Hereditary Effects of Radiation and

Effects of Radiation on Embryo and Fetus

(Chapters 11 & 12)

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Overview

- Genetic/hereditary effects
- Mutation risks
- Megamouse project
- Embryo and fetus effects:
  - lethal effects; malformations; growth disturbances
- Critical exposure factors determining effects
- Spontaneous and induced mutation rates

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Mutation Types

- **Somatic mutations**
  - not inheritable, occurs when the DNA of a non-reproductive cell is damaged
  - radiation-induced somatic mutations affect only the exposed individual
- **Germline mutations**
  - inheritable, occurs when the DNA of a reproductive cell (sperm or ovum) is damaged
  - examples include miscarriages, stillbirths, congenital defects, premature death (first year of life), chromosomal abnormalities, and cancers

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Mutation Risk Estimation

- Relative mutation risk (indirect)
  - number of radiation-induced mutations are compared with the spontaneous mutation rate (at equilibrium)
  - results are expressed in terms of the doubling dose*
- Absolute mutation risk (direct)
  - Is when the incidence of disorders results from mutations (first generation only)

*A dose of radiation expected to double the number of genetic mutations in a generation.

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Genetic Effects

- Study of mutants produced by radiation is difficult
  - Radiation caused mutations are identical to spontaneous mutations
- Sample sizes must be very large to detect a small increase in mutations caused by radiation
- Little human data is available on the genetic effects of radiation
- The estimation of genetic risks in humans is based almost entirely on animal data
  - *BEIR V report (1990) has used ABS data

*. BEIR: Biological Effects of Ionizing Radiation; reports by the national academy of sciences.

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Germ Cell Production: in Male

- Spermatozoa arise from the germinal epithelium and their production is continuous throughout adult life
- These stem cells go through several divisions to progress to spermatozoa (~ 10 weeks in humans)
- The effect of radiation on fertility in men takes several weeks to be fully expressed
  - relative to the stem cells, spermatozoa are fairly radioresistant
- Threshold for temporary sterility is about 15 rad to the testes (permanent sterility is in the hundreds of rads)
- The induction of sterility has no real physical impact

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Germ Cell Production: in Female

- No gamete stem cells after birth
  - all oogonial-stage cells progress to the oocyte stage while still an embryo
- The threshold for permanent sterility is an acute dose in the range of:
  - 200 Rad premenopausal to
  - 1200 Rad Prepubertal
- Pronounced hormonal changes, similar to those of natural menopause, accompany radiation-induced sterilization

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Radiation Sterility – Comparing Male and Female

Male	Female
Self-renewal system: Spermatogonia → spermatocytes → spermatids → spermatozoa	Gonadal kinetics opposite of males; _By 3 days after birth, all cells progressed from oogonial to oocyte stage, no further division
_Latent period between irradiation and sterility _Oligospermia and reduce fertility: 15 cGy _Azoospermia and temp sterility: 50 cGy _Temporary sterlity for 12 months = 250 cGy	Neither latent period nor temporary sterility in females

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Radiation Sterility – Comparing Male and Female

Continued...

Male	Female
Perm. Sterility: 5-6 Gy single dose, 2.5 – 3 Gy: Fractionated 2-4 wks	Radiation can induce permanent ovarian failure; marked age dependence. Permanent sterility: 12 Gy prepuberty, 2 Gy, premenopausal
Induction of sterility does not affect hormone balance, libido, or physical capability	Radiation Sterility produces hormonal changes like those seen in natural menopause

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Basic Genetics

- A gene is a finite segment of the chromosome
- Humans have 23 chromosome pairs (46 total chromosomes); 1 pair is the sex chromosomes (men - XY; women - XX)
- One chromosome of each pair is from each parent
- Homozygous - 2 genes in the pair are alike
- Heterozygous - 2 genes in the pair are different
- A dominant gene expresses itself when paired with a recessive gene

_Homozygous refers to having identical alleles for a single trait.
_Heterozygous refers to having two different alleles for a single trait

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Basic Genetics

- Not all dominant genes are completely dominant
- A completely recessive gene only expresses if it is identical with its pair (person is said to be homozygous with the recessive gene)
- Y chromosome determines gender, but little else
- X chromosome has many other functional genes
- Thus, recessive mutations are critical in the maternal X chromosome passed to a son
- These are called 'X-linked' characteristics

