

Long-term Radiation Effects

- 1) Effects on the Developing Embryo & Fetus
- 2) Heritable Effects

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1

Radiation Effects on the Embryo & Fetus

- Moderate doses of radiation can produce catastrophic effects on the developing embryo and fetus.
- The effects depend on the stage of gestation, the dose, and dose rate.

Radiation Effects on the Embryo & Fetus

- Growth retardation.
- Congenital malformations.
- Embryonic, fetal, or neonatal death.

Radiation Effects on the Embryo & Fetus

- Gestation is divided into three periods – (times given are for *human* gestation):
 - **Preimplantation** 0-9 days
 - **Organogenesis** 10 days-6 weeks
 - **The Fetal Period** 6 weeks to term

Growth Retardation

- Not observed following irradiation during preimplantation.
- Early organogenesis – most intra-uterine growth retardation expressed as weight reduction at term. Can recover later.
- Early fetus – largest degree of permanent growth retardation.

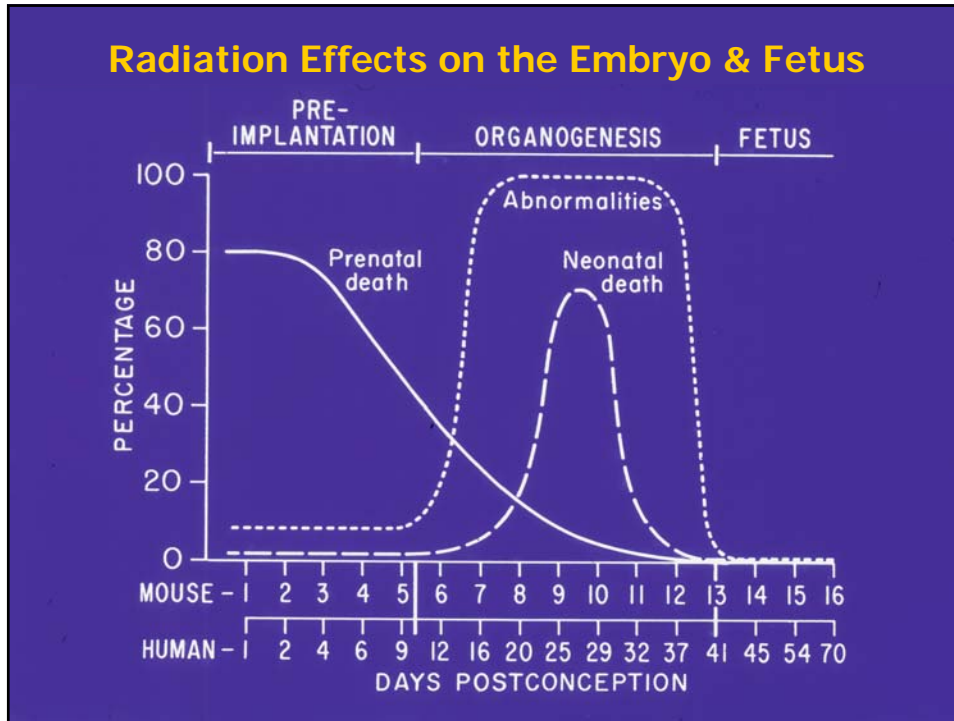
Growth Retardation at Hiroshima by *In Utero* Irradiation

- 80% of 1,613 children exposed *in utero* followed to age 17 years.
- Those exposed within 1500 m* of the hypocenter compared with those more than 3000 m:
 - **2.25 cm** – shorter.
 - **3.0 kg** – lighter.
 - **1.1 cm** – smaller head diameter.

* Average kerma **25 rads** (0.25 Gy).

