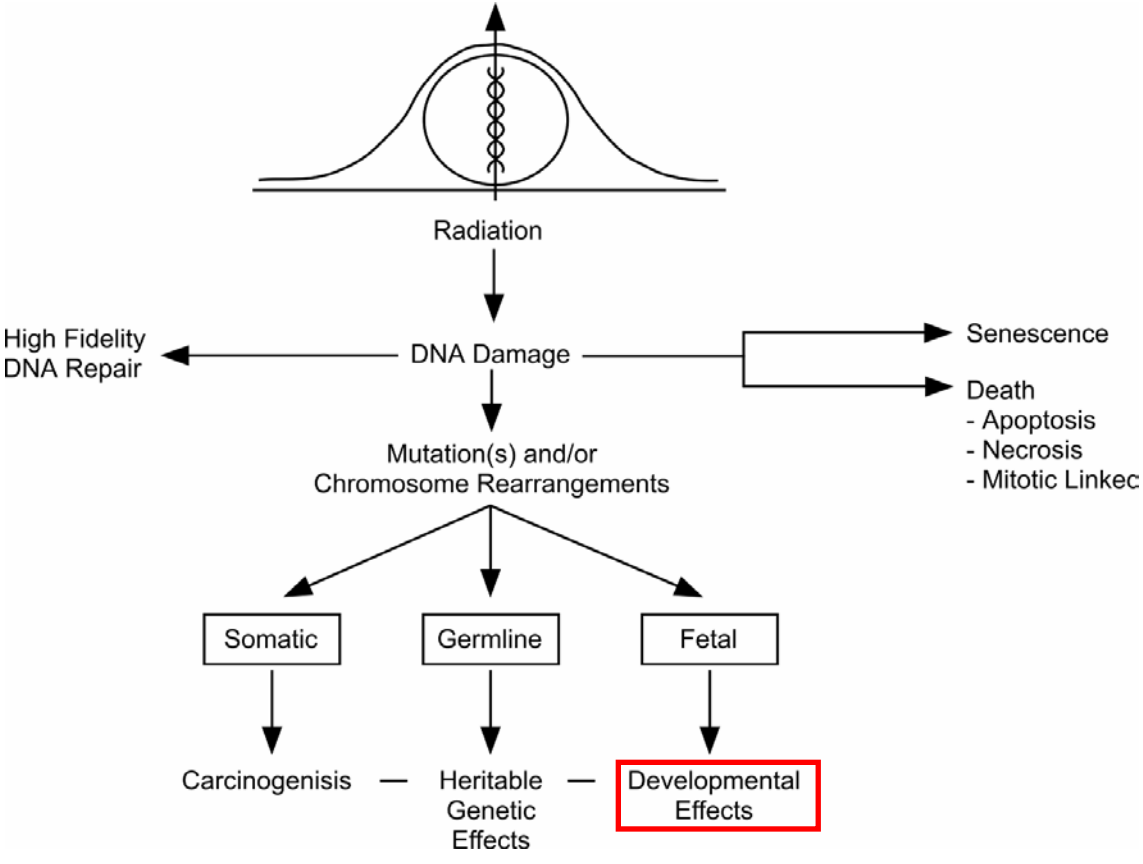
Chapter 12 – Effects of Radiation on the Embryo and Fetus

11/7/2024

DNA as the Target

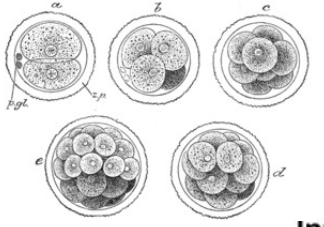


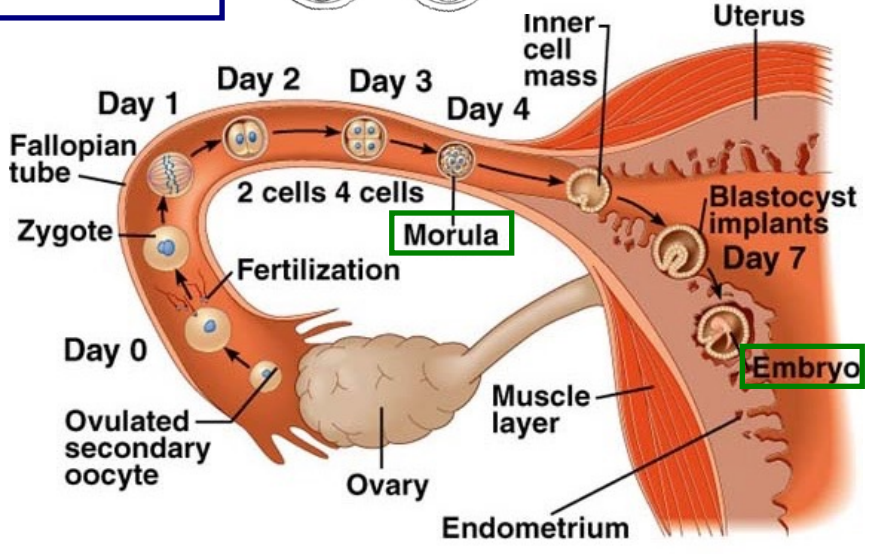
Outline

- **Embryogenesis and Fetal Development**
- Developmental Effects of Radiation on Embryo and Fetus
- Animal Studies
- Human Experience
- Carcinogenesis
- Occupational Exposure of Women
- The Pregnant Patient

From Ovulation to Implantation – Day 0-9

Cell division continues as the fertilized egg move along the fallopian tubes toward the uterus



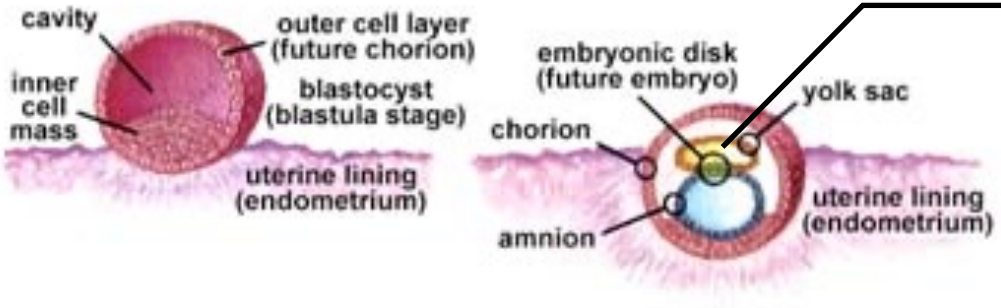


Implantation is the process of embryo embedding into the wall of the uterus, which occurs on **day 9**

