Low Dose Radiation Exposure and Modulation of High Dose Effects on Embryogenesis and Heritable Mutations

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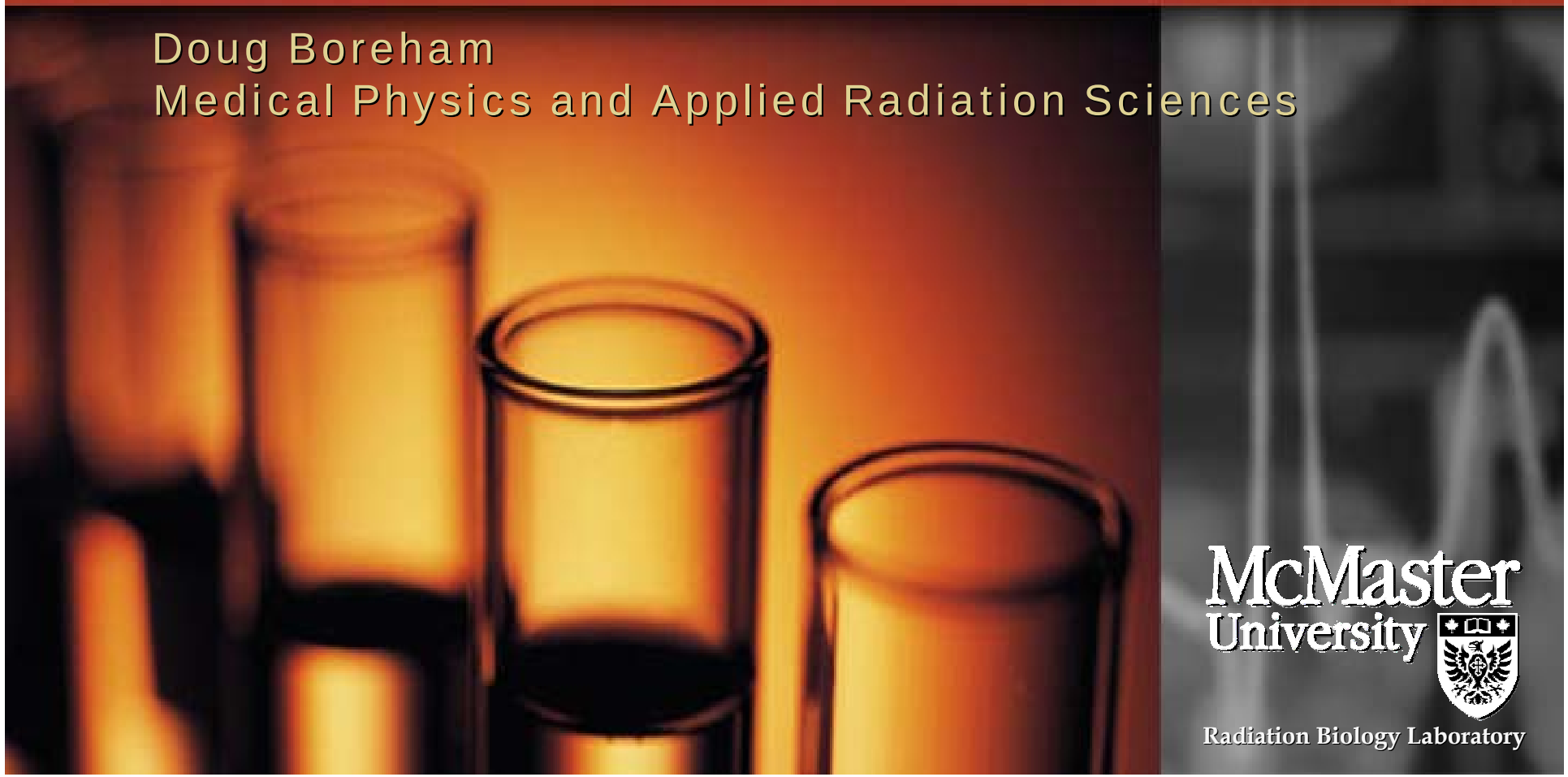


McMaster University
Radiation Biology Laboratory

Effects of Low Doses on Reproduction (non-cancer)

Part 1- Embryogenesis

Part 2- Heritable Mutations

Radiation and Embryogenesis

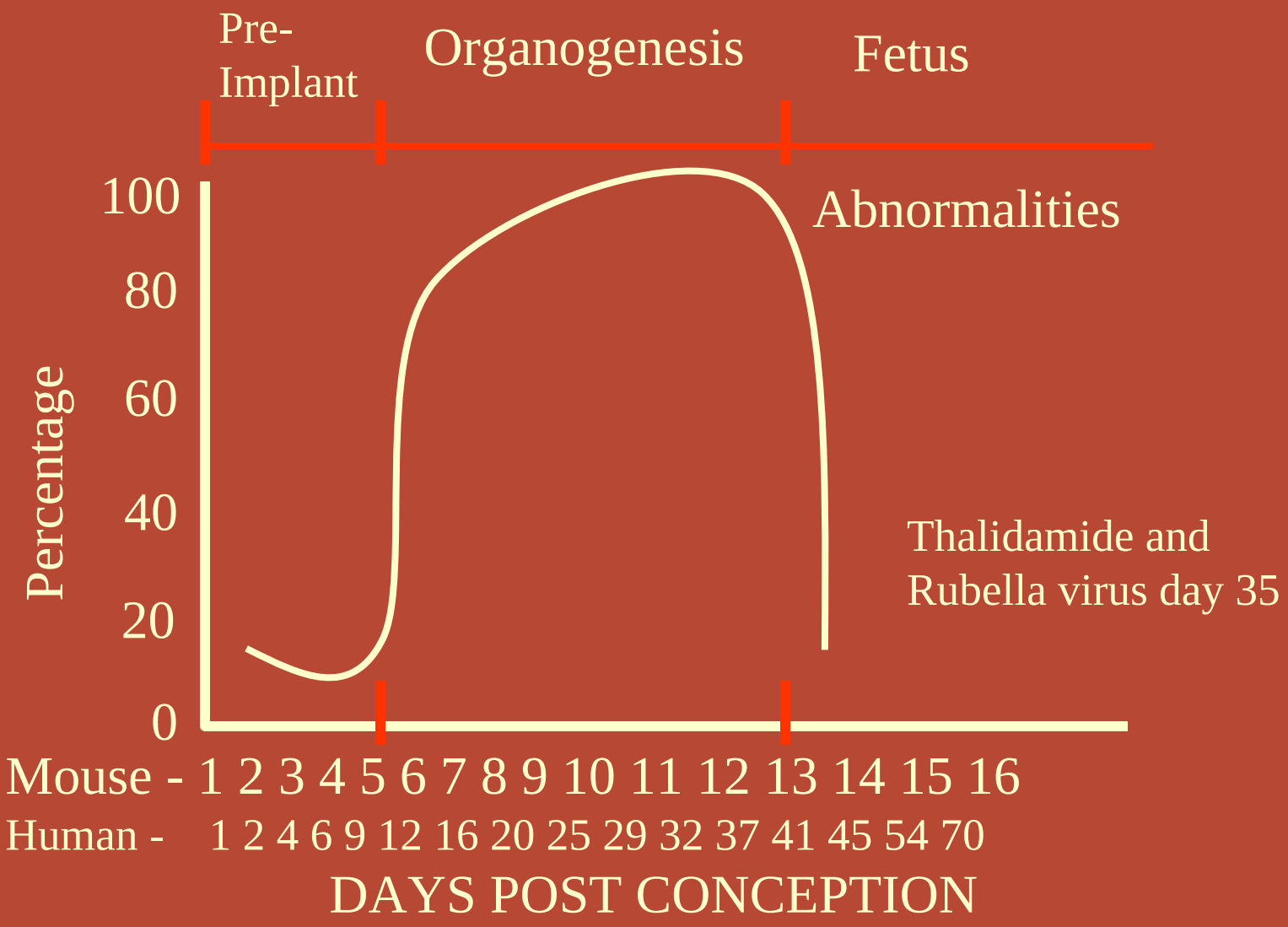
•Early 1900's – mental retardation in children of mothers that were given radiotherapy.