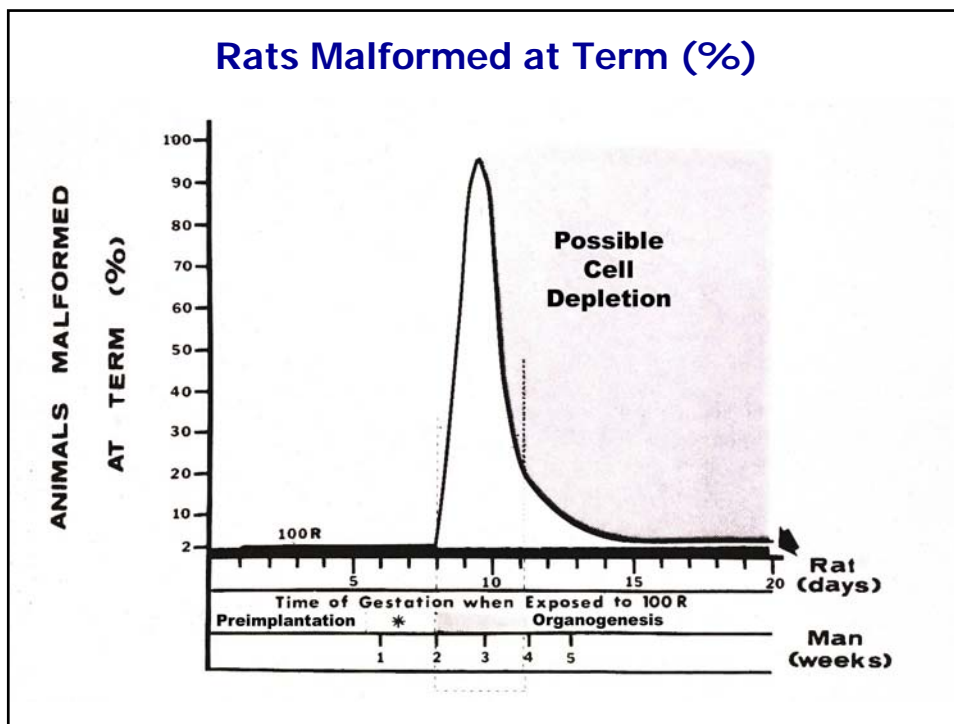
(BEIR III Report)

Effects of Radiation on the Developing Embryo and Fetus – Heritable Effects of Radiation
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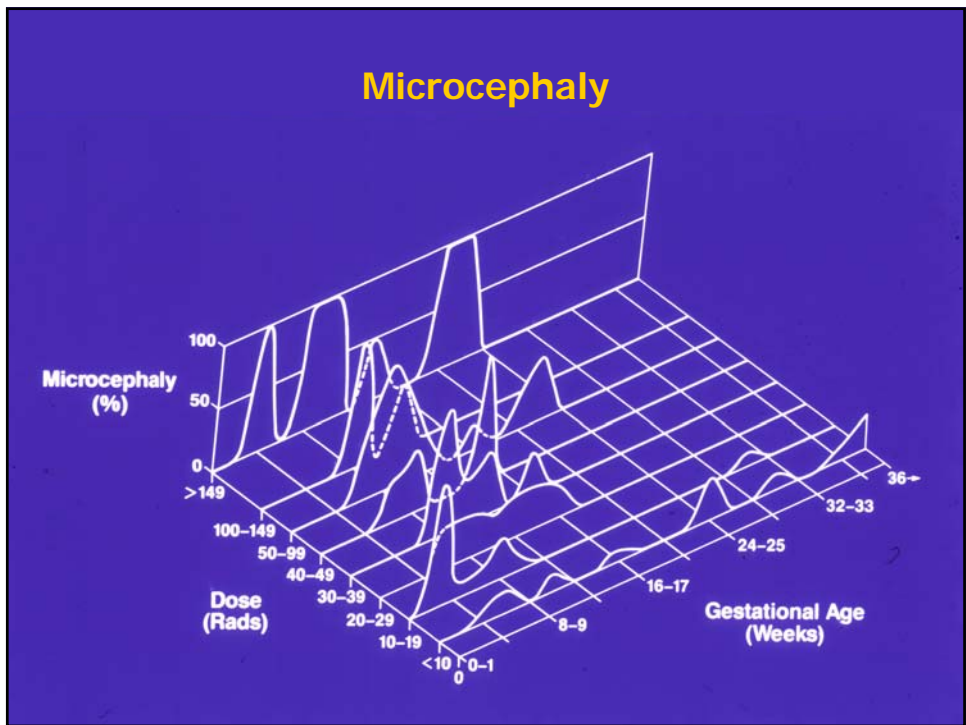