The development of human embryo starts with fertilization of the ovum

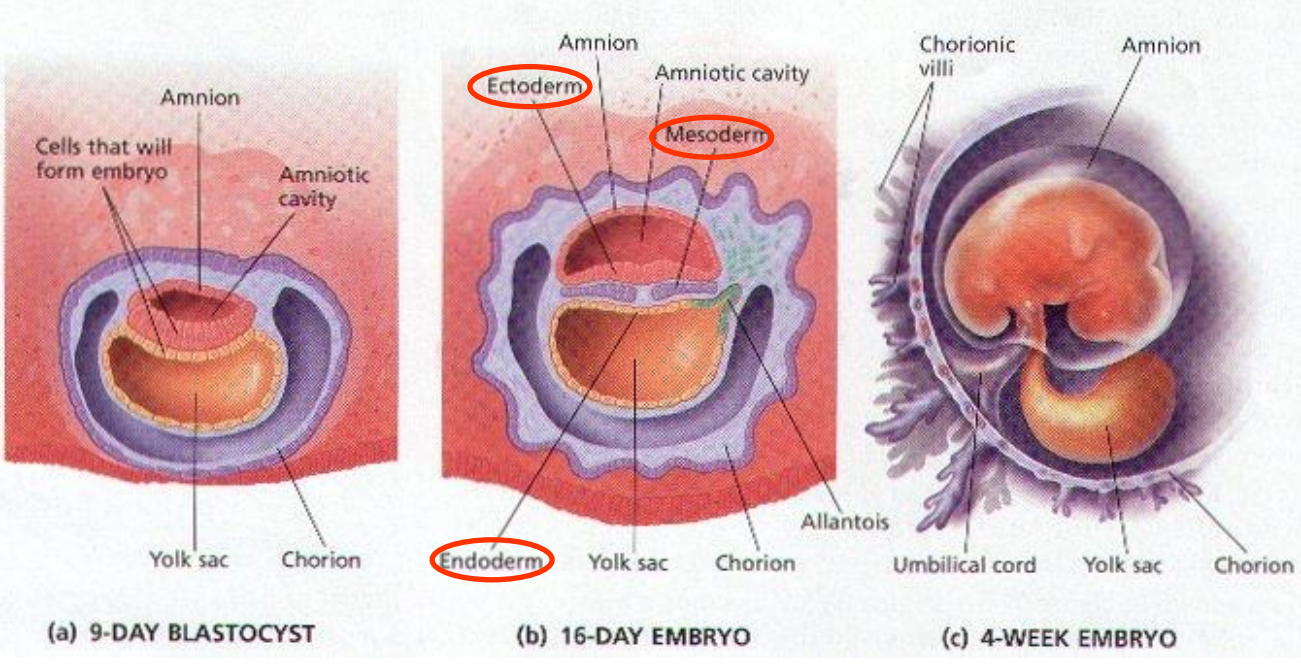
From Ovulation to Implantation

Pre-implantation, the conceptus consists of limited number of cells without differentiation



A **primitive streak** appears on the surface of the embryo, which forms a blueprint for the embryo and guide the organization of all tissues, organs and body systems

Organogenesis – Day 10 through 6 Weeks



Once the streak is present, cells begin to move around to form 3 distinct layers: the ***endoderm***, ***mesoderm***, and ***ectoderm***. These layers will give rise to every cell type and organ. This process is called **organogenesis** and takes place **from day 10 through 6 weeks.**

Organogenesis

4-wk embryo

5-wk embryo

6-wk embryo

The Fetal Period – 6 wks through Term

(measured from last menstrual period)

This is the period during which the growth of the structures already formed take place
In human, the fetal period is from **6 wks through term**

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Developmental Effects

- The classic effects of radiation on the embryo and fetus are of the 3 categories
  - **Lethal Effects**
  - **Malformations**
  - **Growth disturbances without malformation**
- Factors of importance include *dose* and *dose rate*, and *stage of gestation* at which the dose is delivered

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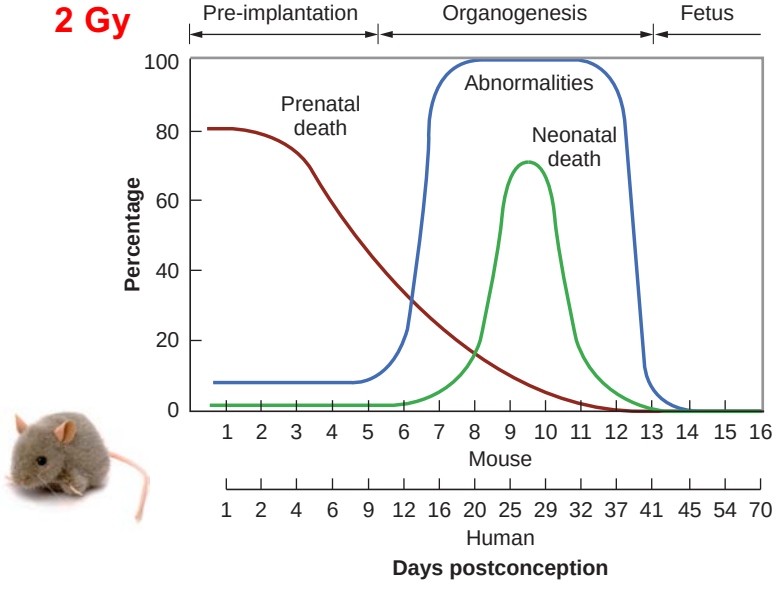
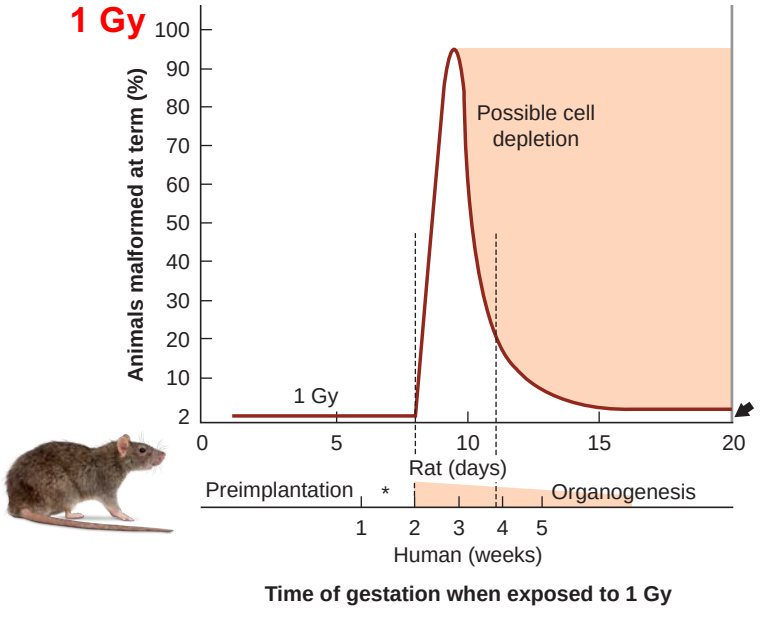
Data from Mice and Rats

Most experimental data on the effect of radiation on the developing embryo or fetus have been obtained with mice or rats





Mice and rats reproduce in quantity with relatively short gestation periods (~ 20 days)

Preimplantation

Lethal Effects

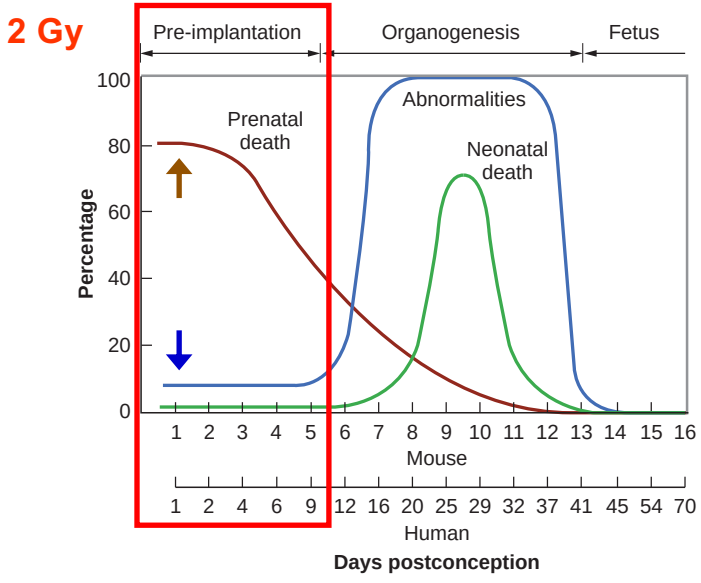
Pre-implantation is the most sensitive to the lethal effects of radiation
An X-ray dose of 0.05 – 0.15 Gy can kill the fertilized egg
Pre-natal death is expressed as a decrease in litter size

