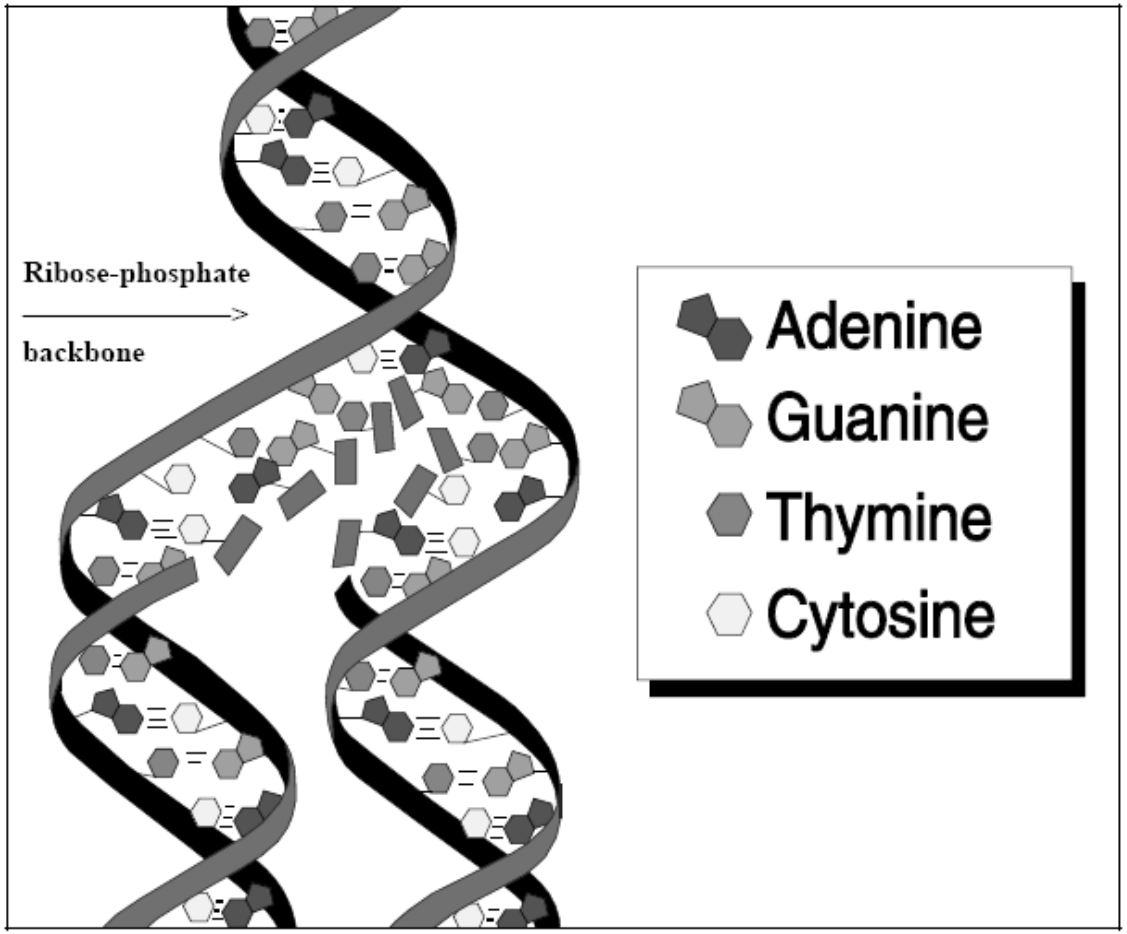
Module 5
Gene Mutations

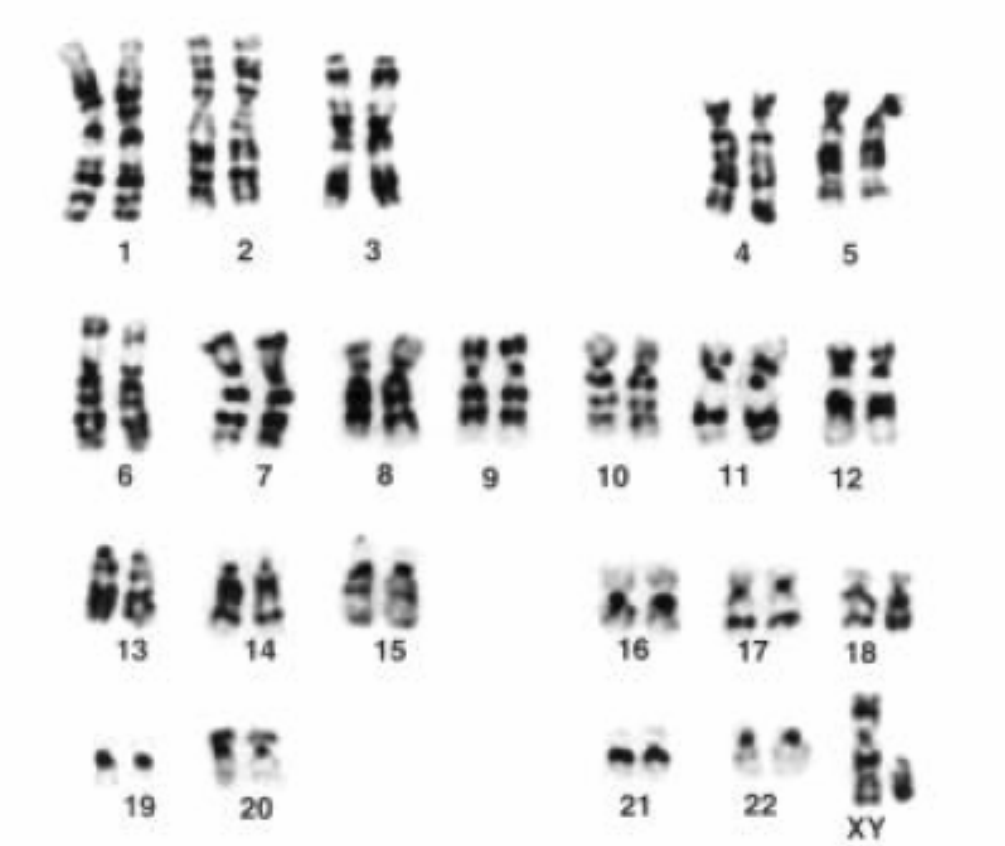
- Gene – a finite segment of DNA specified by an exact sequence of bases.

- Humans have ~$0.5X10^5$ genes per haploid set of chromosomes.

