MUTAGENS-OUTLINE

Basis for spontaneous mutations:

- each base can form tautomers that pair with the wrong partner leading to transitions
- oxidative deamination of C→U but usually repaired, but 5mC is converted to T, leading to CG to TA transitions
- depurination or depyrimidation (base broken from backbone) leads to AP sites where any base can be added opposite the blank during replication
- runs of one base, especially A can lead to insertion or deletion of bases by "slippage and restarting", during replication, especially of the lagging strand

Ionizing radiation (X-rays and α, β, γ- radiation)

- X-rays first proven mutagenic in Drosophila by Muller in the 1930s using the ClB technique
  - 3% increase in recessive X-linked lethals per 1 KR
  - dose administered quickly (acute) or slowly (chronic) same effect in flies, not in mice
- high doses also cause broken chromosomes and rearrangements

UV-light

- Light at 254 nM is absorbed especially well by Thymine
  - TT dimers formed in the same strand lack normal pairing
  - TT dimers across double strands can lead to breaks
  - Most dimers are repaired (see next lecture)

Chemicals

- Direct Acting (react with and alter bases in DNA)
  
  HA → HAC. pairs with A so GC to AT only
  - NA causes oxidative deamination of C, A and G, leading to transitions in either direction
  - Alkylating agents add methyl or ethyl to bases, especially G and lead to transitions and transversions

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- examples include Mustard Gas, EMS, & NG

• *Base Analogs*
  - incorporated into DNA "by mistake" during replication, but tautomerize more often than normal bases
  - examples include 5BU and 2AP

• *Acridine dyes*
  - planar molecules intercalate into DNA double helix between base pairs
  - attempts to repair can cause insertion or deletion of true base pair
  - examples include ethidium bromide, ICR 171 and proflavin

**Trinucleotide repeats:**

• likely represent "slippage" events during DNA replication
• A number of hypervariable human genes have been shown to include multiple repeats of the same 3 base sequence
  - in Fragile X syndrome, a CGG repeat in the leader of the mRNA encoded normally has about 30 copies
  - "premutations" expand the number between 50 and 200 or so
  - if over 230 copies, fragile X and mental retardation expected
  - daughters of a premuational or affected male may be OK but most of their children will be affected
  - expansion occurs in embryonic cells, leading to mosaics, and helps to explain variability on expression
  - in Huntington's disease, a CAG repeat in the coding region can expand
  - -6 to 37 copies are "normal"
  - - as number of copies increase, earlier onset of symptoms occurs
  - expansion seems to occur more in males than females

**Transposons**

In many species, transposable elements account for most of the mutations found. They will be covered later in the course