المنـح: **١٩٩٩**

شـــــــــــــروط عامـــــــــــــة :

يوضع شعار الجامعة على الغلاف الخارجى

جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

التشوهات الخلقية الناتجة من تعرض الجنين للإشعاع
(دراسة تجريبية)

دراسة مقدمة للحصول على درجة دكتوراه الفلسفة فى دراسات الطفولة
(قسم الدراسات الطبية)

مقدمة من الطبيب
محمود حسن محمود محمد
ماجستير طب الأطفال (جامعة عين شمس) ١٩٨٨
هيئة الطاقة الذرية

إشراف

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