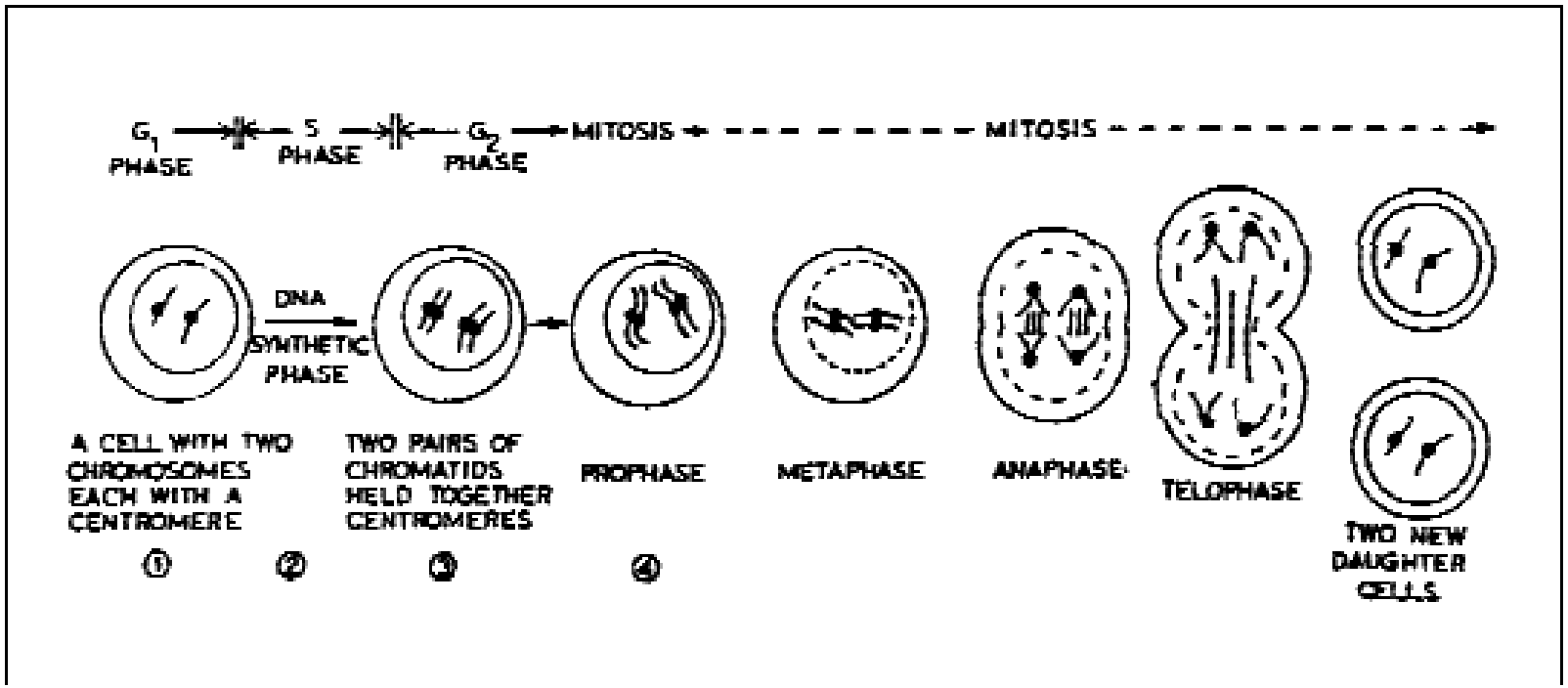
DNA Structure



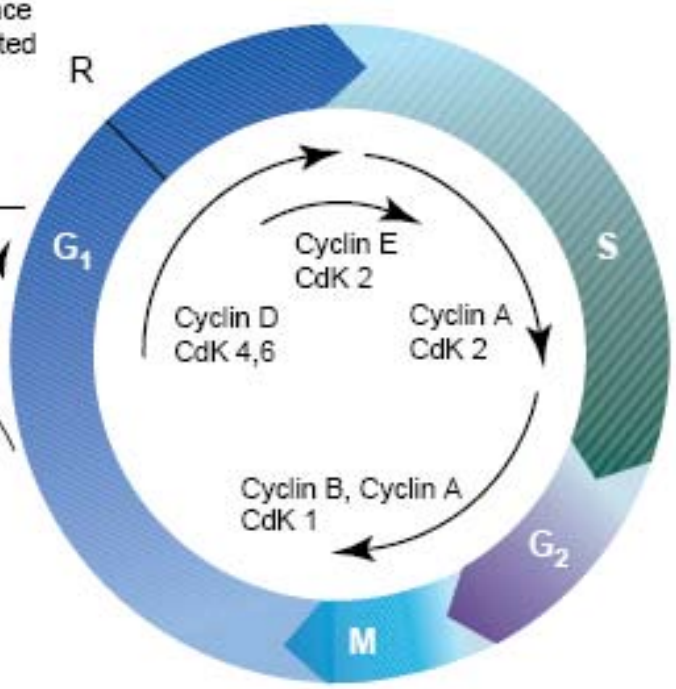
Human Chromosomes



Cel’l Cycle


G1 PHASE
S PHASE
G2 PHASE
MITOSIS
MITOSIS
DNA SYNTHETIC PHASE
A CELL WITH TWO CHROMOSOMES EACH WITH A CENTROMERE
TWO PAIRS OF CHROMATIDS HELD TOGETHER CENTROMERES
PROPHASE
METAPHASE
ANAPHASE
TELOPHASE
TWO NEW DAUGHTER CELLS
①
②
③
④

R is the commitment point. Once past this point, a cell is committed to completing a cell cycle



S phase. The cell synthesizes, or replicates, all its DNA and thereby produces two identical copies of each chromosome.