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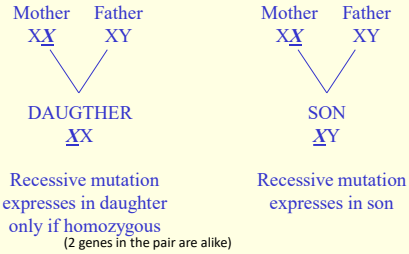
X/Y Chromosomes



X - represents mutant X chromosome

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Mutations

- Exposure to radiation can result in adverse health effects in the descendants from mutations in germ cells
  - Hereditary diseases (i.e., genetic diseases) may result when mutations in parents germ cells are transmitted to progeny).
  - Human genome contains 50 k – 100 k genes so the potential number of mutations is staggering.
  - In contrast most cancers result from mutations in somatic cells.

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Mutations

- Radiation does not result in new or unique hereditary effects
- All radiation-induced mutations also occur naturally
- Radiation only increases the rate of mutations above the spontaneous mutation rate
- Radiation-induced genetic effects may be classified into 3 categories
  - Mendelian (mutations in single genes)
  - Chromosomal aberrations
  - Multi-factorial diseases

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Hereditary Effects of Radiation

Hereditary Effect	Example
Mutations in single genes (Mendelian)	
Single dominant	Polydactyl, Huntington's chorea
Recessive	Sickle-cell anemia, Tay-Sachs disease, cystic fibrosis, retinoblastoma
Sex- linked	Color blindness, hemophilia (bleeding disorder when blood doesn't form clot)
Chromosomal Changes	
Too many or too few	Down's syndrome, mostly embryonic death
Chromosome aberrations, physical abnormalities	Embryonic death or mental retardation

1. More fingers. 2. Involuntary movements, 3. Body makes RED blood cells shape like sickle, 4. A disease that destroys nerve cells 5. A disease that effects lungs, pancreas, 6. An eye disease cancer people get in childhood.

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Hereditary Effects of Radiation

Hereditary Effect	Example
Multifactorial	
Congenital abnormalities present at birth	Neural tube defects, cleft lip, cleft palate
Chronic diseases of adult onset	Diabetes, essential hypertension, coronary heart disease.

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Statistics

Baseline Frequencies of Genetic Diseases in Human Populations (UNSCEAR 2001)

Disease Class	Frequency per Million	
Mendelian diseases		24,000
Autosomal dominant	15,000	
X-linked	1,500	
Autosomal recessive	7,500	
Chromosomal diseases		4,000
Multifactorial		710,000
Congenital abnormalities present at birth	650,000	
Chronic diseases of adult onset	60,000	
Total		738,000

United Nations Scientific Committee on the Effects of Atomic Radiation

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Single-Gene Mutations

- A DNA structural change
  - which may involve the base composition, the sequence or both
- A single base change can cause significant inheritable changes ('point mutations')
- **Recessive mutations** - require that the gene be present in duplicate to produce the trait (unless X-linked)
  - i.e., the mutant gene must be inherited from both parents
- **Dominant mutations** - require only one gene to produce trait
- **X-linked mutations** – where many other functional genes having recessive mutations are critical in the maternal X-chromosome and are passed to a son)

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Chromosomal Aberrations

- Errors in chromosome distribution can result in cells that contain too few or too many chromosomes
  - Down's syndrome, the best known example, results when there is an extra chromosome #23
- Most of the time, however, an incorrect chromosome number leads to embryonic death
- This kind of chromosome error is not believed to be strongly influenced by radiation
  - radiation is much more efficient at breaking chromosomes than in causing errors in chromosome distribution
  - chromosomes that are broken by radiation may rejoin in various ways, however (translocation, deletion, etc.)

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Multifactorial Diseases

- Multifactorial is attributed to a disease that has a genetic component but its transmission pattern cannot be described as single mendelian.
- Represents both common congenital abnormalities present at birth (neural tube defects, cleft lip w or w/o cleft palate) and many chronic diseases of adult onset (diabetes, hypertension, coronary heart disease,, etc.) that aren't the result of single-gene mutations
- Related to various environmental factors, yet known to be genetic

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Early Studies in Radiation Effects

- As early as 1927 exposure of x-rays were found to have cause mutations in fruit flies
- This data led to the recommendation that 5 R be the maximum permissible dose for workers in the 1950s.
- At that time hereditary changes were considered to be the principal hazard of exposure to ionizing radiation.