•1926 – Diagnostic X-rays not considered a hazard

Developmental – lethal, malformation, growth

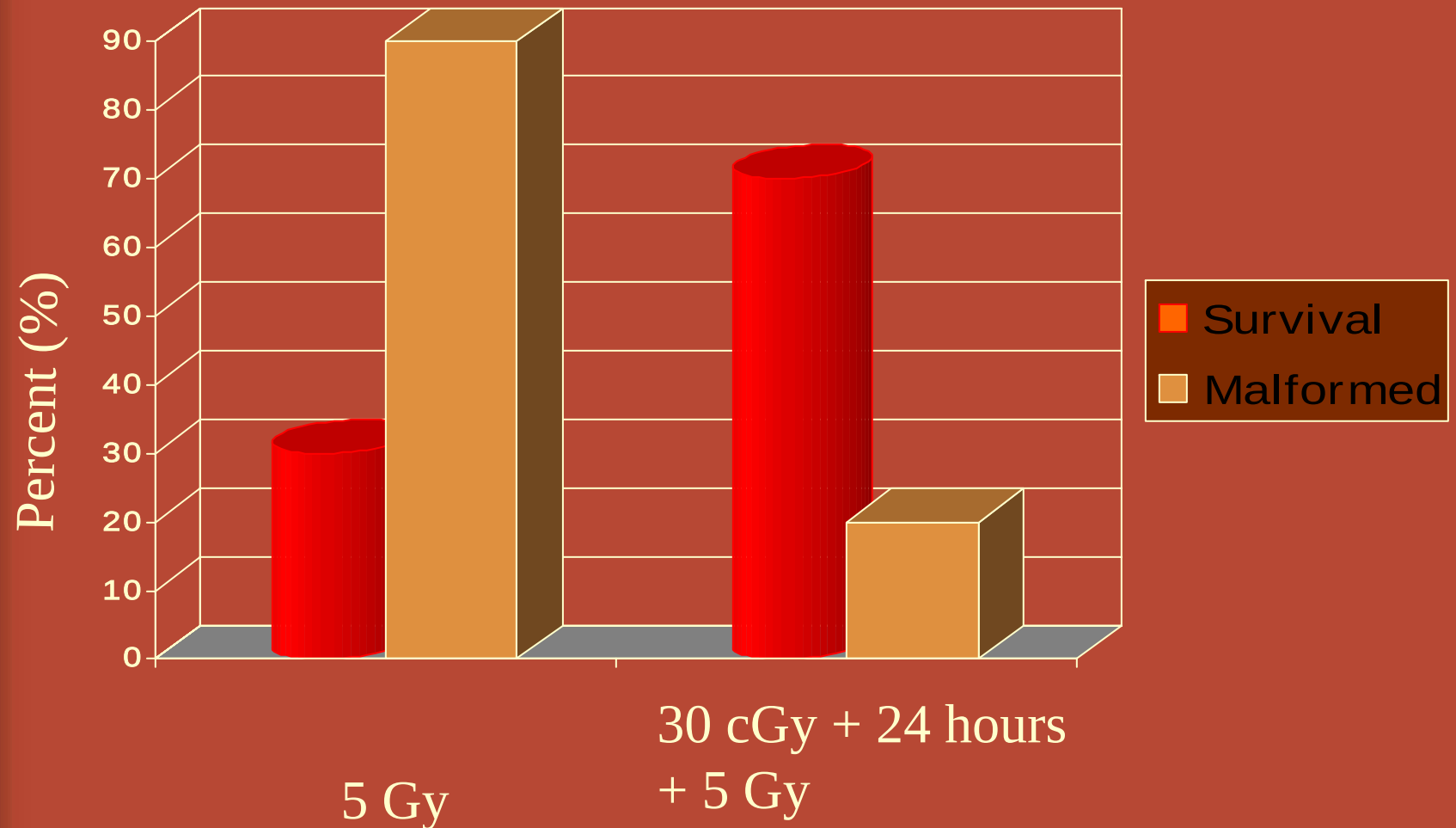
Depends on Dose, Dose Rate and Stage of Gestation

Abnormalities after Fertilization



Adaptive Response and Embryogenesis

Wang et al. 1997



Embryogenesis and p53

p53 is the "guardian of the genome" protein and controls apoptosis

p53 protein plays a major role in development

When p53 is genetically inactivated "Knocked Out" in the cells of a mouse, the mouse has a higher spontaneous cancer risk and is also more prone to radiation-induced cancer

Role in development and radiation???