G_0 State. The cell is in a resting state and does not progress through the cell cycle. Terminally differentiated cells may become permanently arrested at this step.

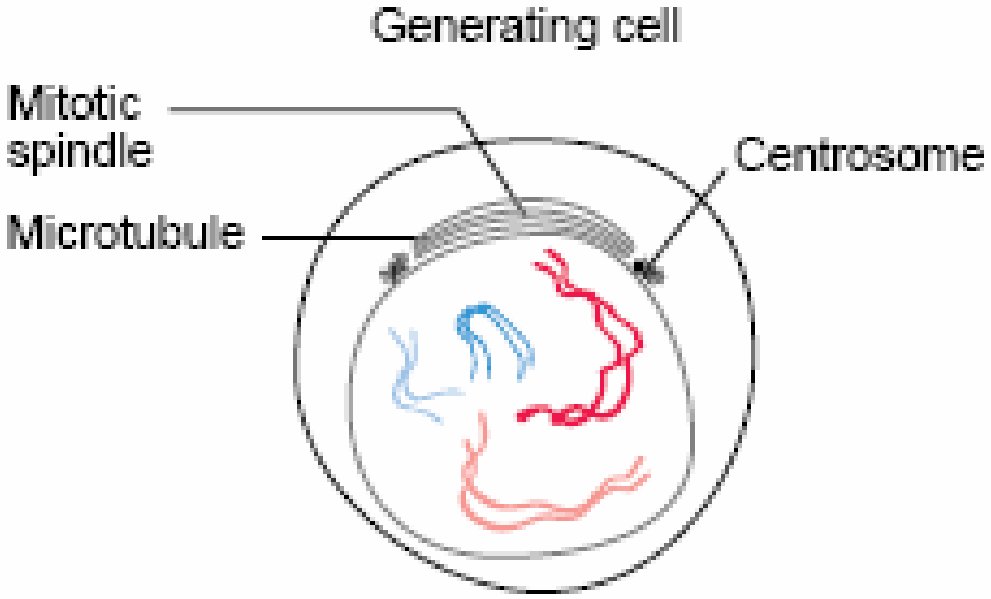
G_2 Phase. The cell continues to grow, checks that DNA synthesis is complete, and prepares itself for cell division, or M phase.

M Phase. The cell's chromosomes condense and the duplicated chromosomes are separated. At the end of mitosis, the cell divides into two daughter cells.

Prophase

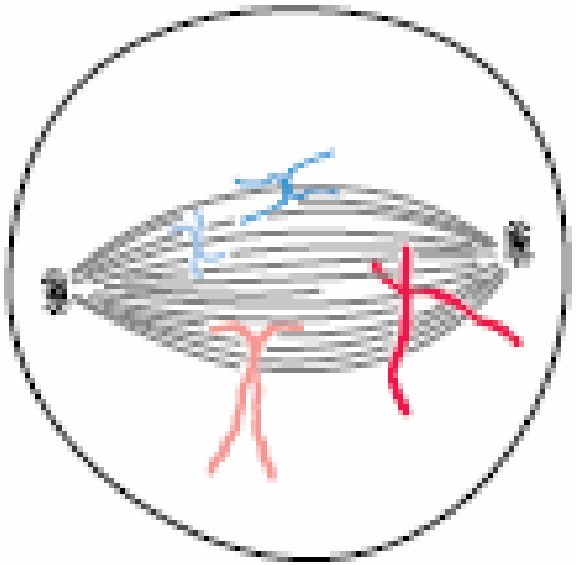
M phase

Prophase. The chromosomes condense into microscopically visible threads. Microtubules radiating from the two centrosomes collectively compose the mitotic spindle.