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Why Hereditary Changes were of Concern in 1950s

- Low doubling dose* (5- 150 Rad) estimated from fruit fly work
- Fruit fly data suggested hereditary effects were cumulative (i.e., accumulated dose adds up to increased genetic burden)
- In 1950s the carcinogenic potential of low-doses was not known

*A dose of radiation expected to double the number of genetic mutations in a generation.

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Why Hereditary Changes are Now of less Concern than in 1950s

- The Japanese bomb-survivor data added to our knowledge of cancer causation by radiation
- Hereditary risks have been down-estimated

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The Megamouse Project

- Conducted over many years at Oak Ridge National Lab, involving > 7 million mice
- Project goal was to determine specific locus mutation rates in the mouse for a variety of radiation exposure modes
- In-bred mice were irradiated and followed for a number of generations
  - to look for radiation-induced mutations
  - to quantify their dose-response relationship

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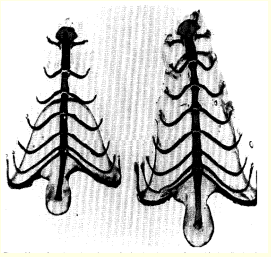
Estimate of the First Generation Incidence of Mutations

- An extra rib was one of the skeletal anomalies in mice used for the direct estimate of first generation genetic risks



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Mutation Risk

- Five major conclusions drawn from Megamouse study:
  - radiosensitivity of different mutations varies significantly
    - only possible to speak in terms of average mutation rates
  - substantial dose-rate effect in mice
    - spreading out dose results in fewer mutations
  - male mice are more radiosensitive than female mice
    - at low dose rates, almost all genetic burden is carried by males

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Mutation Risk

- Genetic consequences of a given dose are greatly reduced if time is allowed between irradiation and conception
- estimate of doubling dose favored by BEIR V is 1 Gy (100 rad)
  - based on ABS data; megamouse data is comparable
  - similar to various other estimates of doubling dose

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Hereditary Effects

- 'Guiding principles' for assessing human genetic risks:
  - most mutations, whether spontaneous or induced by radiation, are harmful
  - any dose of radiation entails some genetic risk (there is no threshold)
  - number of mutations produced is proportional to dose
    - "… a linear extrapolation from high-dose data provides a valid estimate of low-dose effects."
  - risk estimates based on experiments in mice
    - Which appears to be similar for humans

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Hereditary Effects

- In normal exposure situations (as humans would be exposed), mouse data indicate a low mutation yield
  - dose is continuous at very low rate
  - if dose rate is high, doses per exposure are small
- A significant proportion of genetic consequences can be avoided if conception is delayed for ~ 6 months
  - in cases when a large dose is absorbed in an acute exposure, like in criticality accidents

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Current Estimates of Genetic Risks from Continuing Exposure to Low-LET, Low Dose, or Chronic Irradiation (Assumed doubling dose, 1 Gy) (UNSCEAR 2001)

Disease Class	Base Freq. per 10^6 Live Births	Risk per Gy per 10^6 Progeny	
		1st Gen.	Up to 2nd Gen.
Mendelian diseases			
Autosomal dominant & X-linked	16,500	~750 – 1500	~1300 – 2500
Autosomal recessive	7,500	0	0
Chromosomal diseases	4,000	*	*
Multifactorial			
Chronic	650,000	~250 – 1200	~250 - 1200
Congenital abnormalities	60,000	~ 2000	~2400 - 3000
Total	738,000	~ 3000 - 4700	~ 3950 - 6700
Total risk per Gy as % baseline		~0.41 -0.64	~ 0.53 – 0.91

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ICRP Estimates of Hereditary Risks

- ICRP estimates based on UNSCEAR data
  - Based on reproductive population – 0.4% - 0.64% / Sv
  - Apply when doses received by all individuals are genetically significant
  - However, when TOTAL population (all ages) considered, genetically significant dose is lower than the total dose received over a lifetime
  - e.g. Genetic damage to individuals beyond reproductive period /not procreating poses no reproductive risk.
- Avg. 75 yr lifespan, mean reproductive age stopping at 30 y, gives risk coefficient for total population of 30/75 or 40% of reproductive population
- Rounds out to 0.2% / Sv
- For a working population (age 18 – 30 (for reproductive endpoint)) risk is (30-18)/75 or 16% of reproductive population or 0.1% /Sv.