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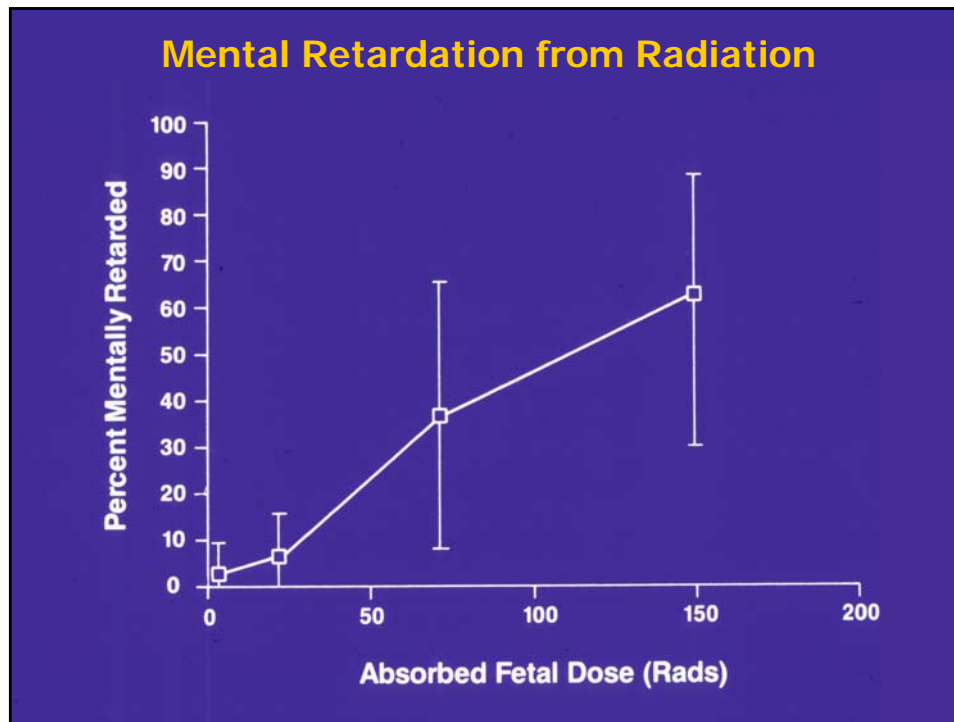
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Radiation Effects on the Embryo & Fetus

- The incidence of severe **mental retardation** as a function of dose is apparently linear without threshold at 8-15 weeks – with a risk coefficient of **0.4 per 100 rad** (0.4 per Gy) – consistent with a threshold of about 20 rad (0.2 Gy).
- The incidence is about 4 times lower at 16-25 weeks.

Japanese Irradiated *In Utero*

- MRI studies indicate **MASSIVE** impairment of cells to migrate from proliferation zone to functional zone.
- The distribution of gray matter is often associated with mental retardation –
 - But then it is usually unilateral.
 - Radiation produces bilateral changes.
- Maximum effect at 8-15 weeks.

Japanese Irradiated *In Utero*

IQ

- Test for irradiation at 8-15 weeks.
- Loss of 21 to 29 points at 1 Gy.
- Normal score 107 points.

Journal Article – 2004

Effect of Low Doses of Ionising Radiation in Infancy on Cognitive Function in Adulthood: Swedish Population Based Cohort Study

Per Hall, Hans-Olov Adami, Dimitrios Trichopoulos, et. al.

British Medical Journal 328(Jan), 2004.