Role of Trp 53

+/- X +/-

PP = Homozygous Normal
Pp = Heterozygous
pp = Knock-out

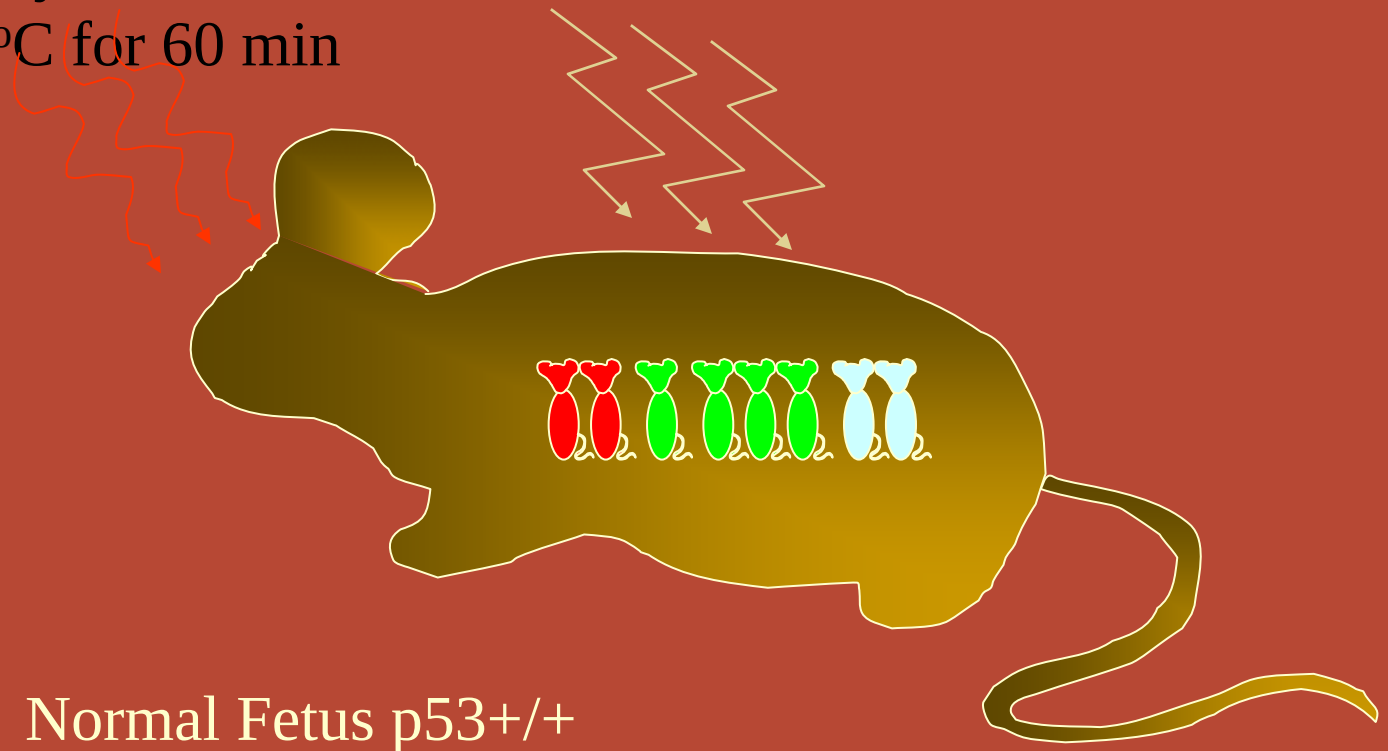
	P	p
P	PP	Pp
p	pP	pp

PP:Pp:pp
1:2:1

Day 10
30 cGy or WBH
40.5°C for 60 min

Day 11
4 Gy TBI

Day 18
Examine Fetuses



Normal Fetus p53+/+

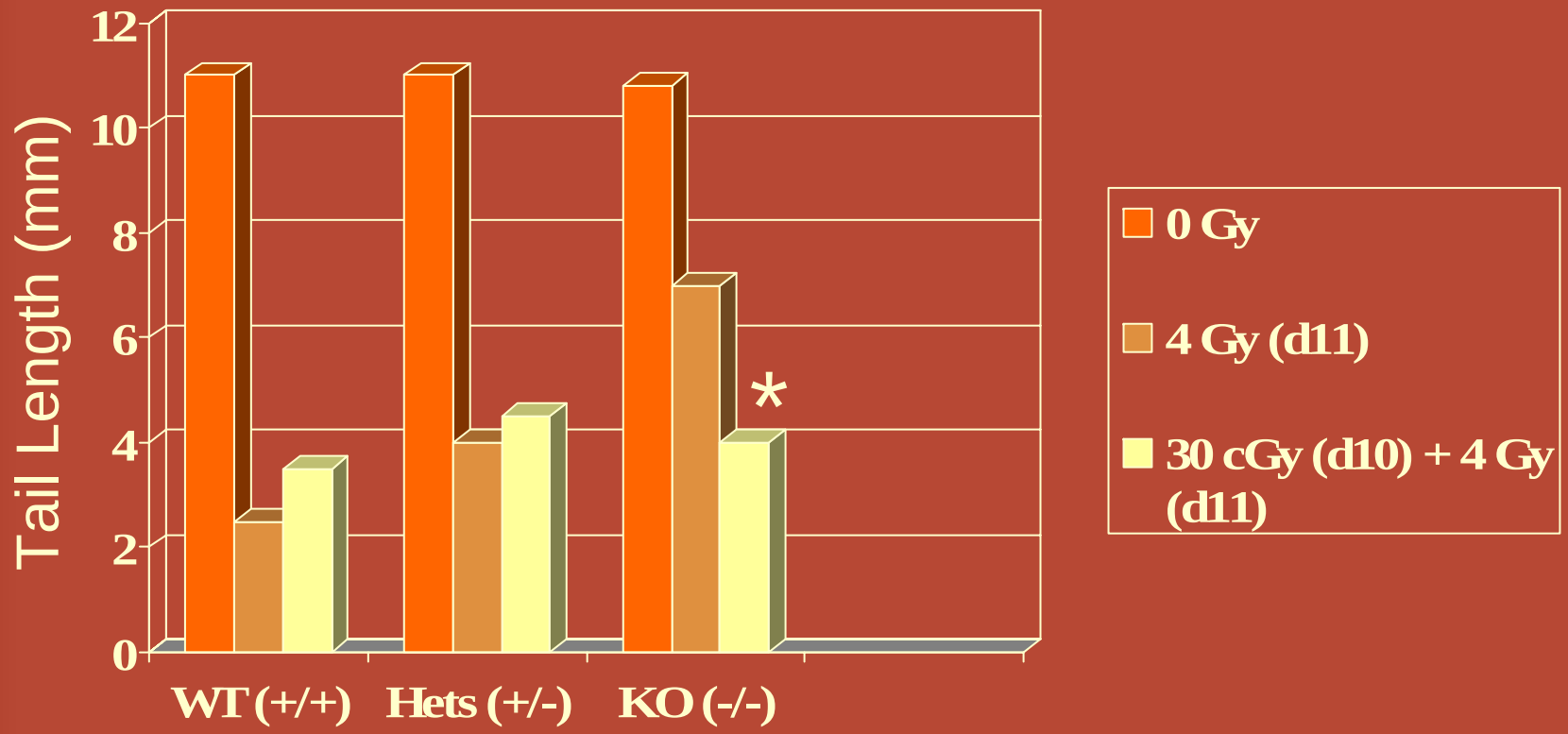
Heterozygous Fetus p53+/-

Knockout Fetus p53-/-

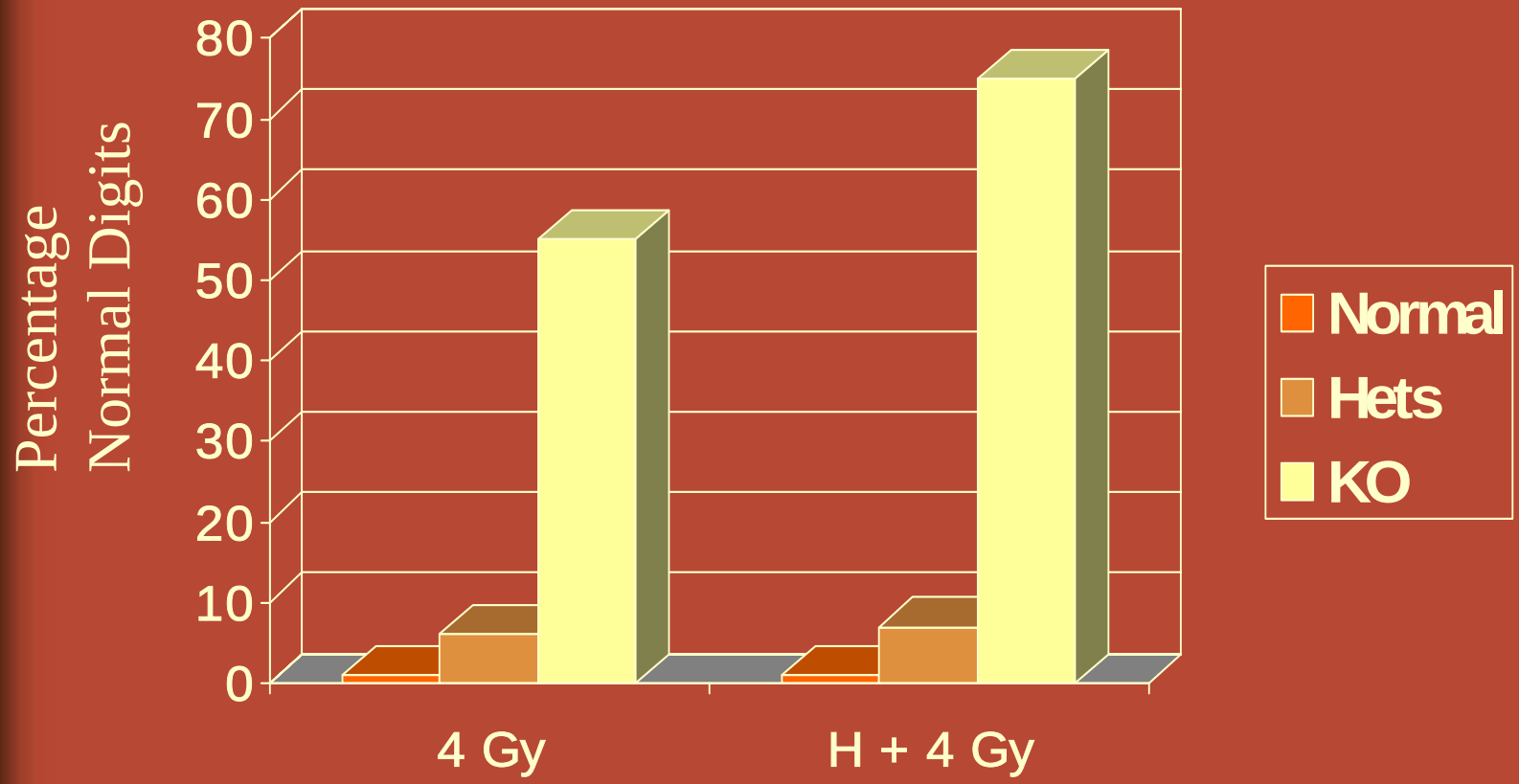
Malformation

- Tail Length
- Digit Number

Adaptive Response for Malformation

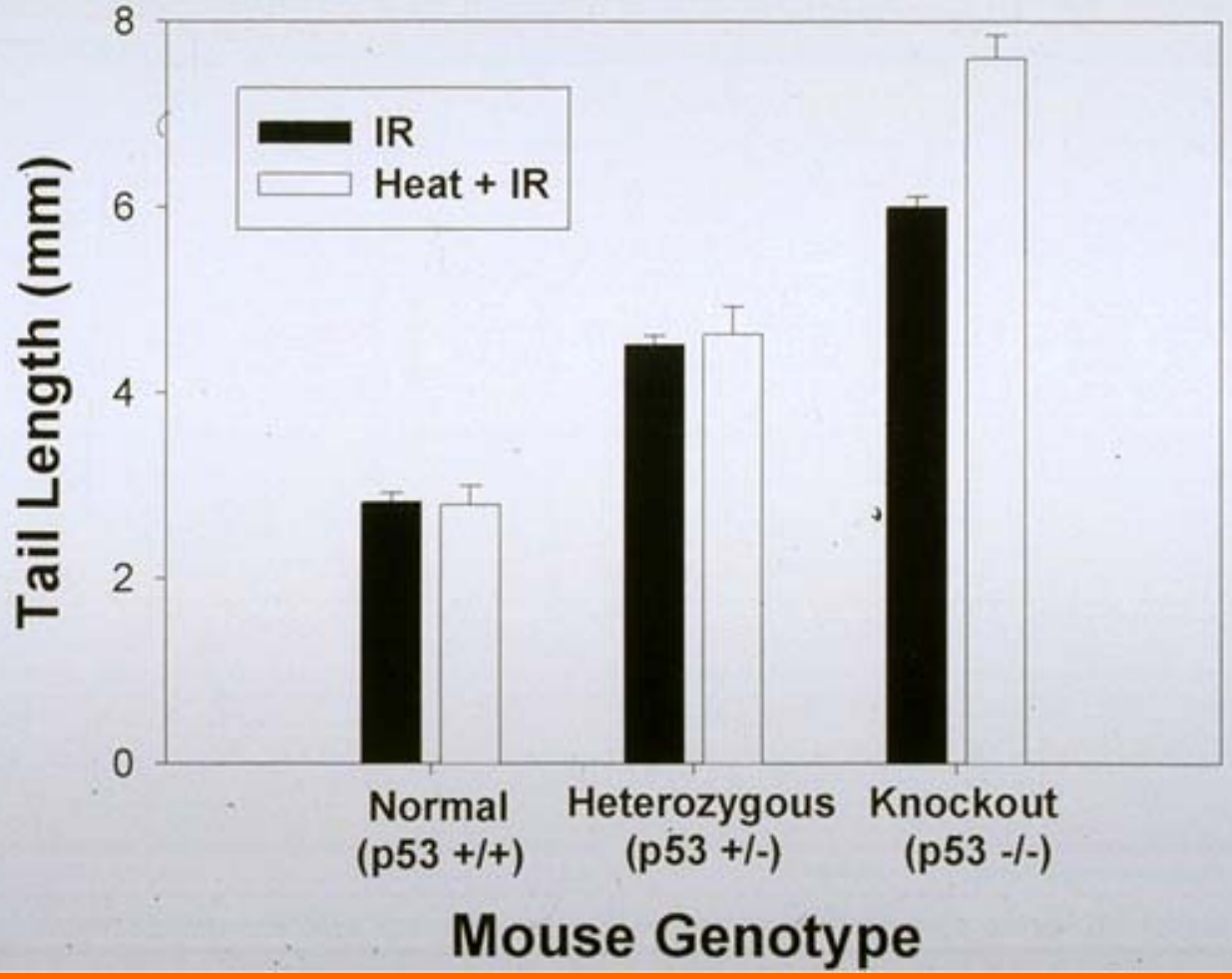


Effect of Heat on Digit Number



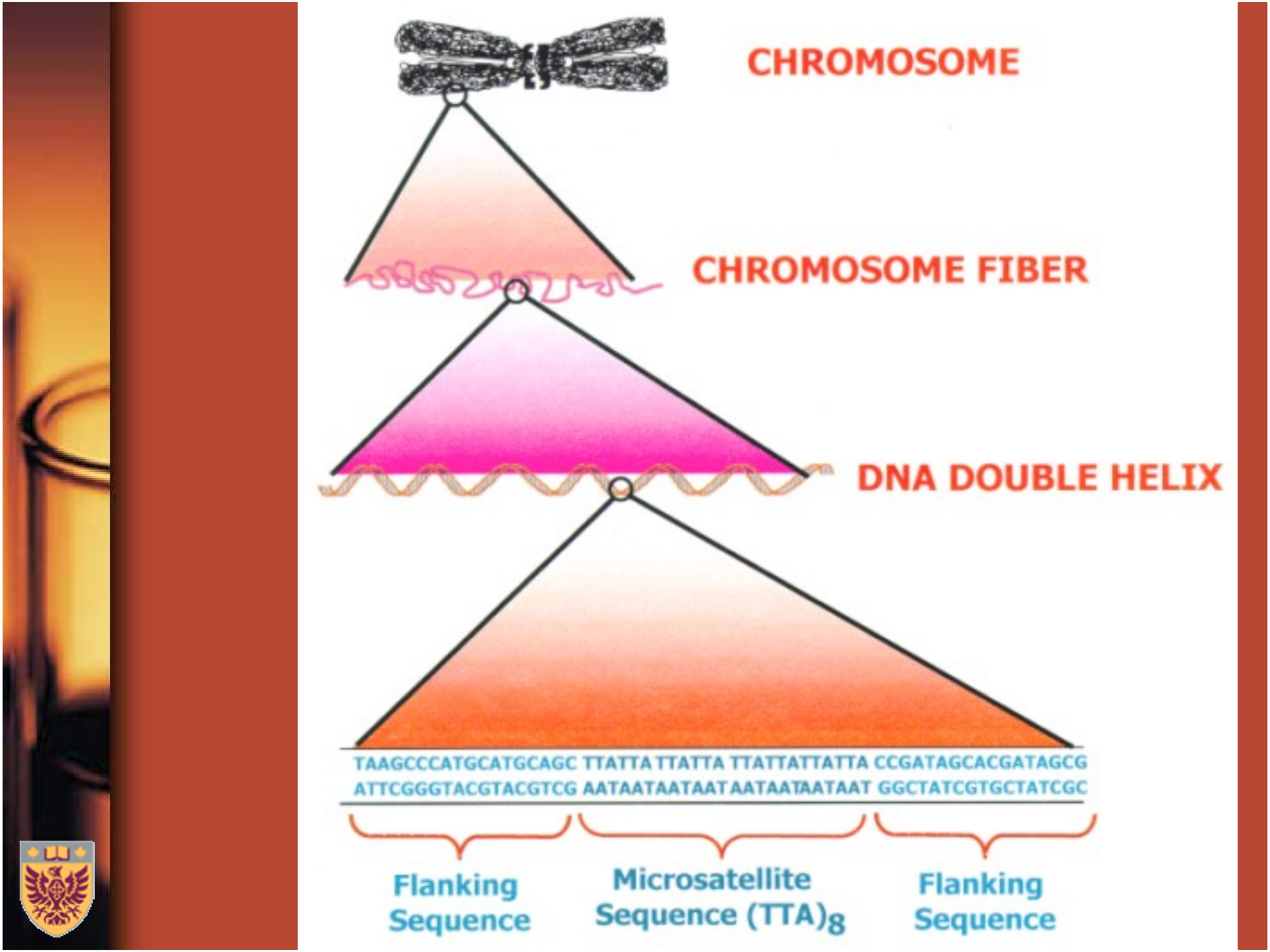
WBH (40°C for 60 minutes) to mother on day 10 and 4 Gy TBI to mother on day 11, Fetuses day 18

Hyperthermia and Adaptive Response during Embryogenesis



Conclusions

- The teratogenic effects of high dose radiation exposure to a developing murine fetus can be modified by a prior low dose exposure to radiation or hyperhermia.
- The time of the adapting exposure during organogensis can change the outcome of the teratogenic effects of the high dose exposure.
- Genotype of the developing fetus can influence the modifying effects of the adapting exposure. There is a p53 dependent process that is modified by low dose exposure at certain times during embryogenesis.

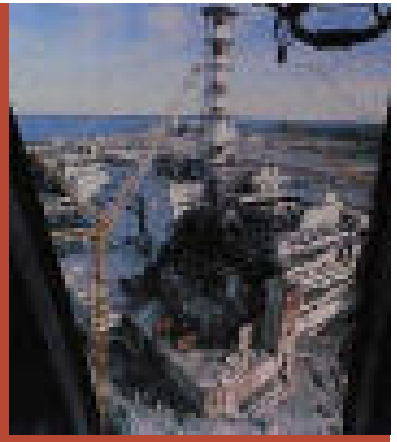

CHROMOSOME
CHROMOSOME FIBER
DNA DOUBLE HELIX