Malformation

Few if any abnormalities are produced

Growth Disturbances

Growth retardation is not observed; if the embryo survives, it grows normally *in utero* and afterwards



All or nothing effect – either the fetus survives and develops normally or there is a spontaneous abortion

This is because the number of cells in the conceptus is small and their nature not yet specialized. If too many cells are killed by radiation, the embryo dies and is resorbed. If only a few cells are killed, one or two cell divisions can make up the damage

Organogenesis

Malformation

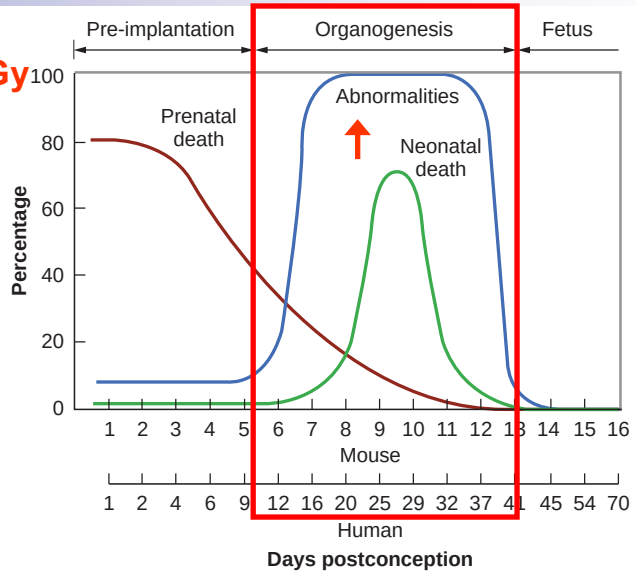
This is the principal effect of radiation at this stage

In mice, a dose of 2 Gy can result in 100% incidence of malformation
In rats 1 Gy during early organogenesis produces close to 100% malformation

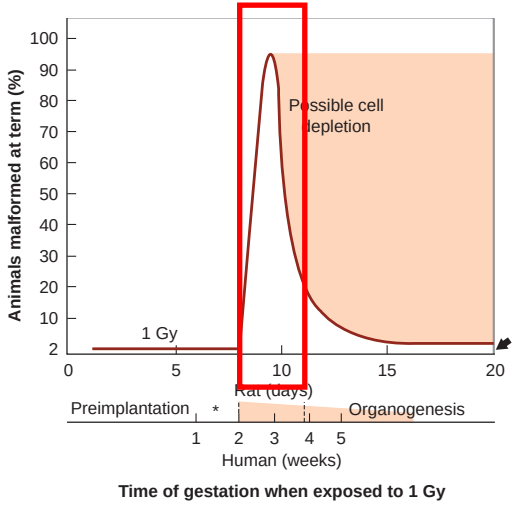
This is because most of the **embryonic cells are in differentiating stage** and are particularly sensitive

This is the period in human at which the deleterious effect of thalidomide and rubella virus are produced

2 Gy

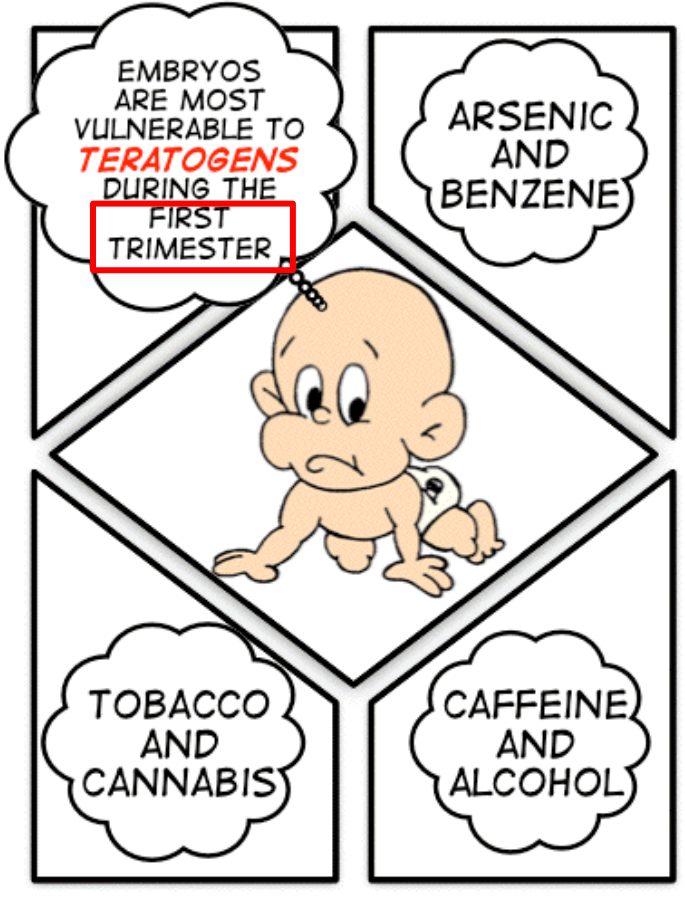


1 Gy

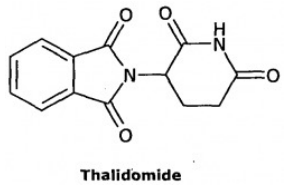


Teratogen


ANYTHING THAT CAUSES MALFORMATIONS OF AN EMBRYO OR FETUS
teratogen


EMBRYOS ARE MOST VULNERABLE TO TERATOGENS DURING THE FIRST TRIMESTER
ARSENIC AND BENZENE
TOBACCO AND CANNABIS
CAFFEINE AND ALCOHOL

Teratogenic Effect of Thalidomide

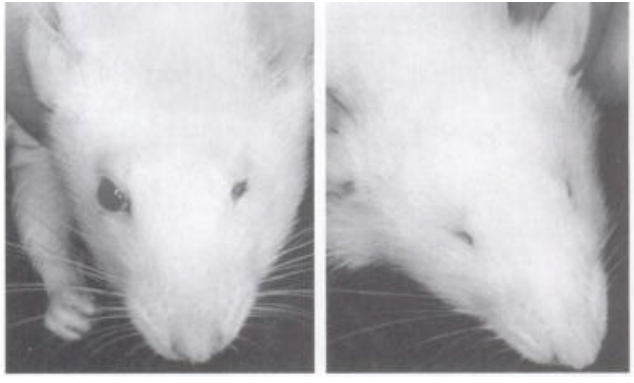


Thalidomide

- Developed in mid-1950s in Germany
- Initially used as a sedative and antiemetic
- Went on the market as a treatment for morning sickness in more than 40 countries in 1958 (not in US)
- Soon found to produce severe malformations in infants born of mother who had taken the drug during early pregnancy, most vulnerable during 27-40 days after conception
- Malformations included phocomelia ("seal limbs" in which the long bones in the arms and legs fail to develop), deformities of the external ear, eye, etc
- Taken off the market in 1961-1962