4577 Boys < 18 Mo. R/T for Haemangioma

- Decrease in % attending high school.
Doses > 100 mGy (10 rad)
- Dose response (20-250 mGy) for cognitive tests.
 - Concept discrimination
 - General instruction
 - Technical comprehension
 - NOT spatial recognition

Ron *et. al.* – Am. J. Epi. 116:149-160, 1982

R/T for Tinea Capitis

Mean age 7 years

Mean dose to brain 140 rad

Observed Increased brain tumors

EEG

Visually evoked responses

School grades declined

Tests for army declined

Radiation Effects on the Embryo & Fetus

Animal experiments show:

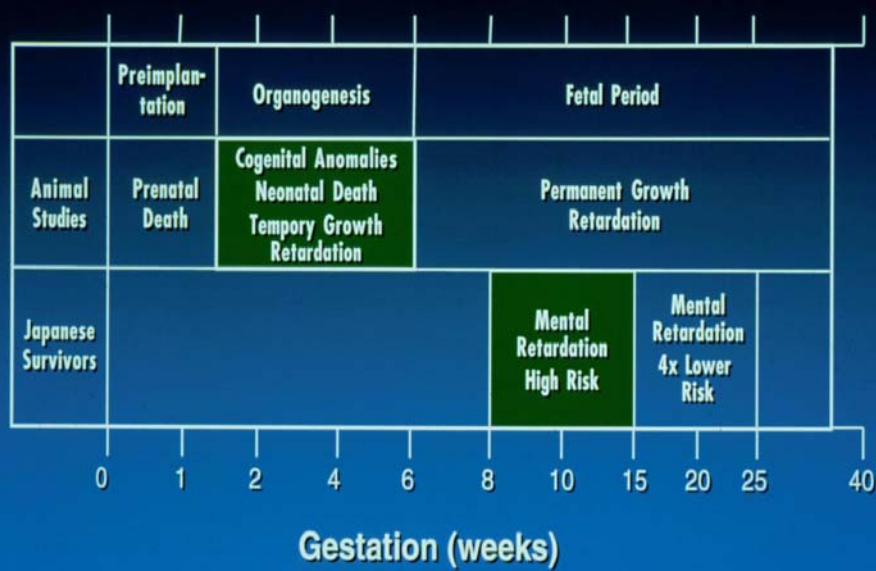
- Embryonic death during pre-implantation (0-9 days).
- Growth retardation. Temporary during organogenesis, permanent during the fetal period.
- Gross congenital malformations during organogenesis (10 days to 6 weeks).

Radiation Effects on the Embryo & Fetus

Japanese A-bomb survivors show:

- Microcephaly from irradiation during much of gestation.
- Severe mental retardation:
 - 40%/Sv at 8 to 15 weeks.
 - 10%/Sv at 16 to 25 weeks.

Summary of Radiation Effects In Utero



The Absence of Congenital Abnormalities in A-Bomb Survivors is explained by...