TAAGCCCATGCATGCAGC TTATTA TTATTA TTATTATTATTA CCGATAGCACGATAGCG
ATTCGGGTACGTACGTCG AATAATAATAAT AATAATAATAAT GGCTATCGTGCTATCGC
Flanking Sequence
Microsatellite Sequence (TTA)8
Flanking Sequence

Measuring Heritable Mutations: ESTR loci

- Expanded Simple Tandem Repeat Loci

  - Hypervariable, non-coding regions of DNA consisting of 1000's of repeated sequences of 4-6 base pairs (…ATCCATCCATCCATCC...)
  - Insertion and deletion mutations allow for detection of radiation-induced genetic mutations at low dose

Human Exposures: Chernobyl

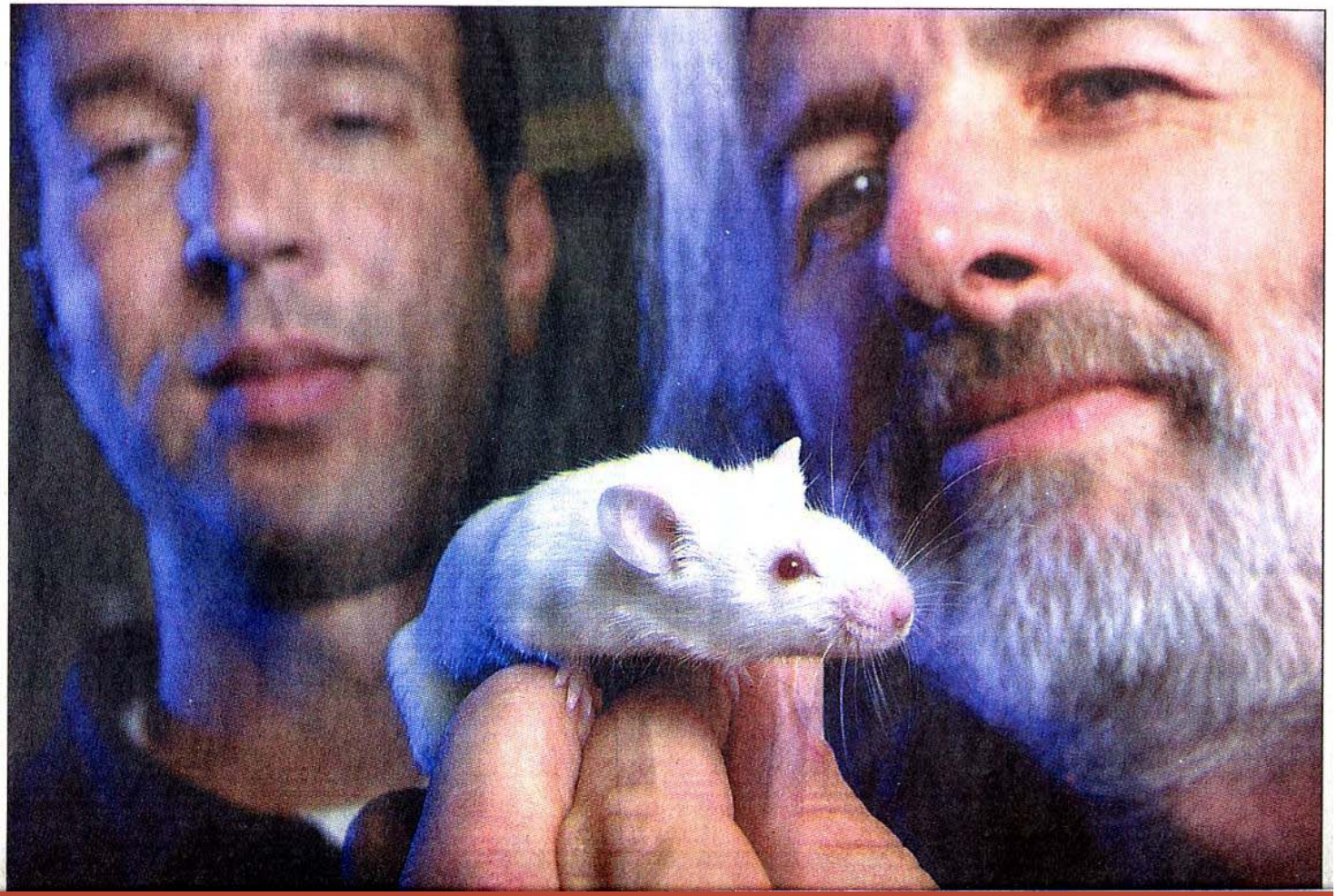


- Those living in contaminated fallout sites demonstrated increased mutation levels at tandem repeat loci in children born after the accident vs. those born before.
- Children of exposed clean-up crew showed variable responses.

Bad air a 'genetic risk'

Mac shows mutated genes hereditary

By ERIC McGUINNESS
Environment Reporter
The Hamilton Spectator



McMaster University research is the first in the world to show that urban air pollution causes gene damage which animals pass from one generation to the next.

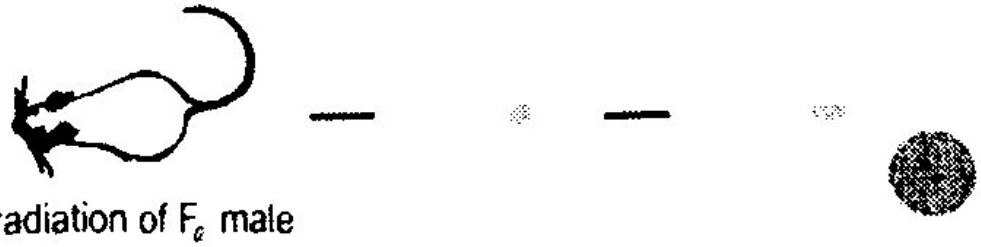
Biologists Jim Quinn and Chris Somers have demonstrated that male laboratory mice exposed to Hamilton steel-mill emissions transfer mutated genes to their young. And they warn the same thing could be happening in humans.