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Mutations in A-Bomb Survivors

- Largest irradiated population studied
- Cohort of 31,150 children born to parents receiving signifcant dose (w/in 2 km of hypocenter)
- Control cohort of 41, 066
- Variety of indicators – congenital, gender, physical, cytogenetic abnormality, occurrence of malignant diseases.
- None of indicators was related significantly to parental exposure, but net regression slightly positive
- None the less, differences between control and cohort used to estimate doubling dose

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Doubling Dose in Offspring of Survivors from A-Bomb

Genetic Indicator	Doubling Dose, Sv
Untoward pregnancy outcome	0.69
Childhood mortality	1.47
Sex chromosome aneuploidy[a]	2.52
Simple average	1.56

[a]Aneuploidy is the condition of having less than or more than the normal diploid number of chromosomes, and is the most frequently observed type of cytogenetic abnormality

1 Sv = 100 Rem

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Bomb Survivor Data

- Sparse human data suggest that doubling dose from mouse data is too low
- Lack of statistically significant excess is consistent with numeric risks developed by the ICRP
- (Number of children involved and range of doses to parents too small for statistically significant hereditary effects to be expected)

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Summary of Pertinent Conclusions

- In the male,
  - doses as low as 15 cGy result in oligiospermia (low counts) after a 6 wk latency
  - Doses above 50 cGy result in azoospermia (no sperm) & temporary sterility – recovery depends on dose
  - Permanent sterility in the male requires a single dose > 600 cGy
  - Fractionated doses causes more gonadal damage than single dose
  - Permanent sterility can result from a dose of 250 – 300 cGy in a fractionated regime in 2- 4 wks

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Summary of Pertinent Conclusions

- In the female
  - Radiation is highly effective in inducing permanent ovarian failure, there is a marked age dependence on the dose required
  - Permanent sterility varies from 12 Gy prepubertal to 2 Gy premenopausal
- Induction of sterility
  - In males doesn't produce significant changes in hormone balance, libido, or physical capability
  - In females leads to hormonal changes similar to menopause

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Summary of Pertinent Conclusions

- Exposure of a population can cause adverse health effects in descendants as a consequence of mutations in germ cells.
  - Commonly called hereditary effects
  - Classified into 3 categories (Mendelian, chromosomal, and multifactorial)
- Radiation does not produce new unique mutations – it increases incidence of same ones that spontaneously occur

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Summary of Pertinent Conclusions

- Information on hereditary effects comes almost exclusively from animal experiments
  - Drosophila melanogaster
  - Relative mutation rates measured in megamouse project
  - Leads to doubling dose estimates of 1 Gy
- ~ 1-6% of spontaneous mutation rates in humans ascribed to background radiation
  - Estimate of radiation induced risk requires baseline mutation rate and doubling dose and 2 correction factors: 1) mutation component and 2) correction for mouse to human extrapolation

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Summary of Pertinent Conclusions

- ICRP estimates hereditary risk of radiation is ~ 0.2% / Sv for general population and 0.1% / Sv for working population
- Children of atomic bomb survivors have been studied for indicators
  - Congenital defects
  - Gender ratio
  - Physical development
  - Survival
  - Published papers estimated doubling dose to be ~ 2 Sv with lower limit of 1 Sv

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Effects of Radiation on Embryo and Fetus

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Overview of Radiation Effects on Embryo and Fetus

- Among somatic effects other than cancer, developmental effects on unborn child are of greatest concern
- Classic effects are
  - Lethal effects
  - Malformations
  - Growth disturbances

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Animal Data

- Most data originates from experiments with mice and rats
- The developmental period *in utero* can be divided into three stages:
  - preimplantation
  - organogenesis
  - the fetal period
- All three periods have different radiosensitivities and exhibit different effects

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Preimplantation

- Begins at conception and extends to the 5th day in mice; and to the 10th day in humans
- Preimplantation is the most sensitive stage to the **lethal** effects of radiation
- Growth retardation is not observed when irradiated in this stage
  - if the embryo survives it will grow normally
- "All-or-nothing" effect of radiation during preimplantation