Organogenesis

Pregnant mouse irradiated during organogenesis and sacrificed at 19 days



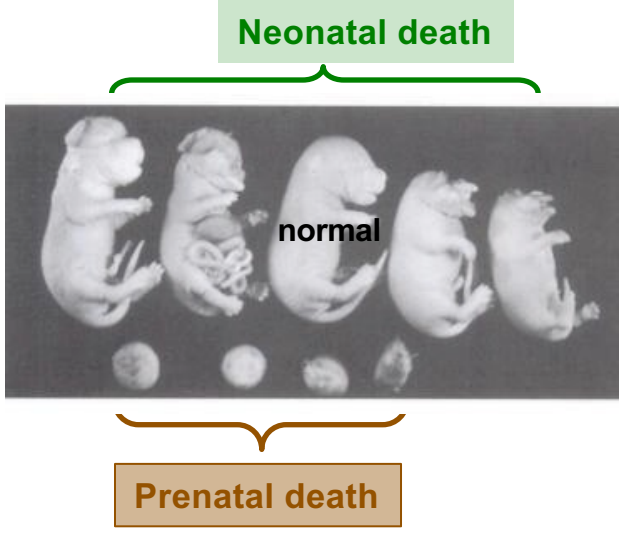
2 rats exposed to 1Gy at 9.5 days after conception

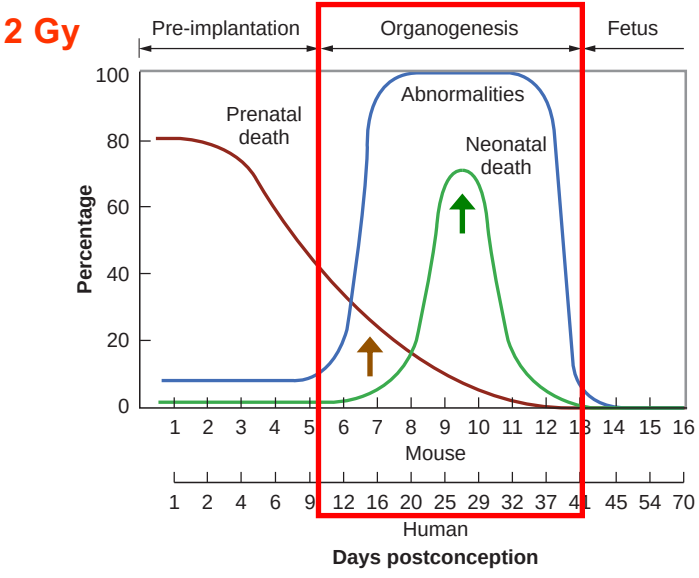
Numerous different organ malformations have been observed in mice irradiated during organogenesis

Organogenesis

Lethal Effects

If death occurs, it is likely to be **neonatal death** (as opposed to prenatal death observed with irradiation at the preimplantation stage)





Organogenesis

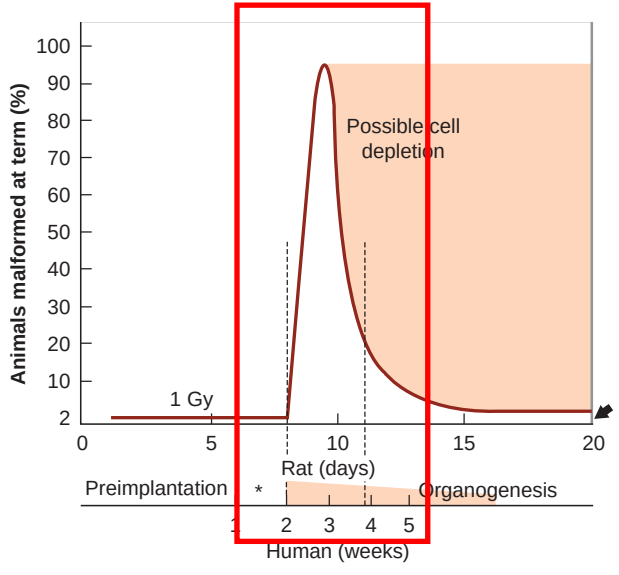
Growth Disturbances

Embryos exposed during early organogenesis also exhibit the greatest **intrauterine growth retardation**

This is expressed as weight reduction at term and results from **cell depletion**

Animals show a remarkable ability to recover from the growth retardation produced by irradiation during organogenesis, and ***although they may be smaller than usual at birth, they may achieve a normal weight as adult***

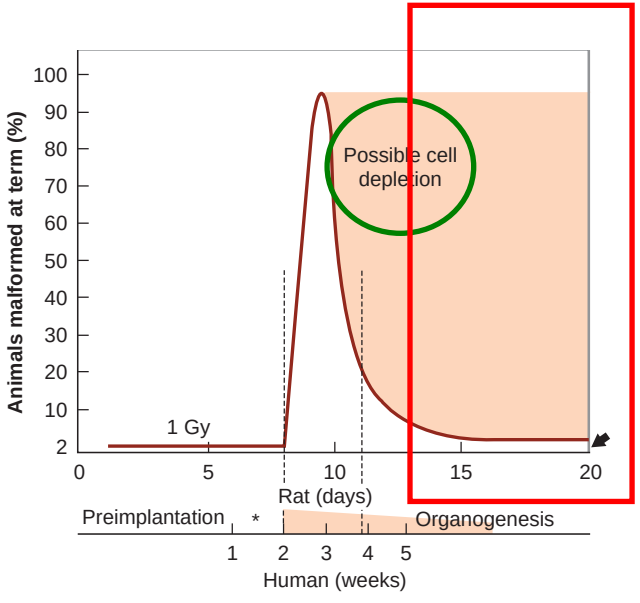
1 Gy



Time of gestation when exposed to 1 Gy

Fetal Stage

1 Gy



Time of gestation when exposed to 1 Gy

During fetal stage, a dose of 1 Gy causes an irreversible loss of cells that is expressed as growth retardation **persisting to the adulthood**

In contrast to the embryo in early organogenesis, which exhibits the most *temporary growth retardation*, irradiated early fetus exhibits the largest degree of **permanent growth retardation**

Fetal Stage

Malformation

Usually not observed in this period

Lethal Effects

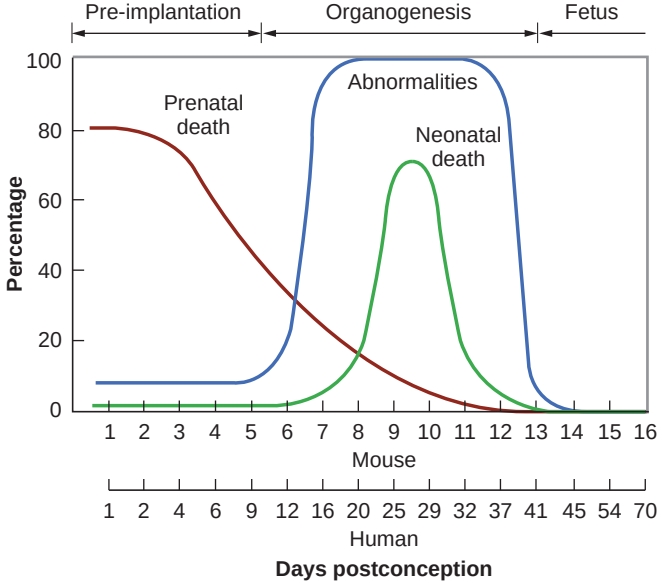
Much higher doses are required to cause fetal deaths (e.g., still births) during this period

Growth Disturbances without malformations

During this post-organogenesis stage, one would expect **growth retardation**, functional abnormalities, reduced sterility, all requiring **relatively high radiation doses**