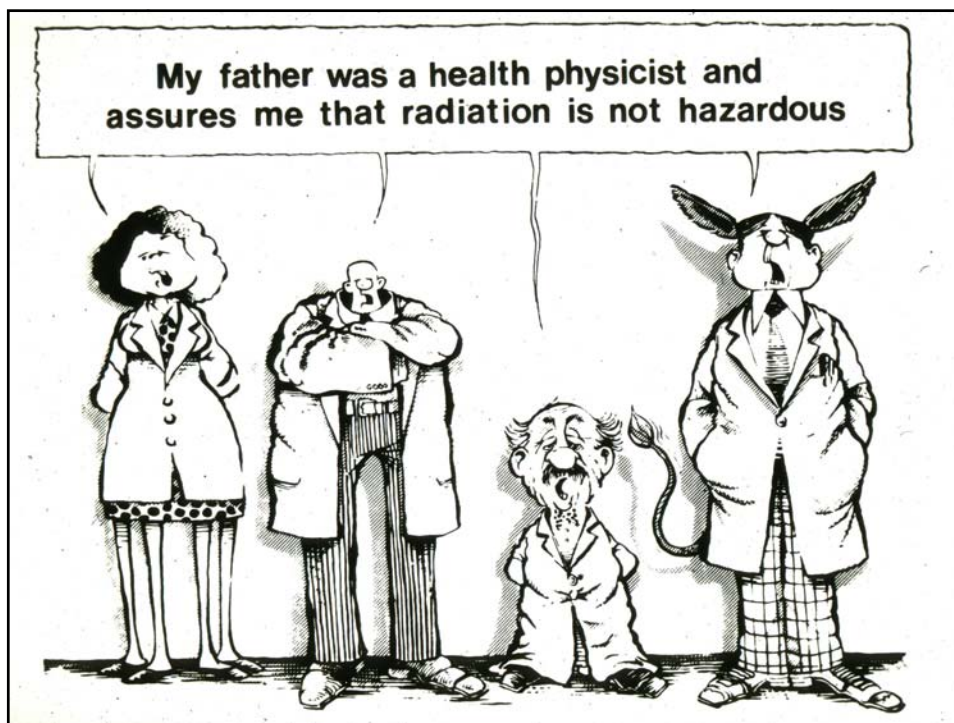
- Too few were exposed at any one period in the long Gestation period characteristic of the Human for an excess to show up.
- U.S. epidemiologists had not arrived in time to observe an excess of congenital abnormalities since almost all children were born at home with a midwife

Hereditary Effects of Radiation

- Adverse health effects in descendants due to mutations induced in germ cells.

Hereditary Effects of Radiation

- Radiation *does not* produce *new unique mutations*, but increases the incidence of the *same mutations* that occur *spontaneously*.
- Information on the genetic effects of radiation comes almost *entirely* from animal experiments.