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Organogenesis

- From ~10 days to 6 weeks in human
  - extends from the end of preimplantation to the beginning of the fetal period
- During this period major organs and structures are being developed
- Irradiation during organogenesis primarily results in structural and congenital anomalies
- In mice, a dose of 200 rad to the embryo during the period of maximum sensitivity can result in a 100% incidence of malformations at birth
- Embryos exposed in early organogenesis have the greatest temporary growth retardation

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The Fetal Period

- The fetal period extends from about the 14th day onward in mice; or at about 6 weeks onward in humans
- Irradiation of an early fetus results in the largest degree of permanent growth retardation
- A variety of effects from radiation exposure during the fetal period have been documented in animals:
  - hematopoietic system
  - kidney
  - liver

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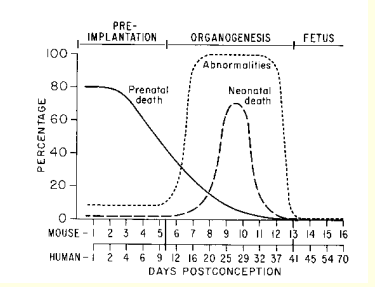
Incidence of abnormalities and prenatal and neonatal death in mice as a function of time of irradiation with 200R



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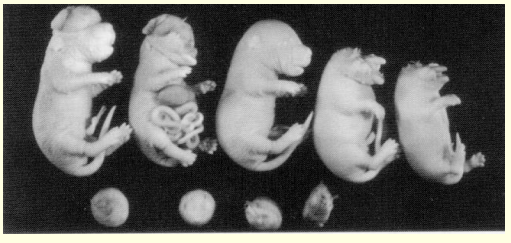
Abnormalities



Liter from female mouse irradiated with X-ray during organogenesis and sacrificed at 19 days. Four resorbed embryos in bottom, and 5 fetuses that would have been born alive on top. First shows exencephaly; 2nd excencephaly and evisceration; 3rd is apparently normal; and the last two are anencephalics with stunning.

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Embryogenesis

- The duration of these phases differs considerably among species

Table 19.1. Phases of embryogenesis in various species (days after conception). (After UNSCEAR, 1977)

type	preimplantation	organogenesis	fetal period
hamster	0 - 5	6 - 12	13 - 16.5
mouse	0 - 5	6 - 13	14 - 19.5
rat	0 - 7	8 - 15	16 - 21.5
rabbit	0 - 5	6 - 15	16 - 31.5
guinea-pig	0 - 8	9 - 25	26 - 63
dog	0 - 17	18 - 30	31 - 63
man	0 - 8	9 - 60	60 - 270

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Human Data

- Two major sources of information on humans irradiated *in utero*:
  - medical exposures
  - atomic bomb survivors
- Most common human abnormalities associated with *in utero* irradiation:
  - microcephaly
  - mental retardation
  - central nervous system defects
  - growth retardation

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ABS Exposed *In Utero*

- Children exposed *in utero* to the Japan A-bomb attacks have been carefully studied
- These data provide insight into the dose effect relationship in human embryos
- Radiation exposure *in utero* resulted in permanent growth retardation:
  - embryos exposed at a range of less than 1.5 km were shorter, weighed less and had smaller head diameters (than embryos exposed at distances greater than 3 km)

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ABS Exposed *In Utero*

- Principle effects were microcephaly and mental retardation
- Frequency of small head circumference is highest in the heavily exposed groups
  - but doses as small as 10 rad were enough to induce it.
- Relationship between mental retardation and exposure appears to be linear
- The dose-response relationship for exposure and mental retardation appears to have a threshold value between about 12 and 20 rad

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Effects of radiation on the embryo and fetus for A-bomb survivors

- The principal effects:
  - **Microcephaly**
    - cranium is small, but the face is normal size
    - these infants may be retarded mentally because brain development is rudimentary

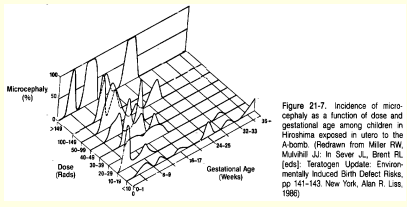

Figure 21-7. Incidence of microcephaly as a function of dose and gestational age among children in Hiroshima exposed in utero to the A-bomb. (Redrawn from Miller RW, Mulvihill JJ: In Sever JL, Brent RL [eds]: Teratogen Update: Environmentally Induced Birth Defect Risks, pp 141–143. New York, Alan R. Liss, 1986)