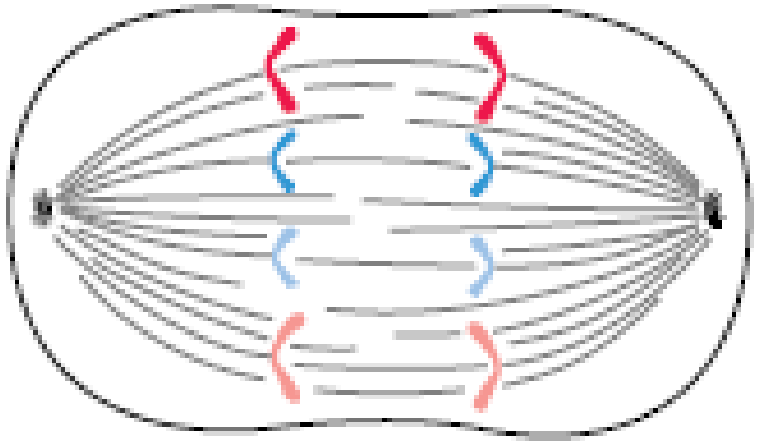
Prometaphase

Prometaphase. The centrosomes migrate to opposite sides of the cell. The nuclear membrane disintegrates so that the microtubules can bind to each chromosome at the centromere.



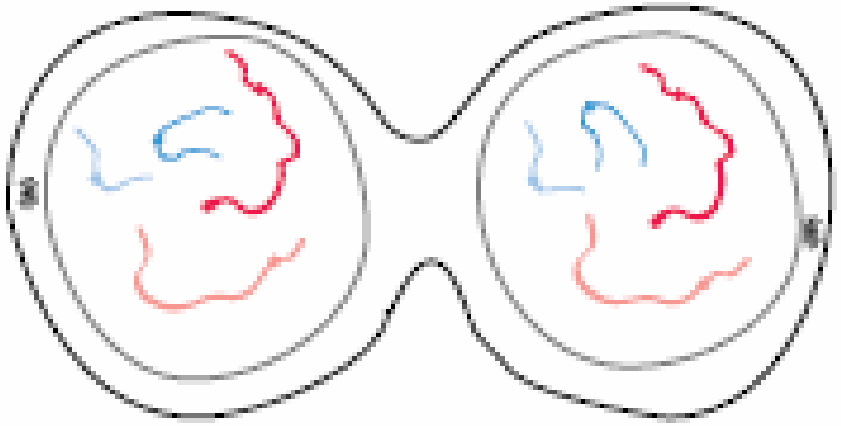
Anaphase

Anaphase. The bond joining the chromosome breaks, and each moves towards opposite sides of the cell. The cell begins to elongate and narrow at the midplane.



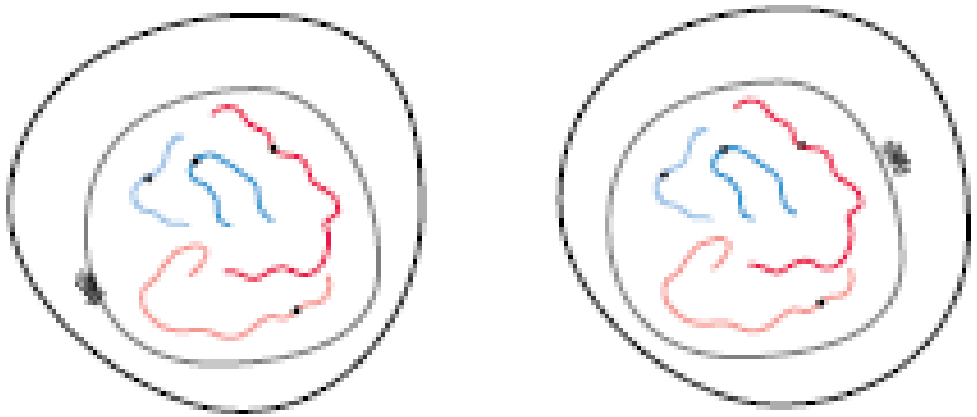
Telophase

Telophase. A new nuclear membrane forms around each segregated set of chromosomes, the chromosomes begin to de-condense, and the cell begins to divide.