Ionizing Radiation as a Mutagen

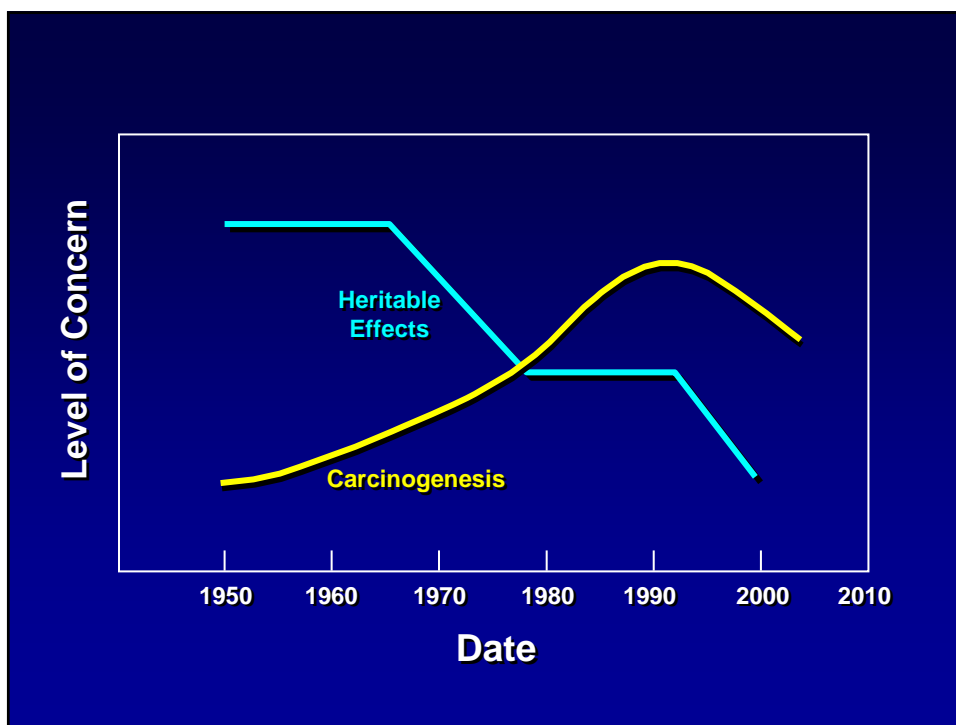
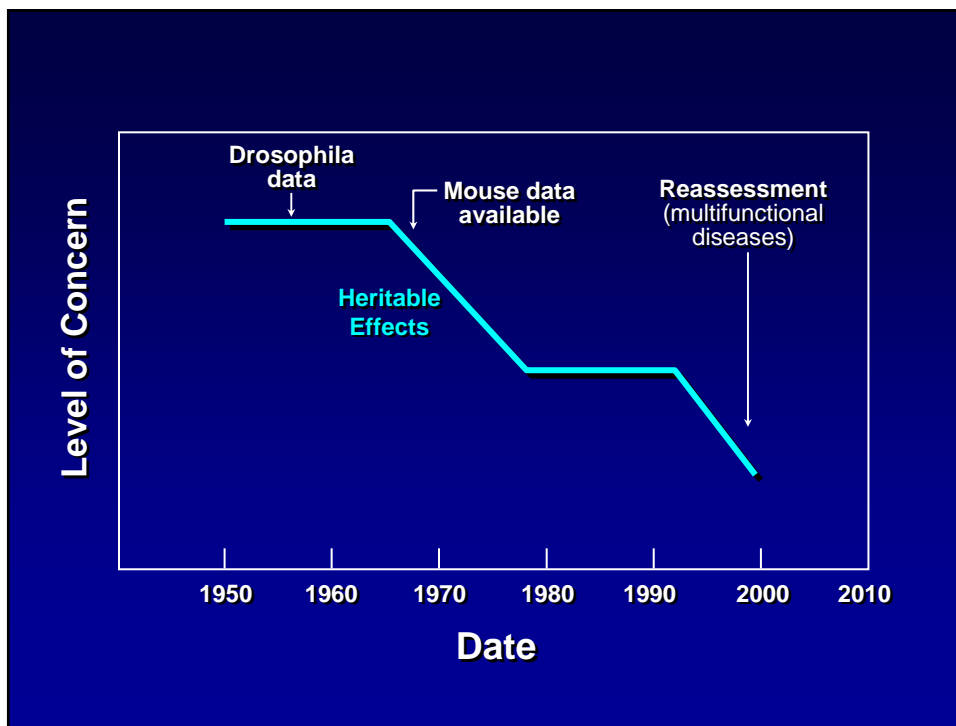
- First shown in *Drosophila* (The fruit fly) by H.J. Müller in 1927.
- Radiation increases spontaneous mutation rate.
- No evidence for a threshold.

The Changing Scene

- In the 1950's, genetic effects (now called heritable effects) were thought to be the most significant consequence of exposure to radiation, since at that time the excess incidence of solid cancers had not shown up in the A-bomb survivors.
- The opposite is true today.

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Hereditary Effects

- Mendelian
- Chromosomal
- Multifactorial

Mendelian

- **Autosomal dominants**
 - Due to mutations in a single gene on one chromosome.
- **Autosomal recessive**
 - Defective copy of same gene from each parent.
- **Gender linked**
 - Males have **one X**
 - One mutation can cause disease.
 - Females have **two X**
 - Two mutant genes needed.

Multifactorial

- Diseases known to have genetic component.
- Transmission pattern not simple Mendelian.
- Congenital abnormalities – cleft lip ± cleft palate, neural tube defects, adult onset diabetes, essential hypertension, coronary heart disease.
- Interaction with environmental factors.

Heritable Effects of Radiation

- First-generation mutations in mice have been measured by observing skeletal anomalies in the offspring of irradiated mice.
- Relative mutation rates have been measured in the **Megamouse Project** by observing specific locus mutations.