Animal Data Summarized

2 Gy



	Preimplan-tation	Organogenesis	Fetal period
Animal studies	Prenatal death	Congenital anomalies neonatal death, temporary growth retardation	Permanent growth retardation

Outline

- Embryogenesis and Fetal Development
- Developmental Effects of Radiation on Embryo and Fetus
- Animal Studies
- **Human Experience**
- Carcinogenesis
- Occupational Exposure of Women

Human Experience

- Information on the effect of radiation on human embryo and fetus came from 2 major resources
  - Atomic-bomb survivors in Japan
  - Exposure to medical radiation

Background Congenital Anomalies

- It should be recognized that spontaneous congenital anomalies arise in all animal species
- In humans, the average incidence of malformed infants at birth is about **6%**
- Some malformations disappear after birth, but more become evident later in life
- The global incidence roughly doubles to **12% in grown children**

Any assessment of the effect of radiation must be viewed against this natural level of inborn defects

Radiation Effects Research Foundation

RERF A-Bomb Cohorts

Cohort	Size	Objective
Life Span Study	120,000	Allows an estimates of cancer incidence and mortality
In-Utero Cohort	3,600	Allows estimates of malformation, growth retardation, microcephaly, mental retardation
Children of Exposed Individuals (F1)	77,000	Allows estimate of heritable effects

Survivors of the A-bomb Attacks Irradiated *in Utero*

- The gestational age at the time of A-bomb was determined for children exposed *in utero*
- The growth to maturity of these children has been followed carefully
- The principal effects of irradiation *in utero* are **microcephaly** (small head size) and **mental retardation**
  - Of 1,600 exposed children (*in utero*), 62 had microcephaly, 30 showed clinically severe mental retardation

Survivors of the A-bomb Attacks Irradiated *in Utero* – Early Gestation

Findings

There are very few individuals who were younger than 4 wks of gestation at the time the bomb was dropped

No birth defects were found as a result of irradiation before 15 days of gestational age

Interpretation

This observation is in accord with the animal data, i.e., exposure during **preimplantation** had an ***all-or-nothing effect***, death of the embryo or normal development

Japanese Data – Growth Retardation

Avg air kerma = 0.25 Gy

Comparison of children exposed within 1500 m of the hypocenter with those > 3,000 m

Height	2.25 cm shorter
Weight	3 kg lighter
Head diameter	1.1 cm smaller

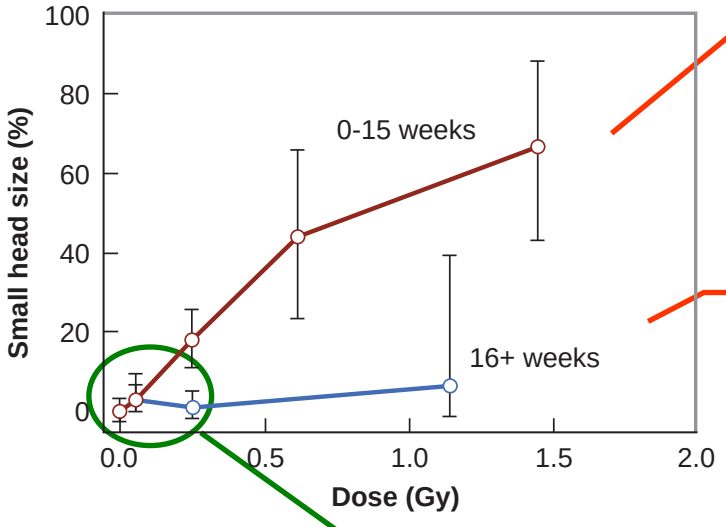
Observation

Exposed children were shorter, weighed less, and had head diameters significantly smaller

There was **no catch-up growth** – the smallness of the head size was maintained into adulthood

Microcephaly

Proportion of exposed individual with microcephaly as a function of dose and gestational age



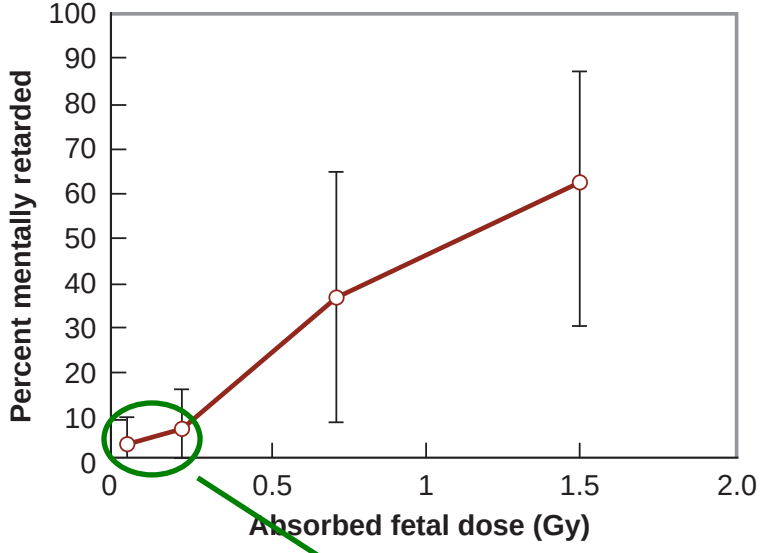
Microcephaly is observed only in the periods of **0-15 wks**

No significant excess was seen among individuals exposed at **16 wks or more**

The proportion of microcephaly increases with dose, but there is **little evidence for a threshold** in dose

Mental Retardation

Frequency of MR as a function of dose



Severe MR was not observed to be induced by radiation before **8 wks** after conception or after **25 wks**

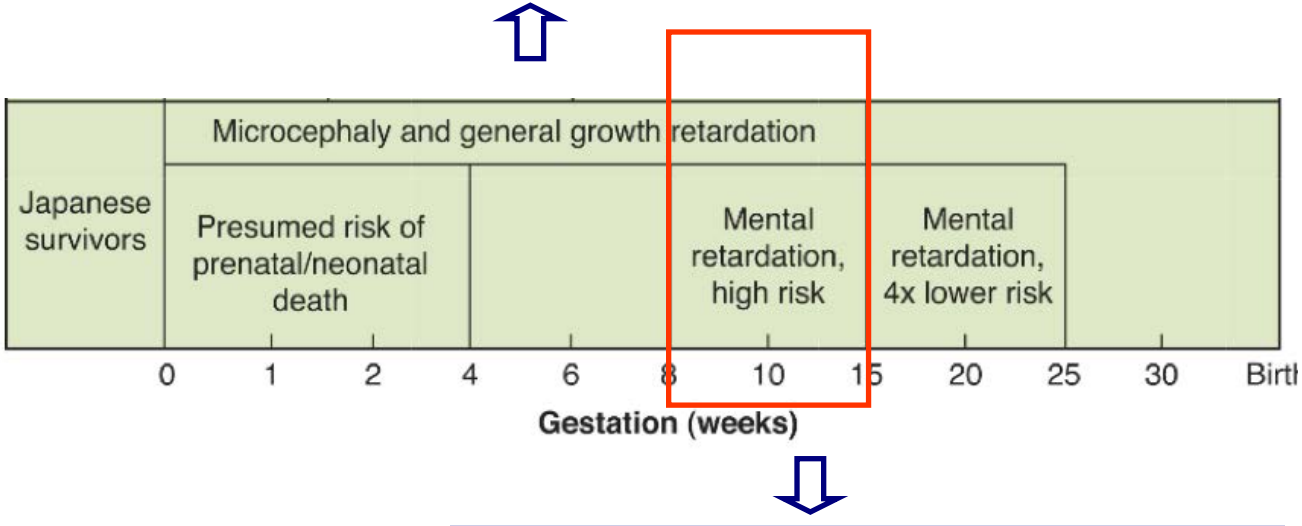
The period of **highest risk** for MR is **8-15 wks**
Exposure during the **weeks 16-25**, the risk is **4x smaller**