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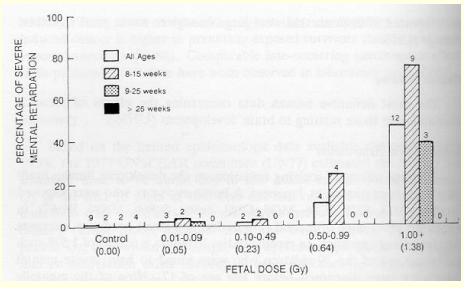
Frequency of mental retardation



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ABS Exposed *In Utero*

- Most sensitive period is 8 to 15 weeks for inducing mental retardation
- Interestingly, cells killed before 8 weeks can cause small head size without mental retardation
- During the most sensitive period for exposure, the observed shift in intelligence test scores corresponds to a decrease of about 30 IQ points per gray

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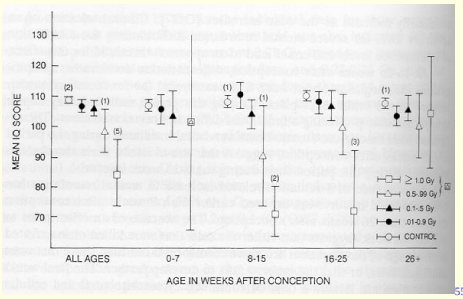
Effect on IQ
~30 IQ points per Gy



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Medical Exposures

- Medical exposures provide insight into the effects of radiation on the embryo and fetus in humans
- Generalizations from data on pelvic x-ray exposure in pregnant women:
  - large doses (250 rad) before 2 to 3 weeks of gestation are not likely to produce severe abnormalities in most born children, but many of the embryos may be resorbed or aborted
  - irradiation 4 to 11 weeks would lead to severe abnormalities of many organs

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Medical Exposures

- irradiation 11 to 16 weeks may produce a few eye, skeletal, and genital organ abnormalities
  - stunted growth, microcephaly, and mental retardation are often present
- irradiation 16 to 20 weeks may lead to a mild degree of microcephaly, mental retardation and stunting of growth
- irradiation after 30 weeks is not likely to produce gross structural abnormalities, but could cause functional disabilities

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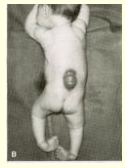
Effects of radiation on the embryo and fetus
Medical Exposures

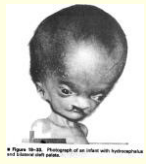
Spina bifida

- refers to a defect of vertebral column
- severe anomalies involve the spinal cord -**spina bifida cystica**
  - appears a protrusion of spinal cord through the defect in the vertebral arches



Hydrocephalus

- abnormality characterized by accumulation of cerebrospinal fluid in the cranial vault
- enlargement of the head



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Human vs Animal Data

- Exposure during preimplantation leads to a high incidence of embryonic death, but embryos that survive develop normally
- Irradiation during organogenesis causes a wide range of malformations in animals, but in humans this is not seen
- Irradiation to humans after organogenesis (after eight weeks) leads to microcephaly, with or without mental retardation
- To be safe, it should be assumed that malformations can be induced by radiation from about 10 days to 25 weeks

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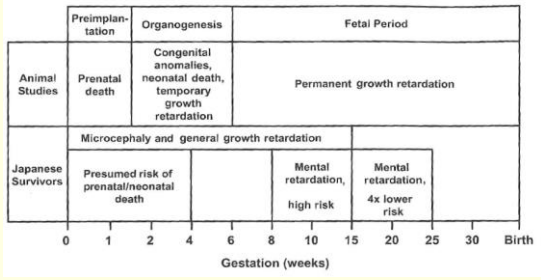
Animal/Human Comparison



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Minimum Doses for Observable Effects

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

Animal data	
Oocyte killing (primates)	50% lethal dose at 5 rad (0.5 Gy)
Central nervous system damage (mouse)	Threshold at 10 rad (0.1 Gy)
Brain damage and behavioral damage (rat)	Threshold at 6 rad (0.06 Gy)
Human data	
Small head circumference	Air kerma 10–19 rad (0.1–0.19 Gy)
Summary	Fetal dose 6 rad (0.06 Gy)
Readily measurable damage caused by doses below 10 rad (0.1 Gy) (acute exposure) delivered at sensitive stages	