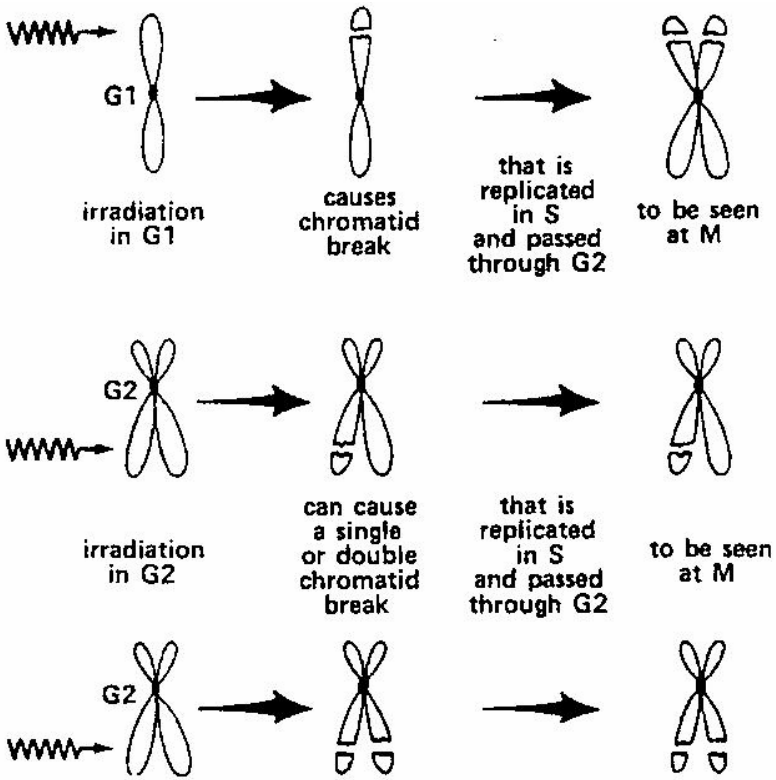
G1 Phase

G_1 phase. The cell has cleaved into two cells. The chromosomes decondense to their normal extended state for the resumption of normal cell activities.