Deterministic effect
Tissue Reaction

Data consistent with a **threshold** from **0.3 Gy** and a slope of **40%/Gy** (ICRP 90)

Microcephaly and MR

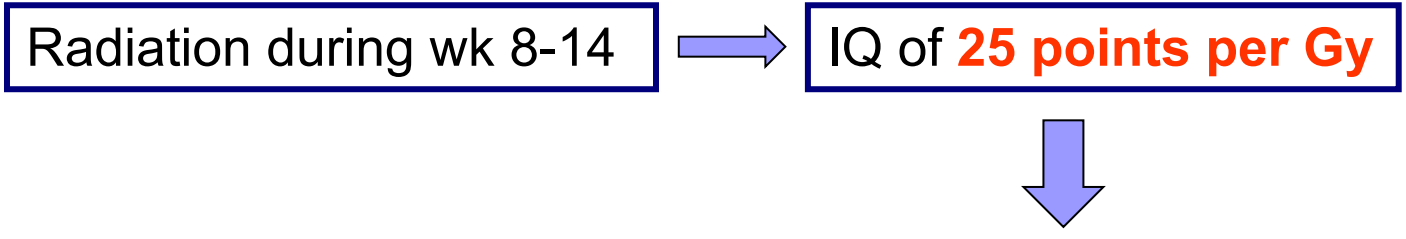
Before 8 wks – depletion of glial cells which provide structural support for the brain **(brain size)**



From 8-15 wks – impairment of proliferation, differentiation, and migration of neurons **(cognitive function)**

Mental Retardation

- Initial data included only children with severe MR
- Later studies showed mental impairment of less severity



Any effects on IQ following in utero doses less than **0.1 Gy** would be of no practical significance *(ICRP No. 103, 2003)*

Children of the Atomic Bomb

A UCLA Physician's Eyewitness Report and Call to Save the World's Children

How Radiation Affects Pregnant Women and Children

One of the initial Atomic Bomb Casualty Commission studies conducted at Nagasaki in 1950 was the outcome of the pregnancy in mothers exposed to the radiation from the atomic bomb. Note the abnormally shaped small head—microcephaly—accompanied by mental retardation.

Microcephaly due to in-utero exposure (seven week gestation in estimate). Exposure distance of 1.2km from Nagasaki hypocenter. Delayed grown in whole body and microcephaly observed (right). Fifteen years and eight months old. Died March 1962. Twelve year old normal child (left).

Outcome of pregnancies of mothers who were within 2,000 metres of the hypocenter was finally initiated and concluded just prior to my return to the U.S. In mothers who demonstrated signs of radiation sickness compared to mothers who did not develop such findings there was a significant increase in perinatal loss and some of their children had an abnormally shaped small head who were mentally retarded. The incidence of miscarriage, stillbirth and death during infancy was 43 percent, seven times the incidence in a control group who were considered to have received no radiation. In an interdisciplinary laboratory investigation initiated at UCLA following my return, the effect of radiation alone revealed the marked vulnerability of the developing brain. The brain lesions and neurological abnormalities were greater in the younger animals and the severity was a function of the radiation dose.

http://www.aasc.ucla.edu/cab/200708230012.html

Medical Exposure

- Similar to Japanese A-bomb survivors exposed *in utero*, microcephaly and MR were also observed among those irradiated during intrauterine life for medical reason
- In addition, a variety of other defects were also reported, including *spina bifida*, *bilateral clubfoot*, *ossification defects of the cranial bones*, *deformities of the upper extremities*, *hydrocephaly*, *alopecia of the scalp*, *divergent squint*, and *blindness at birth*

Medical Exposure

Study of pelvic irradiation of pregnant women demonstrated:

0-3 Wks of Gestation

Large doses (2.5 Gy) unlikely to result in abnormalities, although a considerable # of number of embryos may be resorbed or aborted

4-11 Wks of Gestation

Risk of severe organ abnormalities of many organs in most children

Medical Exposure

11-16 Wks Gestation

A few eye, skeletal, and genital organ abnormalities; stunted growth, microcephaly, and mental retardation are frequently present

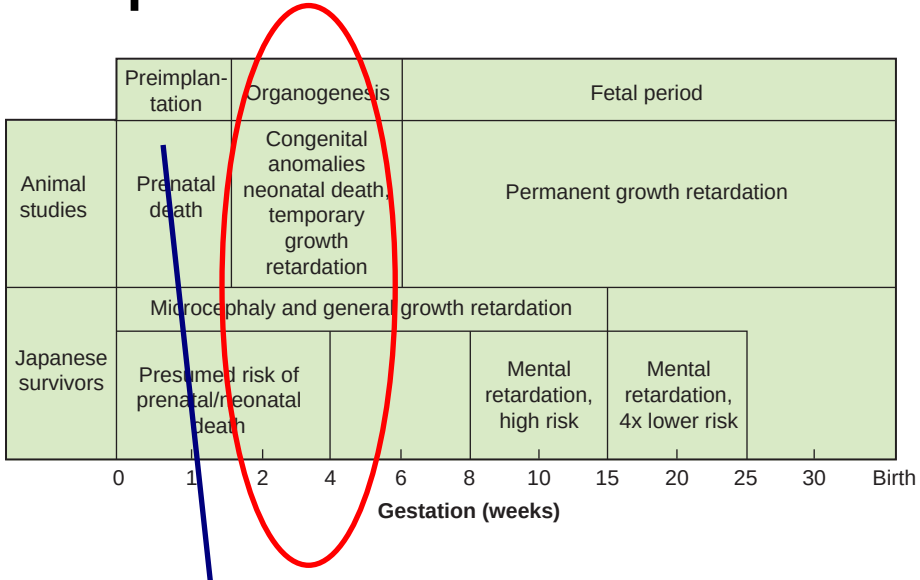
16-25 Wks Gestation

Mild degree of microcephaly, mental retardation, and stunting of growth

30 Wks+ Gestation

Unlikely to produce gross structural abnormalities leading to a serious handicap in early life but cause functional disabilities

Comparison of Human and Animal Data



Unlike animal data, a wide range of malformation was not observed in the Japanese survivors

? These were simply not recorded

? CNS development lasts longer than other organ systems, so when sample size is small, MR will be overrepresented

Preimplanation – animal and human data are consistent

Note that data from pts exposed to therapeutic doses of medical radiation show a range of congenital malformations that more closely mirrors the animal results

Minimum Dose

Tissue Reaction
Deterministic effect

TABLE 12.2 Minimum Doses at Which Effects on the Embryo and Fetus Have Been Observed

	Threshold dose
Animal data	
Oocyte killing (primates)	50% lethal dose at 0.5 Gy
Central nervous system damage (mouse)	Threshold at 0.1 Gy
Brain damage and behavioral damage (rat)	Threshold at 60 mGy
Human data	
Small head circumference	Air kerma, 0.1–0.19 Gy
Summary	Fetal dose, 0.06 Gy
Readily measurable damage caused by doses less than 0.1 Gy (acute exposure) delivered at sensitive stages	

Summarized from Committee on the Biological Effects of Ionizing Radiation. *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. BEIR III. Washington, DC: National Academy of Sciences; 1980.