While gene mutations may increase risk of cancer and birth defects, the McMaster scientists say they can't make a direct comparison to human health.

At the same time, they say

F_o Generation

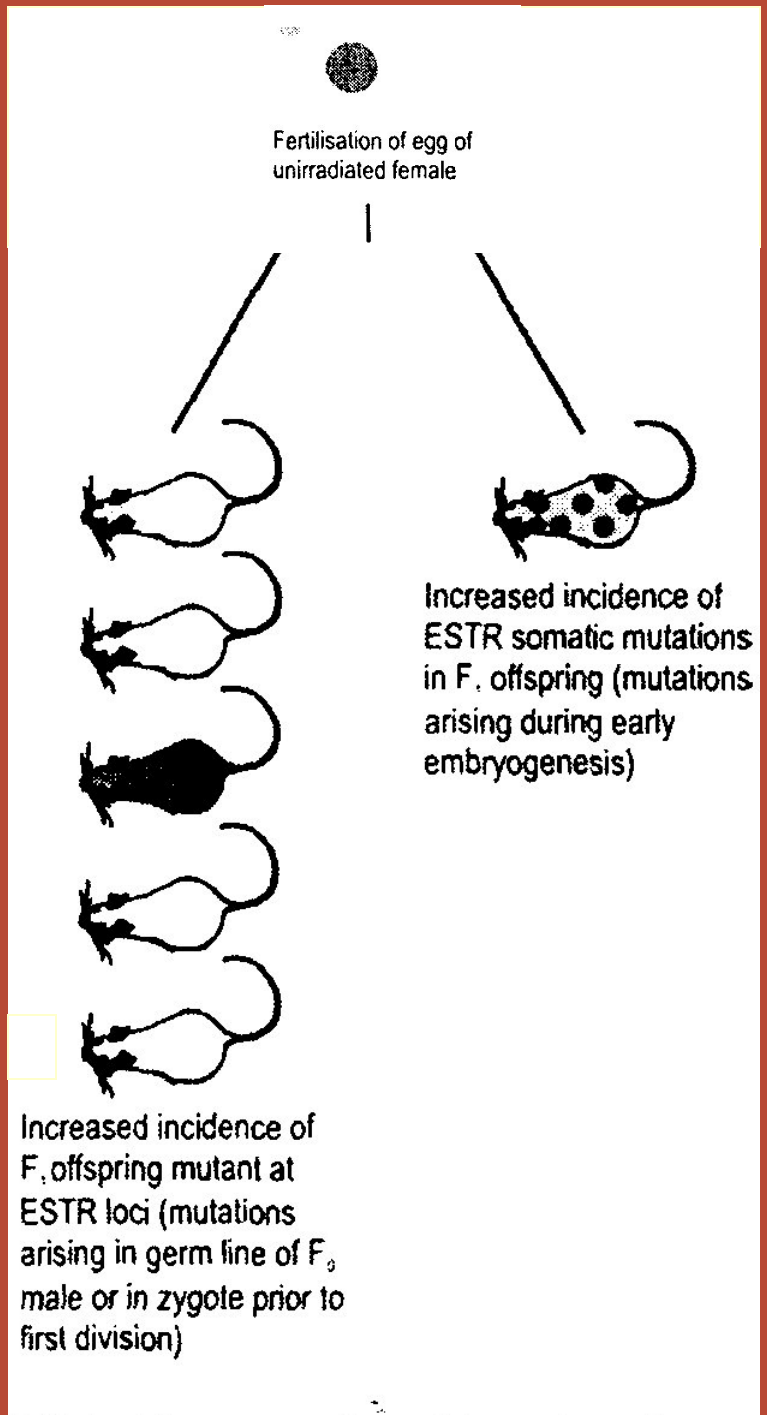
B.A. Bridges / DNA Repair 2 (2003) 1269–1272



Irradiation of F_o male

Fertilisation of egg of unirradiated female

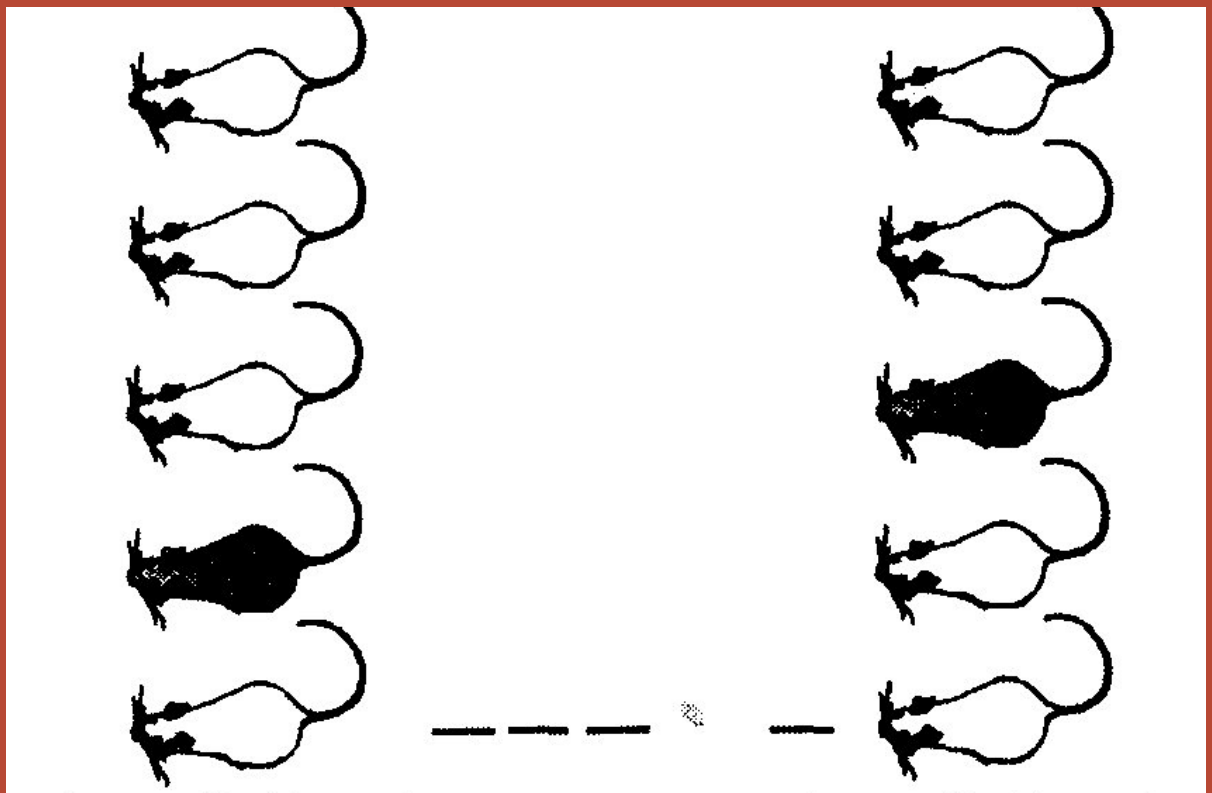
ESTR loci are Expanded Simple Tandem Repeats. The number of repeats is unstable in many such loci.



F_1 Generation

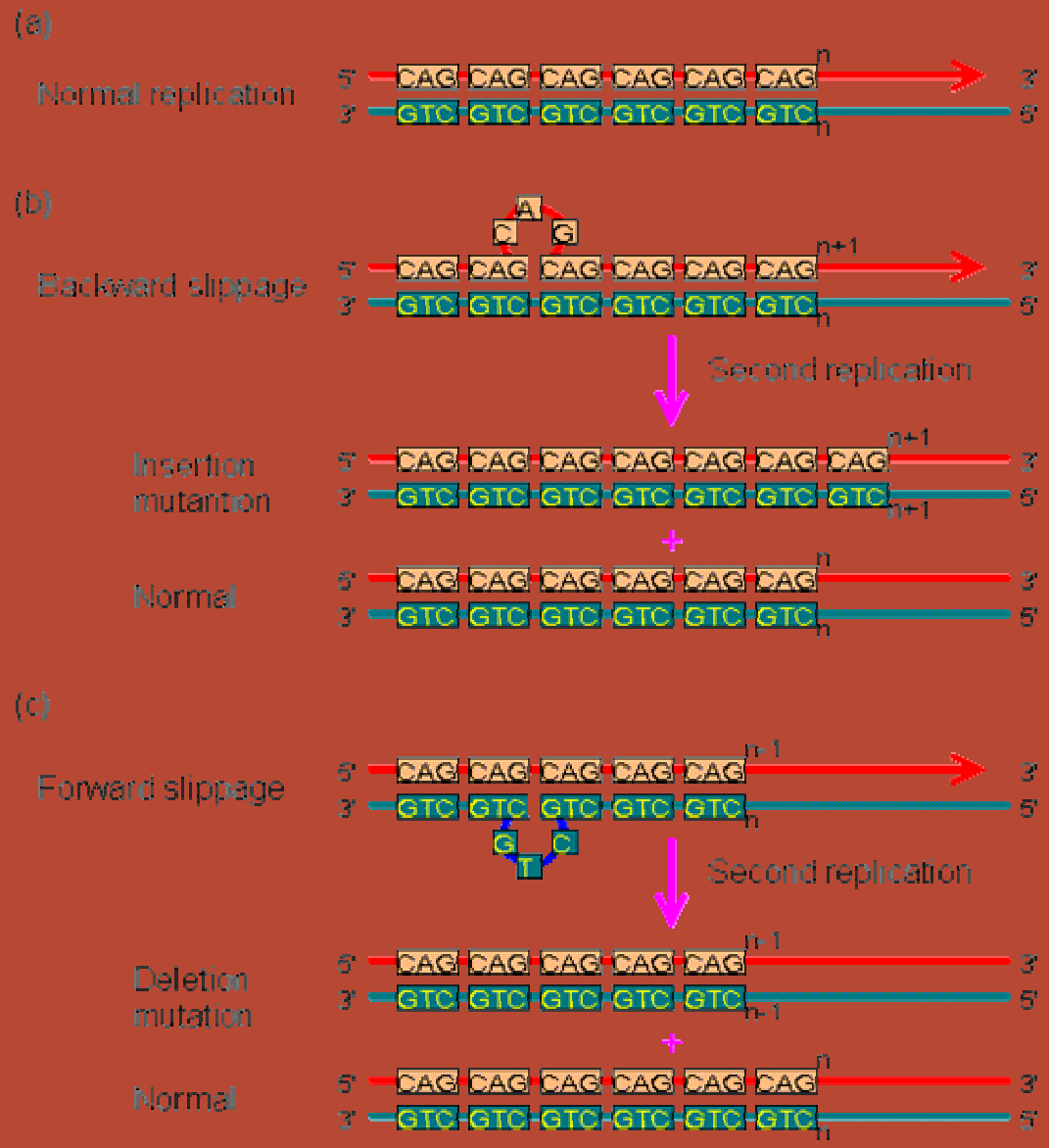
100 times the number of mutations then expected based on frequency of DNA lesions.