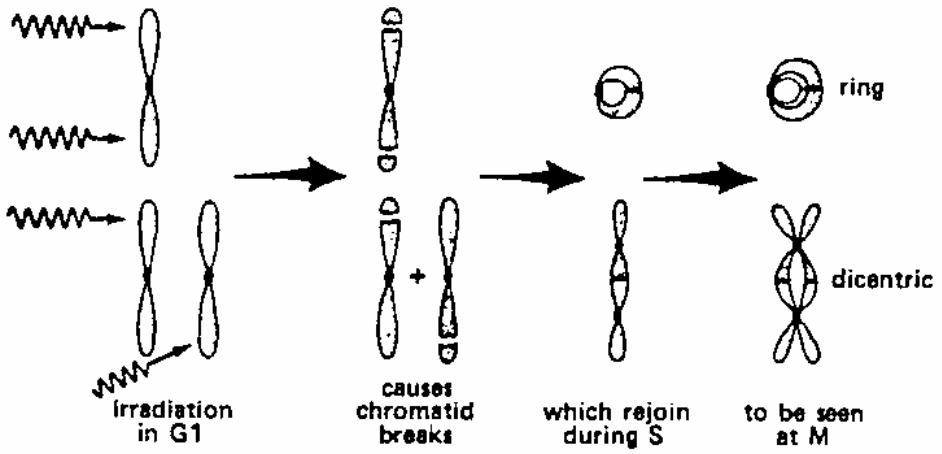


Progeny

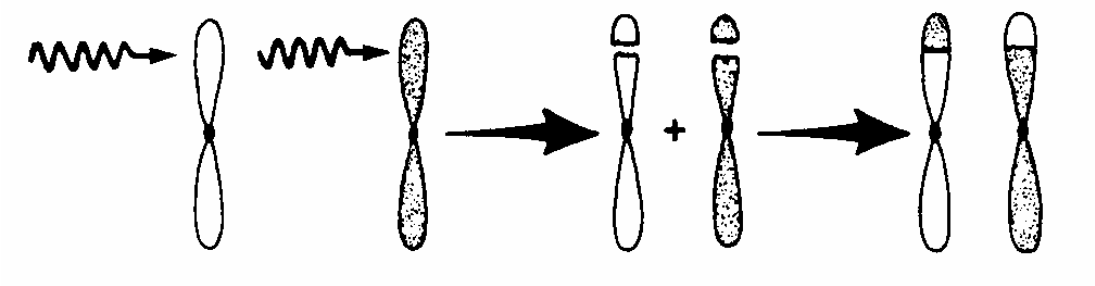
Chromosome Damage



Extreme Chromosome Damage



Translocation



Dominant Mutations

- Dominant Mutations appear in the immediate offspring if it is found in at least one parent.

- Examples of dominant gene diseases include polydactyly, achondroplasia, huntington’s Chorea, and retinoblastoma

Recessive Mutation

- Recessive Mutation only appear in both parents contribute the same gene.
- It may take generations for a recessive mutation to be expressed.
- Over 500 recessive diseases have been identified.
- These include sickle cell anemia, cystic fibrosis and Tay-Sacs disease.

Sex Linked Diseases

- The Y chromosome is missing a large amount of DNA.
- This allows expression of recessive genes on the X chromosome.
- There are more than 80 know sex linked diseases.
- These include hemophilia, color-blindness and Duchene muscular dystropy.

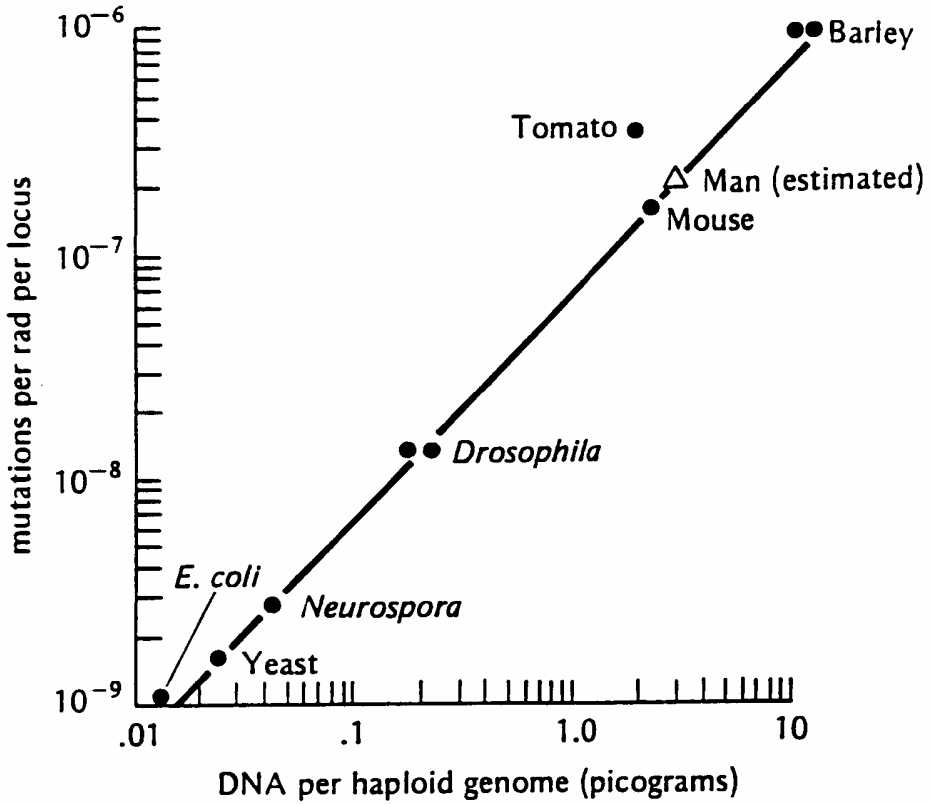
L.B. and W.L. Russell, “Megamouse Project”

- Over 1 million white rats were given total doses of 1000 rad (10 Gy).
- Mutations were found to be more common in mice receiving a higher dose rate.
- This implies a repair mechanism for the radiation damage.