To be on the safe side, it must be assumed that the entire period of gestation from about **10 days to 25 wks** is sensitive to the induction of malformation by radiation

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- **Carcinogenesis**
- Occupational Exposure of Women
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Carcinogenesis – Diagnostic X-rays

TABLE 12.3 Childhood Cancer and Irradiation In Utero

Number of children with leukemia or cancer before age 10 years	7,649
Number x-rayed in utero	1,141
Number of matched controls	7,649
Number of controls irradiated in utero	774
Number of films	1–5
Fetal dose per film	4.6–2 mGy
Relative cancer risk estimate assuming radiation to be the causative agent	1.52

Based on Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancer. *Lancet*. 1970;1:1185–1188.

Stewart and Kneale (1970) studied the x-ray records of over 7,000 children who died of leukemia in the 1950s in the Oxford area. These were compared with the records of an equal number of controls (no leukemia).

A subsequent study in New England also reported an association b/w prenatal x-rays and childhood leukemia

Oxford Study

- There has been considerable controversy about their conclusion – is the radiation causative or is there a selection bias
- **Selection bias** – why were these mothers x-rayed and why so frequently? Could it be selecting a particular group of children prone to cancer?
- Subsequent study of twins (pelvic X-ray routine w/ multiple births) confirmed increased risk of cancer without the “sick mother” bias

Cancer Risk of *in Utero* Exposure Summarized

- Doll and Wakeford summarized all of the studies of *in utero* exposure and came to the following conclusions

Low-dose irradiation of the fetus *in utero* **causes an ↑ risk of childhood malignancies**. Most of the data refer to exposure in the **3rd trimester**

An obstetric x-ray exam results in a **40%** ↑ in the risk of childhood cancer over the spontaneous level (this is RR)

Cancer Risk of *in Utero* Exposure Summarized

Radiation doses of around **10 mGy** ↑ the risk

The excess **absolute risk** is about **6% per Gy**
Note that this is not too different from the radiation-induced cancer lethality risk of the general public

These risk estimates are highly uncertain except to say that **they are not zero**
(Recall that radiation-induced carcinogenesis is a **stochastic effect**)

Another Helpful Summary Slide

Gestational Period	Gestation (Weeks)	Main Risk	Additional Risk
Preimplantation	0-1.5 weeks	Prenatal Death	Microcephaly
Organogenesis	1.5-6 weeks	Congenital Malformations	
Early Fetal Period	6-8 weeks		
	8-15 weeks	Mental Retardation **(High Risk)** *Risk ~0.4 per Gy* *~25 IQ points per Gy.*	
Late Fetal Period	16-25 weeks	Mental Retardation (Lower Risk) *Risk ~0.1 per Gy*	Growth Retardation Carcinogenesis
	26-40 weeks		

Adapted from Figure 12.9, Hall EJ and Giaccia AJ, Eds. *Radiobiology for the Radiologist*, 8th Ed. Lippincott Williams & Wilkins, Philadelphia, 2018.

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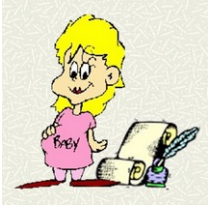
- **Occupational Exposure of Women**
- **The pregnant Patient**

Occupational Exposure of Women

- NCRP (116) recommends **a monthly limit of 0.5 mSv** to the embryo or fetus **once pregnancy is declared**



- This recommendation is designed to limit the risk of mental retardation, congenital malformations and carcinogenesis
- Pregnant workers should be interviewed and counseled to decide whether radiation duties should be discontinued or curtailed

The Pregnant or Potentially Pregnant Patient

- Patients undergoing diagnostic imaging should always be asked if they are, or may be, pregnant
- Pregnancy tests should be ordered whenever large doses of radiation are to be administered to the pelvic region
- Irradiation of fetuses should be avoided whenever possible

The Pregnant or Potentially Pregnant Patient

- In cases of inadvertent exposure, It may be useful to ask the **medical physicists** to make measurements in a phantom after carefully reconstructing the setup that was used
- Doses of **100 mSv** *at sensitive stage (10 days – 25 wks)*and **200 mSv** *during fetal period* are often considered the cut-off point above which patients should be counseled about the possibility of a therapeutic abortion (Hammer-Jacobsen “rule”, 1959)

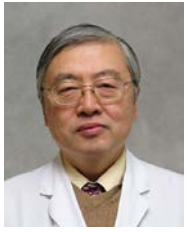
Case Study

- Female patient with a h/o extraskeletal chondrosarcoma in cerebellar area, s/p post radiation therapy 10 years ago
- Developed recurrent tumor in the occipital area, s/p surgical resection but tumor quickly recurred
- She is 20 weeks pregnant

Can she have resection followed by GammaTiles?

Is it better to proceed with surgery followed by Gammaknife to the resection cavity?

Case Study





- Should consider waiting till 25 weeks of gestation
- Keep dose to the fetus under 10 cGy, the lower the better

- Beam Energy
  - GammaTile - 30keV
  - GK - 1.25MeV
  - External Beam - 6MV
- Gamma knife – at 1m from the focus point (or beam isocenter), the total cumulative dose with 16mm collimators is 0.06 cGy by assuming the dose rate of 300cGy/min, which is the current source strength.
- GammaTile – gives nearly zero dose to fetus
- External beam therapy – dose would be too high to the fetus

The Need for Protection

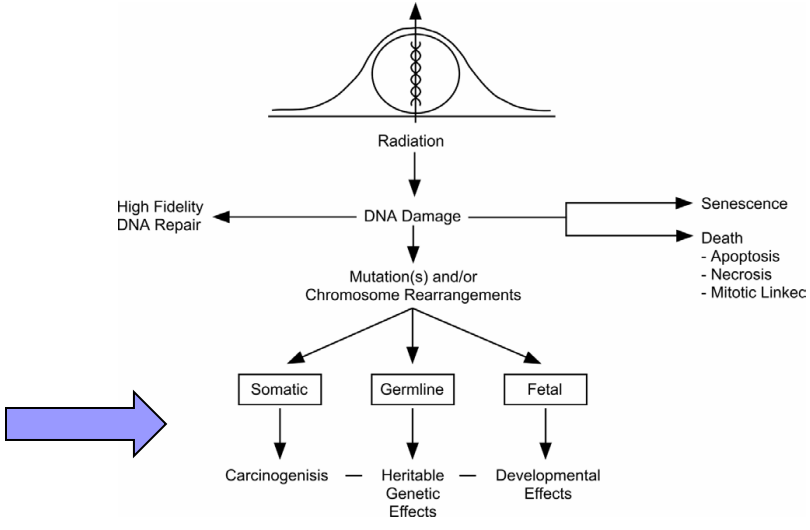


Table 16.4 Deleterious Effects of Radiation that Highlight the Need for Protection

END POINT	RISK ESTIMATE	
Severe mental retardation		
Exposure of embryo/fetus (8–15 wk)	40%/Sv	Relative risk
Carcinogenesis		
General population (low dose, low dose rate)	5%/Sv	Absolute risk
Heritable effects		
General population	0.2%/Sv	Relative risk

Based on International Commission on Radiological Protection (ICRP), Biologic Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