F_2 Generation

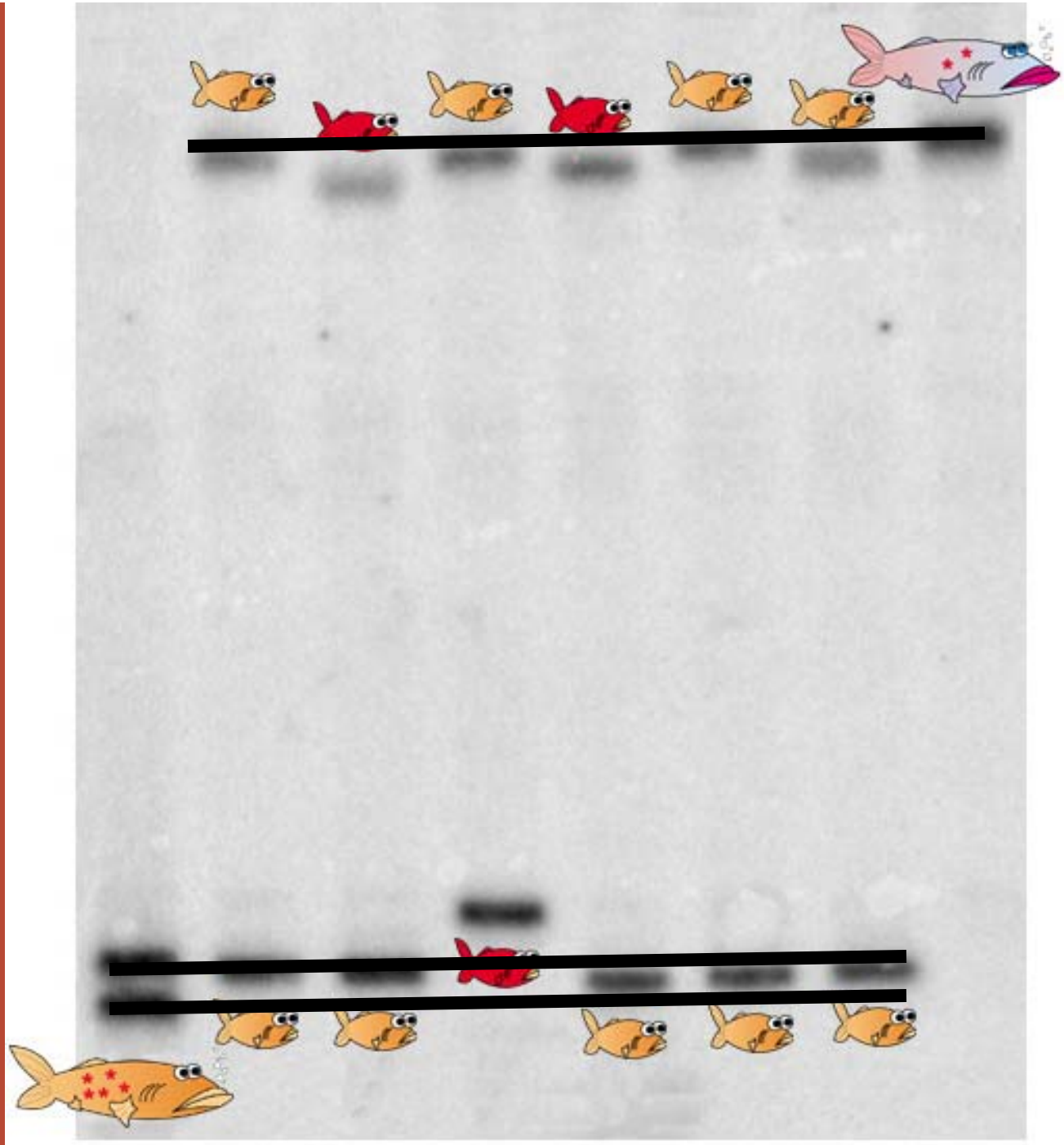


Increased incidence of F_2 offspring mutant at ESTR loci (mutations arising in germ line of F_1 *male or in zygote prior to* first division)

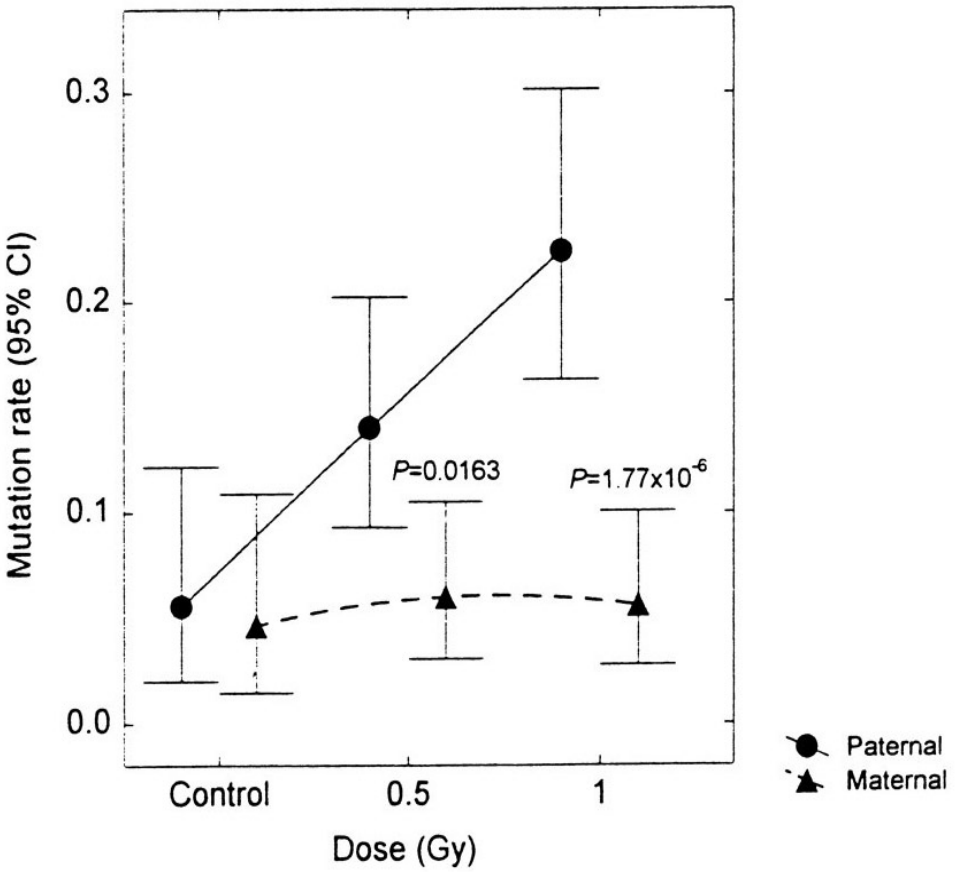
Increased incidence of F_1 offspring mutant at ESTR loci (mutations arising in germ line of F_0 *male or in zygote prior to* first division)


(a)
Normal replication
5'
3'
CAG CAG CAG CAG CAG CAG
GTC GTC GTC GTC GTC GTC
n
n
(b)
Backward slippage
A
C
G
n+1
Second replication
Insertion mutantion
n+1
n+1
Normal
(c)
Forward slippage
n-1
G
T
C
Second replication
Deletion mutation
n-1
n-1
Normal

Detecting Genetic Mutations:

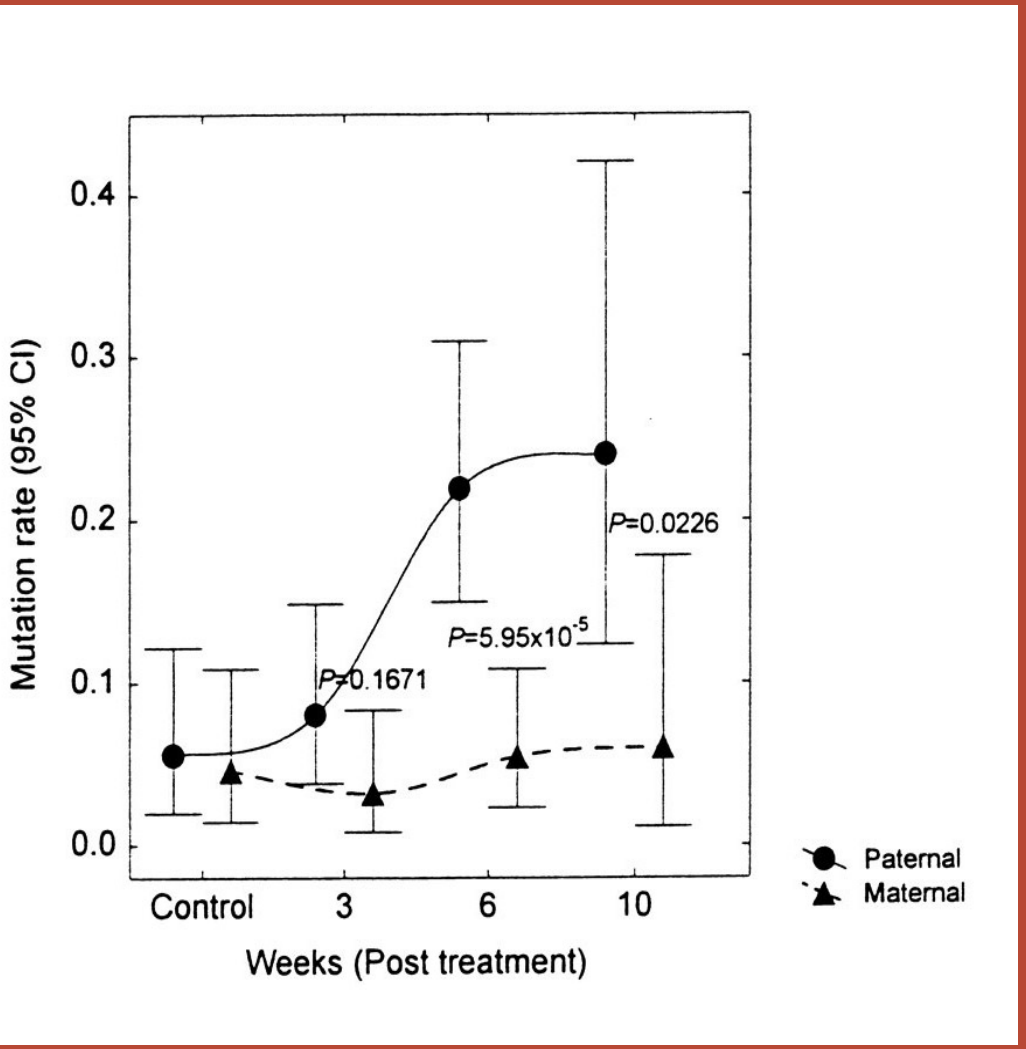


Dose Dependency



Dubrova *et al*., 1998

Stage Specificity



Dubrova *et al*., 1998

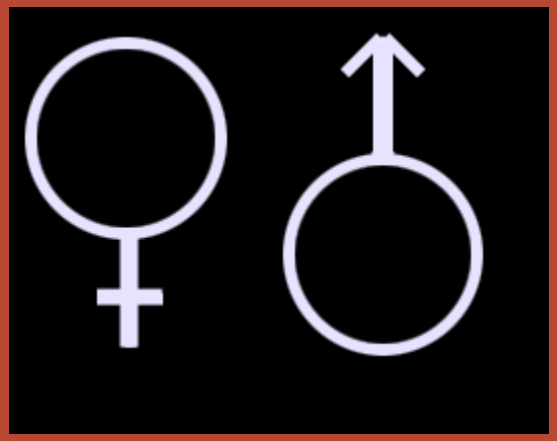
Experiment

0.0 Gy
0.5 Gy
1.0 Gy

+ 24 h

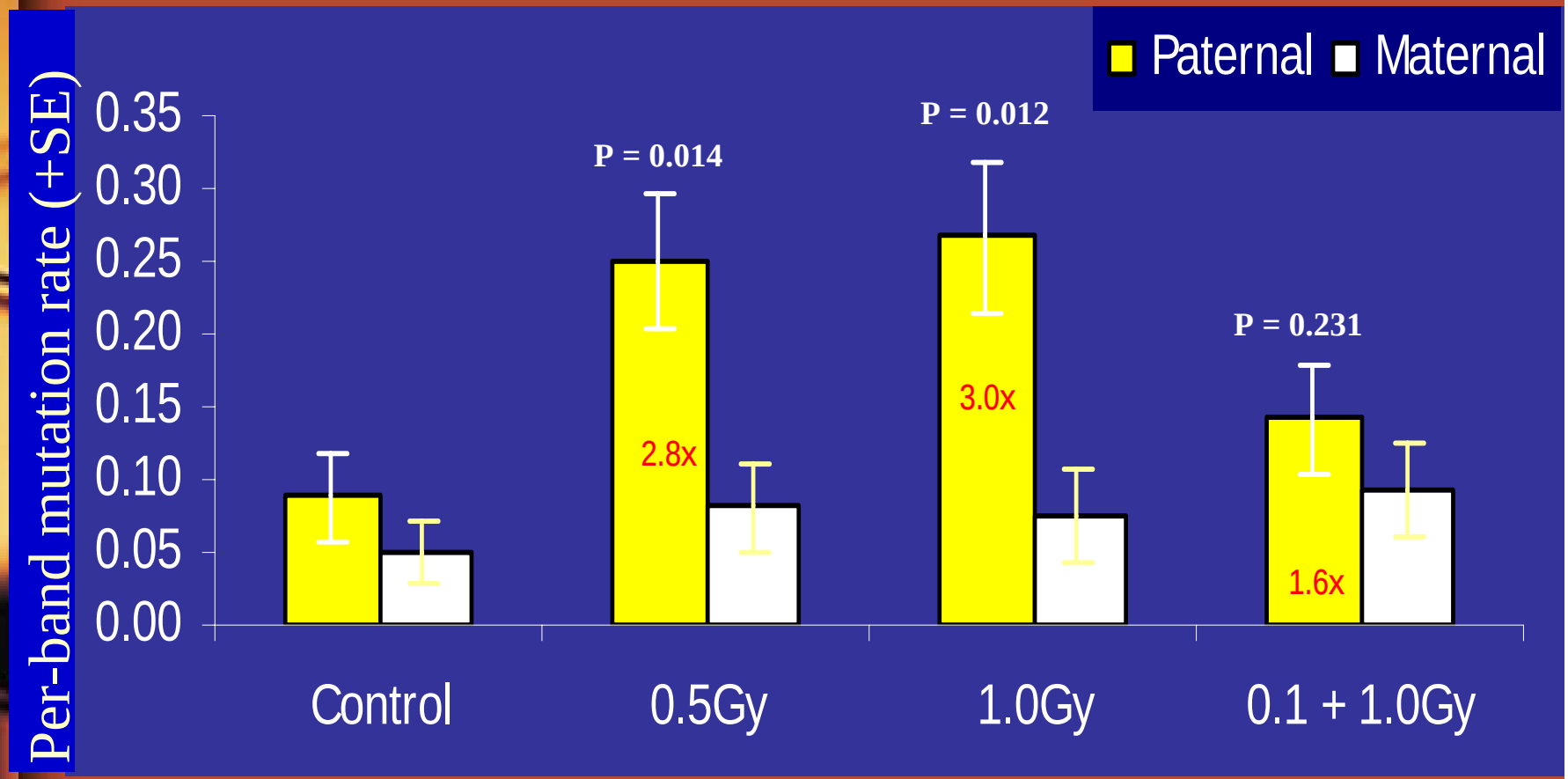
100 mGy

10 weeks

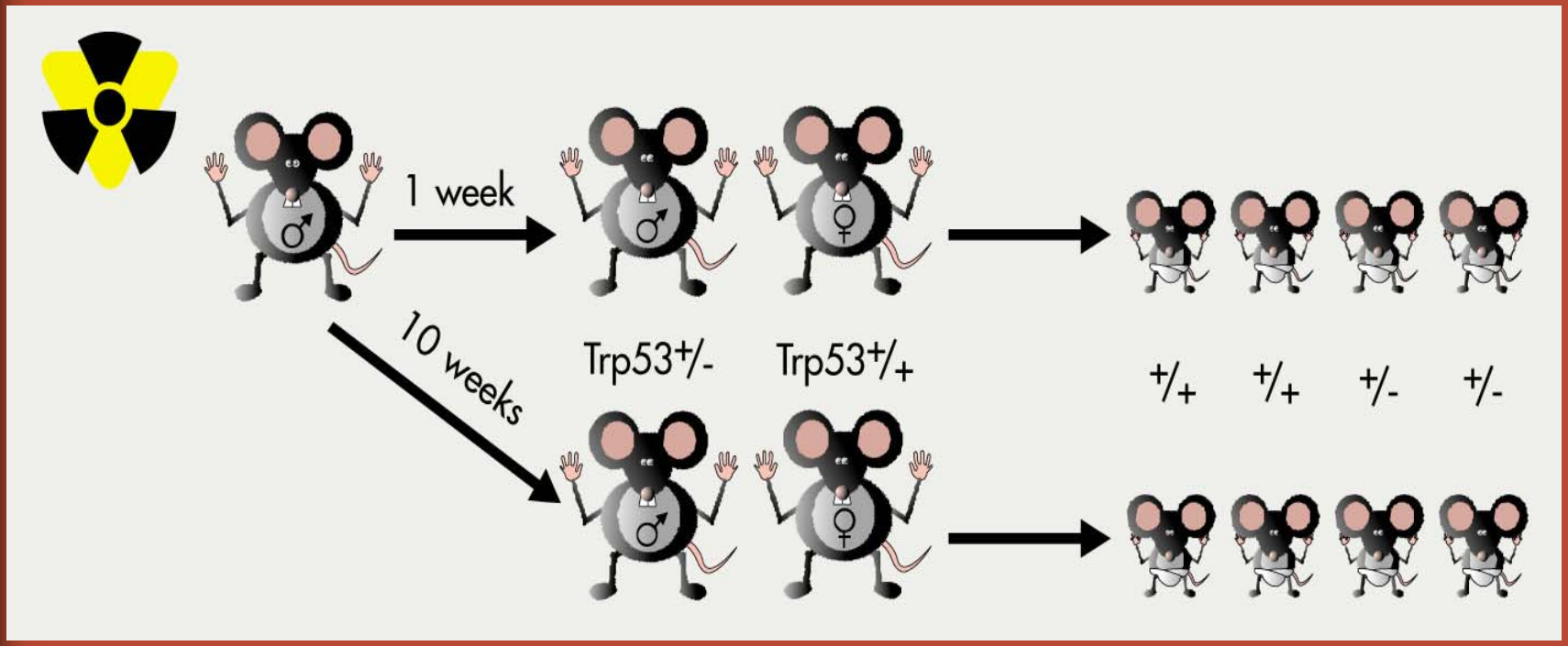


Breed to un-irradiated female

Adaptive Response to Radiation-Induced Genetic Mutations



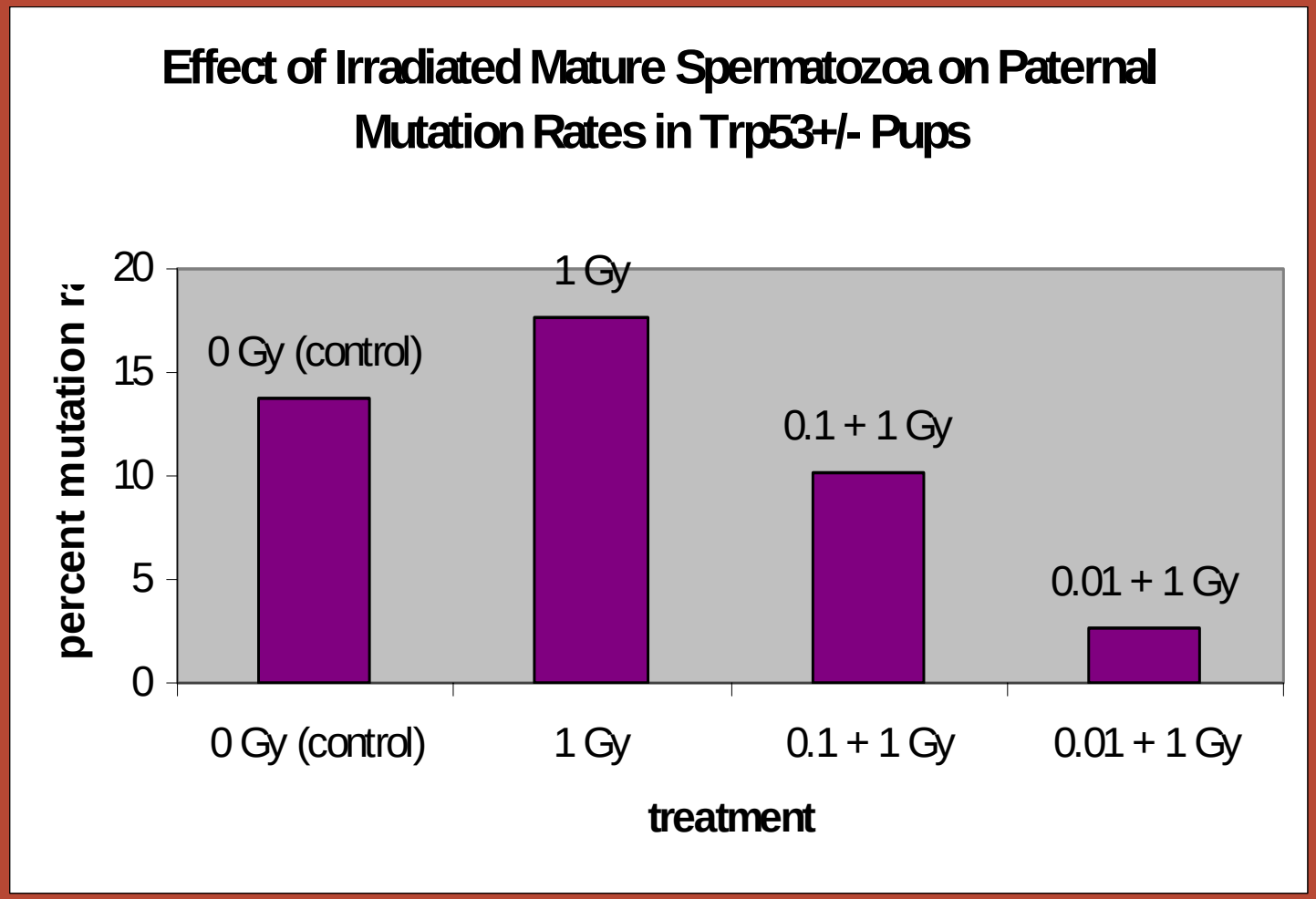
Is p53 involved in adaptive response to radiation-induced heritable mutations?



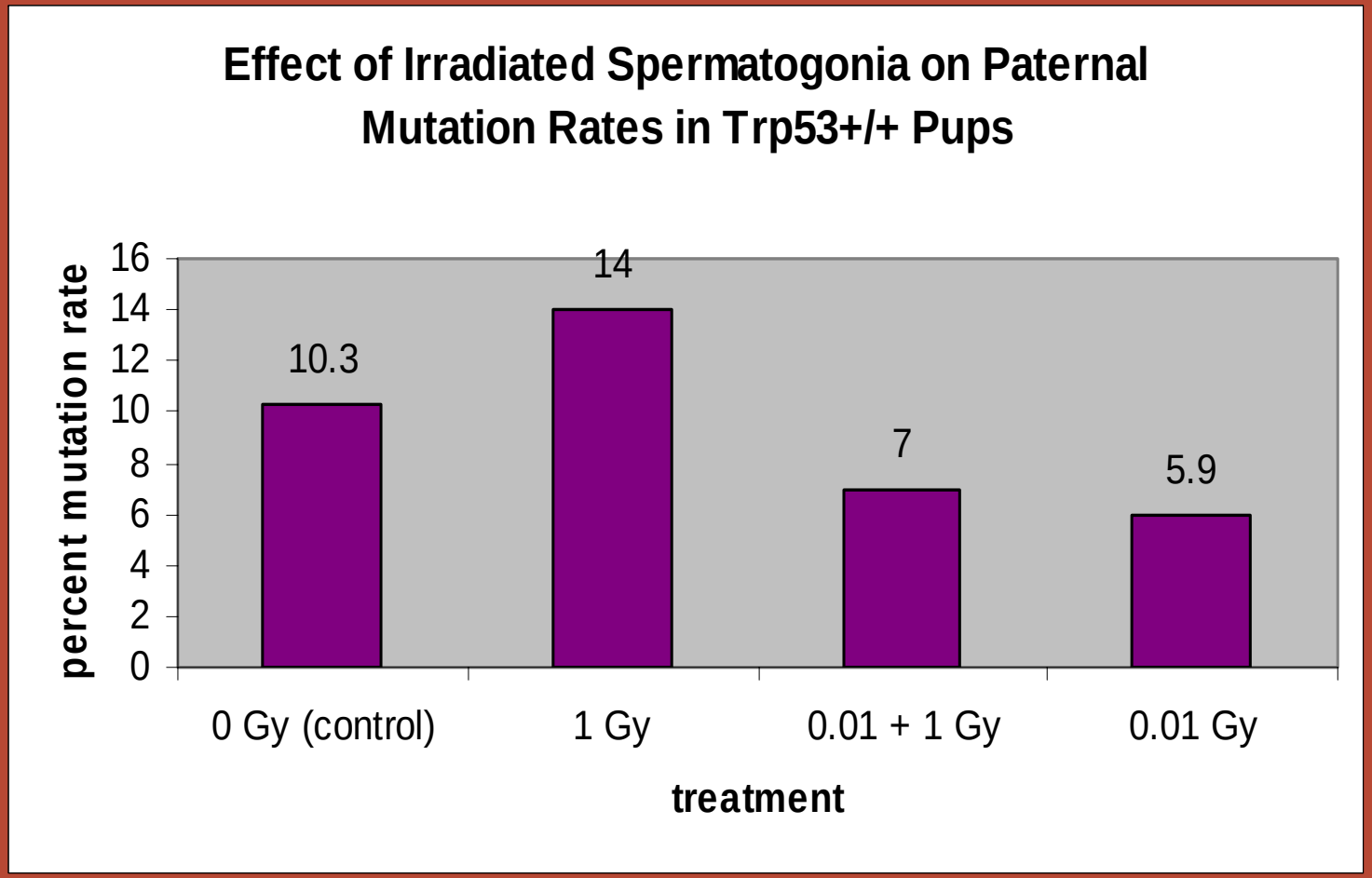
Treatment Groups

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Priming Dose	0 Gy	10 mGy	100 mGy	0 Gy	0 Gy	0 Gy
Challenge Dose	1 Gy	1 Gy	1 Gy	10 mGy	100 mGy	0 Gy

Genotype and Risk
Sperm (1 week post IR)



Genotype and Risk Sperm from Irradiated Germ Cells



Conclusions

Changes in minisatelite DNA caused by high dose exposure to germline cells can be modified by prior low dose expsoures.

Genotype of parent can influence the modifying effects of low dose exposures prior to a high dose.

The relationship between minisatelite mutations and risk is unknown.

Acknowledgments

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