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Childhood Cancer After Exposure *In Utero*

- Some studies conclude that the incidence of childhood leukemia and some other childhood cancers may be increased as a result of *in utero* exposure
- Data supports the conclusion that susceptibility to the carcinogenic effects of radiation is high during *in utero* development
- Estimated risk of 200-250 excess cancer deaths per 10,000 person-Gy in the first ten years of life from *in utero* exposures

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Pregnant Workers

- NCRP recommends dose to the fetus should not exceed 5 mSv, and a monthly exposure should not exceed 0.5 mSv (50 mRad)
- Once a pregnant worker declares her pregnancy, she should be interviewed to determine whether her duties should be changed or curtailed

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Pregnant Workers

- An occupational worker has the right to, and the right not to, declare her pregnancy
- The declaration of pregnancy must be in writing and include the estimated date of conception
- A pregnant worker has the right to rescind their declaration of pregnancy

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Occupational Limits

- A declared pregnant woman receives the 5 mSv limit for the duration of the pregnancy and a fetal dosimeter must be worn
- An undeclared pregnant woman receives the normal limit (50 mSv/yr) for radiation workers
- A pregnant worker cannot be discriminated against on the basis of her pregnancy

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Medical Exposures: Pregnancy

- Female patients should be interviewed to determine likelihood of pregnancy
- In the event that a procedure must be performed on a pregnant woman, medical professionals say that an abortion should be considered if a dose in excess of 0.1 Gy is delivered to the fetus during the sensitive period of gestation (~ 10 days to 25 weeks)

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Summary of Pertinent Conclusions

- Moderate doses of radiation can produce catastrophic effects on developing embryo and fetus
  - Depends on gestational age
  - Dose
  - Dose rate
- Gestation divided into 3 phases (preimplantation, organogenesis, fetal period)

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Summary of Pertinent Conclusions

- Principal effects on embryo and fetus are embryonic, fetal or neonatal death, congenital malformations, growth retardation, and functional impairment such as mental retardation
- Irradiation during pre-implantation leads to potential death of embryo – growth retardation or malformations are not seen in animals from irradiation – human data are consistent with this conclusion

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Summary of Pertinent Conclusions

- Animals –
  - embryos exposed to radiation in early organogenesis exhibit the most severe intrauterine growth retardation from which they can later recover;
  - irradiation in the fetal period leads to greatest degree of permanent growth retardation
  - Lethality from irradiation varies with stage of development
  - Embryonic 50% lethal dose lowest during early pre-implantation –
  - In organogenesis prenatal death is replaced by neonoatal death (at or near time of birth)
  - During fetal stage 50% lethal dose approaches that of adult

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Summary of Pertinent Conclusions

- In animals peak incidence of teratogenesis or gross malformations occurs in fetus if irradiated in organogenesis
- In contrast – Japanese survivors irradiated *in utero* showed primarily malformations of central nervous system – but malformations of other body structures have been seen in patients exposed to therapeutic doses of medical radiation

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Summary of Pertinent Conclusions

- Data on A-bomb survivors indicates that microcephaly can result from exposure at 0 – 7 and 8 – 15 wks postovulation – but not at later times and little evidence for threshold dose
- Variety of effects documented in experimental animals after irradiation during fetal stage – including hematopoietic, liver and kidney – all requiring high doses
- There is an association between diagnostic x-rays *in utero* and subsequent development of childhood malignancies

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Summary of Pertinent Conclusions

- Multiple studies imply that radiation at low doses in utero increases spontaneous cancer incidence in first 10 – 15 yrs by 50%
- Still argued if radiation is causative agent or if other factors are involved – summarized evidence suggests absolute risk is about 6% per Gy (about same as that from a-bomb survivors for adults)
- Until pregnancy is declared, no special limits apply to US workers; once declared, max permissible dose is 0.5 mSv and duties of worker should be reviewed
- Dose of 0.1 Gy to the embryo during 10 d – 25 weeks of gestation is often considered cutoff point for consideration of therapeutic abortion - but this must be flexible

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