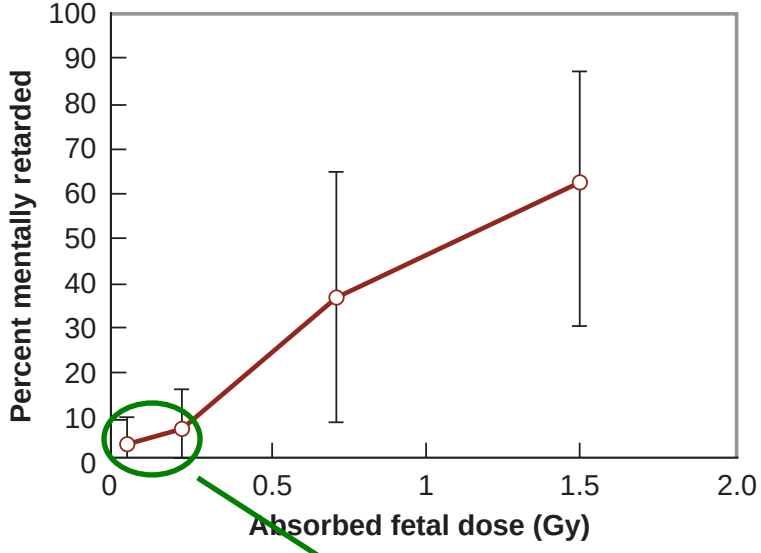
Mental Retardation

Table 16.4 Deleterious Effects of Radiation that Highlight the Need for Protection

END POINT	RISK ESTIMATE
Severe mental retardation	
Exposure of embryo/fetus (8–15 wk)	40%/Sv
Carcinogenesis	
General population (low dose, low dose rate)	5%/Sv
Heritable effects	
General population	0.2%/Sv

Based on International Commission on Radiological Protection (ICRP), Biologic Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

Frequency of MR as a function of dose



Severe MR was not observed to be induced by radiation before **8 wks** after conception or after **25 wks**

The period of **highest risk** for MR is **8-15 wks**
Exposure during the **weeks 16-25**, the risk is **4x smaller**

Deterministic effect
Tissue Reaction

Data consistent with a **threshold** from **0.3 Gy** and a slope of **40%/Gy** (ICRP 90)

ICRP Summary Risk Estimates

Table 16.4 Deleterious Effects of Radiation that Highlight the Need for Protection

END POINT	RISK ESTIMATE
Severe mental retardation	
Exposure of embryo/fetus (8–15 wk)	40%/Sv
Carcinogenesis	
General population (low dose, low dose rate)	5%/Sv
Heritable effects	
General population	0.2%/Sv

Based on International Commission on Radiological Protection (ICRP), Biologic Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

TABLE 10.4. *International Commission on Radiological Protection Summary of Risks of Cancer Lethality by Radiation*

	High Dose High Dose Rate	Low Dose Low Dose Rate
Working population	8×10^{-2} per Sv	4×10^{-2} per Sv
Whole population	10×10^{-2} per Sv	5×10^{-2} per Sv

DDREF = 2

The value for the whole population are a little higher because of the sensitivity of the young

BEIR VII Estimate

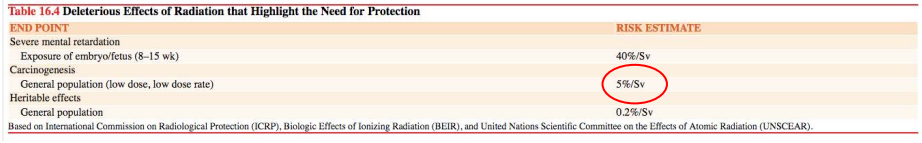


Table 16.4 Deleterious Effects of Radiation that Highlight the Need for Protection

END POINT	RISK ESTIMATE
Severe mental retardation	
Exposure of embryo/fetus (8–15 wk)	40%/Sv
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Heritable effects	
General population	0.2%/Sv

Based on International Commission on Radiological Protection (ICRP), Biologic Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

Population Average Cancer Risk Percent per Sievert

	Cancer Incidence	Cancer Mortality
Male	8.6%/Sv	4.6%/Sv
Female	12.8%/Sv	6.2%/Sv
Combined	10.8%/Sv	5.4%/Sv

National Research Council (2006) *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. The National Academies Press, Washington, DC.

ICRP Estimates of Hereditary Risks

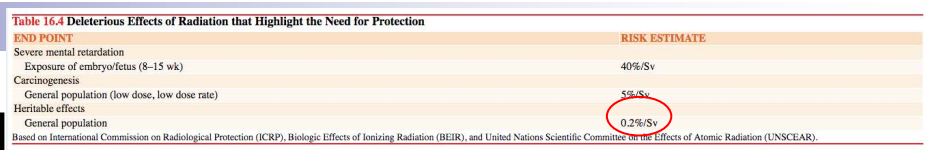


Table 16.4 Deleterious Effects of Radiation that Highlight the Need for Protection

END POINT	RISK ESTIMATE
Severe mental retardation	
Exposure of embryo/fetus (8–15 wk)	40%/Sv
Carcinogenesis	
General population (low dose, low dose rate)	5%/Sv
Heritable effects	
General population	0.2%/Sv

Based on International Commission on Radiological Protection (ICRP), Biologic Effects of Ionizing Radiation (BEIR), and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

Total Population

Assumption – average life expectancy of 75 years; mean reproduction age stopping at 30 years
The risk coefficients = 30/75 = 40% for reproductive population

Risk ≅ 0.5% (UNSCEAR data) x 40% = **0.2%/Sv**

Radiation Workers

Radiation workers start working at age 18, so the relevant reproductive years = 30-18 = 12 years
The risk coefficients = 12/75 = 16%

Risk ≅ 0.5% (UNSCEAR data) x 16% = **0.1%/Sv**

Review Questions

Question 1

Which of the following pairs of gestational stage and radiation-induced developmental defect is CORRECT?

A. Preimplantation – congenital malformations
B. Organogenesis – prenatal death
C. Early fetal period – mental retardation
D. Late fetal period – neonatal death
E. Entire gestation period – malformations of the kidney

Another Helpful Summary Slide

Gestational Period	Gestation (Weeks)	Main Risk	Additional Risk
Preimplantation	0-1.5 weeks	Prenatal Death	Microcephaly
Organogenesis	1.5-6 weeks	Congenital Malformations	
Early Fetal Period	6-8 weeks		
	8-15 weeks	Mental Retardation **(High Risk)** *Risk ~0.4 per Gy* *~25 IQ points per Gy.*	
Late Fetal Period	16-25 weeks	Mental Retardation (Lower Risk) *Risk ~0.1 per Gy*	Growth Retardation Carcinogenesis
	26-40 weeks		

Adapted from Figure 12.9, Hall EJ and Giaccia AJ, Eds. *Radiobiology for the Radiologist*, 8th Ed. Lippincott Williams & Wilkins, Philadelphia, 2018.

Question 2

Based on animal studies, the most radiosensitive gestational age in terms of embryonic mortality (i.e., prenatal death) in humans is approximately:

A. 0-1 weeks

B. 1-4weeks

C. 4-8weeks

D. 8-15 weeks

E. 15-40 weeks

Question 3

Once a pregnancy is declared, the maximum permissible dose to the fetus is:

A. 0.005 mSv per month

B. 0.05 mSv per month

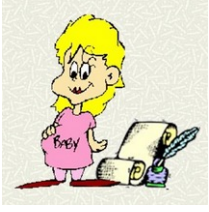
C. 0.5 mSv per month

D. 5 mSv per month

E. 50 mSv per month

Occupational Exposure of Women

- NCRP (116) recommends **a monthly limit of 0.5 mSv** to the embryo or fetus **once pregnancy is declared**



- This recommendation is designed to limit the risk of mental retardation, congenital malformations and carcinogenesis
- Pregnant workers should be interviewed and counseled to decide whether radiation duties should be discontinued or curtailed