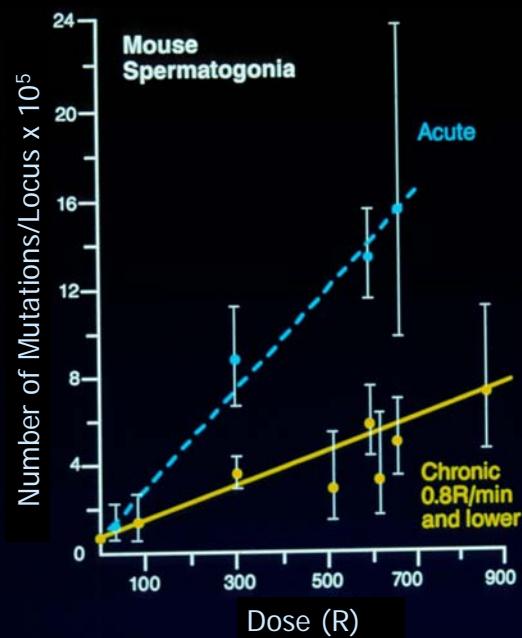
Conclusions from Megamouse Project – #1

- Different mutations differ significantly (factor of 20) in the rate at which they are produced by radiation.

Conclusions from Megamouse Project – #2

- There is a substantial dose-rate effect in the mouse (unlike *Drosophila*) so that spreading a given dose out over time reduced the number of mutants.

The Dose Rate Effect for Mutations



Conclusions from Megamouse Project – #3

- The **Male** is **more sensitive** than the **Female**.
 - At low dose-rate no mutations were observed in irradiated females.

Conclusions from Megamouse Project – #4

- The genetic consequences of a given dose can be greatly **reduced** if a time interval is allowed between irradiation and conception.

Conclusions from Megamouse Project – #5

- The **doubling dose** is the dose required to double the spontaneous mutation incidence – i.e., the dose required to produce an incidence of mutations equal to the spontaneous rate.
- **BEIR III estimate: 50 to 250 rem (0.5 to 2.5 Gy).**
- **UNSCEAR (1986) estimate: 100 rad (1 Gy).**

Data Needed to Estimate Risk of Heritable Effects in Humans

- Base-line spontaneous mutation rate in humans – 738,000 per million.
- The doubling dose (from the mouse): 1Gy.

Two Correction Factors

- Not all mutations lead to disease.
The mutation component (MC):
 - 0.3 for autosomal dominant.
 - 0.0 for autosomal recessive.
 - 0.01-0.02 for chronic multifactorial.
- The 7 specific locus mouse mutations are not representative; they are genes not essential for viability. Only a small proportion of human genes, when mutated, would result in live births.

Hereditary Effects – ICRP

- Total population 0.2%/Sv
- Working population 0.1%/Sv
- Based on:
 - Hereditary risks for first two generations.
 - Life expectancy 75 yrs; reproductive age 30 yrs.
 - Total population $\frac{30}{75}$ of reproductive pop.
 - Working population $\frac{30-18}{75}$ of reproductive pop.

Hereditary Effects of Radiation - Human

- Children of the survivors of Hiroshima and Nagasaki have been studied for **untoward pregnancy outcomes, death of live-born children, sex chromosome abnormalities, electrophoretic variants of blood proteins.**
- Though no genetic indication is statistically significant, the average doubling dose is **158 rem** (1.58 Sv).

Doubling Dose (Gametic) in the Offspring of Survivors of Hiroshima and Nagasaki

<u>Genetic Indicator</u>	<u>Doubling Dose (rem)</u>
Untoward pregnancy outcome:	69
Childhood mortality:	147
Sex chromosome aneuploidy:	252
Simple average:	156

Mutations in Germ Cells

- Animal experiments show that large doses cause abnormalities in offspring (7 million mice used).
- No detectable increase in mutations in 70,000 offspring of Japanese A-bomb survivors.
- Must assume that high doses of radiation can cause heritable effects.

Deleterious Effects Compared

- Mental retardation
(in utero 8-15 wks): **40%/Sv**
- Fatal cancers
(workers, low dose + d/r): **4%/Sv**
- Heritable effects
(workers): **0.1%/Sv**

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End