L.B. and W.L. Russell, “Megamouse Project” cont.

- The radiosensitivity of different mutations varies by a factor of 35 – it is only possible to speak of an average mutation rates.
- At low dose rate the genetic burden is carried by the male.
- Genetic consequences of a dose can be reduce by increasing the time from exposure to conception.

Mutation Sites versus DNA Mass



Doubling Dose

- Doubling dose is defined as the amount of radiation needed to produce twice the rate of genetic mutations than that would have been observed without radiation.
- The doubling dose for humans ranges from 50 to 250 rads (0.5 -2.5 Gy).
- Drosophila fruit flies have a doubling dose 15 times greater than this

Guiding Principles for Doubling Dose

- Most mutations are harmful.
- Any dose of radiation, however small, entails some genetic risk.
- The number of mutations produced is proportional to dose.
- Risk estimates based on experiments with the mouse are very similar for human values.

Genetically Significant Dose

- Genetically significant dose is an index of a presumed genetic impact of radiation on the whole population.
- Assume the dose is given uniformly to an entire population.
- This is a calculated gonadal dose for the population weighted by the expected number of future children for a person of that age and sex.

Mammalian Cell Culture Studies

- Mammalian cell cultures were stressed by absence of needed amino acids or by addition of drugs.
- Looked for growth of mutated cells.
- Rate for a specific locus ranged from $1.5\text{-}3.0 \times 10^{-7}$ mutations/rad.

Natural Mutations

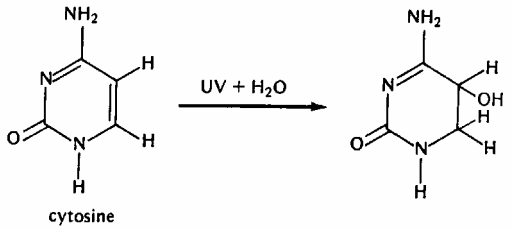
- Observed mutation rates for Humans are 0.5 to 10 per 100,000 for Huntingtons' Chorea to neurofibromatosis.
- Similar rates have been found in diverse organism from bacteria to hamsters.

Repair Mechanisms

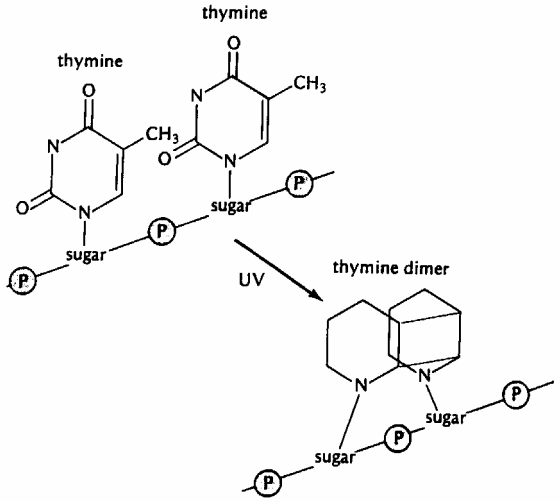
- Excision-Repair mechanism of DNA repair. This repairs a segment of DNA based on the complementary half.

- Repair on point defects is well established.

Damage to Nucleic Acids



(a) hydrolysis of cytosine



(b) formation of thymine dimer

Examples for human repair

- Xeroderma pigmantosum – inability to repair damage from UV radiation causing skin maladies
- Cockayne Syndome – UV damage interferes with cell division. The result is dwarfism and premature aging.
- Ataxia telangrectasia is a disorder of the DNA repair mechanism. People with this disorder have increased risk for cancer.

Risk of Genetic Mutations

- The ICRP estimates the probability per capita for radiation-induced hereditary disorders to be 0.6×10^{-2} per Sv.
- The congenital abnormalities are much more important than this.