MUTATION AND MUTAGENS

DEFINITIONS

*mutation*; a sudden, *heritable* change in the DNA

There are many terms that are used to describe mutations:

*At the level of the organism or phenotype expressed:*

**recessive** mutation produces recessive allele: A → a

**dominant** mutation produces dominant allele: b → B

In general, we expect more recessive mutations since many changes in a protein-encoding gene can cause a "loss of function" while only a few changes, perhaps in the promoter, lead to "gain of function" or over-expression.

**somatic** mutation: a mutation in a somatic cell; somatic mutations produce "mosaic" or "chimeric' organisms since they have sectors of cells with different genotypes. In some plants and fungi tissue from the "mutant" sector may be grown into a whole reproducing organism; some of our better apple varieties arose from mutant sectors on a tree. Somatic mutations in animals can lead to cancer when genes that regulate cell division are mutated.

**germline** mutations: mutations in the cells that produce gametes; these are inherited in successive generations, so are or primary concern to genetics.

a **forward** mutation is a mutation from a common allele to a new allele

a **reverse** mutation is a return from a mutant allele to the original allele
There are also cases where a second mutation appears to correct the initial mutation, without correcting the original change in the DNA. These changes are called **suppressor** mutations. Suppressors can be due to:

- *intragenic*- a 2nd amino acid change restores folding/activity of a coded protein, or a compensating frameshift restores the correct amino acid sequence
- *intergenic*- change at second gene locus masks error
  
  ex. *nonsense suppressor*; tRNA anticodon change permits recognition of stop codon (in competition with Release Factors)

**At the DNA level:**

- **point**; a single base change; can be reverted

  - *transition*: (AT ↔ GC changes; purine for purine)
  - *transversion*: (purine for pyrimidine);
  
  (AT ↔ TA or AT ↔ CG or GC ↔ CG)

- **chromosomal** changes result from broken chromosomes
  
  (discussed in later lectures)
MUTAGENS

**X-rays and ionizing radiation** *(radioactive disintegration)*

In 1927 H. J. Muller, then working at the University of Texas, showed that X-rays can cause mutations. X-rays thus became the first mutagenic agent to be identified.

Muller used fruit flies (*Drosophila melanogaster*), to prove that increasing the "dose" or exposure to X-rays led to increasing numbers of mutations. To avoid the problem of arbitrary decisions that might come from a phenotype such as eye or body color, Muller looked for recessive lethal mutations that occurred on the X chromosome. In *Drosophila*, just like humans, females have 2 X chromosomes but males only have one. Thus, after a special series of crosses starting "marked females" mated with irradiated males, Muller could identify new mutations from females that had daughters but no sons. The females crossed to irradiated males all had "wide bar" eyes, a phenotype that showed they were heterozygous for a gene called Bar eyes. The same X also carried one recessive lethal and another dominant gene called C that prevented exchanges (crossovers) between the 2 X chromosomes during meiosis. Wide Bar daughters from this cross thus had to have the "C, l, B" genes on one X chromosome, the one from their mother, and an irradiated X from their father. If these females had no sons when mated to normal males, then the irradiated X also had a new recessive lethal mutation. A schematic of his results is shown on the next page; at low doses, every increase of 1 kr increased the % of females with no sons 3%. This linear dose response proved that
X-rays indeed cause mutations. The curve levels off in part because no more than one lethal mutation can be detected from each irradiated male.

Roentgens refer to a specific number of ionizations per unit volume. Thus the same dose, say 1,000 roentgens (1Kr) can be administered in a very short period of time (acute dosage) or over an expended period of time (chronic dosage).

Decay of radioactive compounds also produces ionizing radiation, so can also cause similar changes in DNA. Especially important are high energy (gamma) emissions. In Drosophila, it doesn't matter if the males are irradiated with acute or chronic dosages; 1 Kr still results in 3% lethal mutants in the next generation. When mice were tested, it was found that chronic treatments at low levels were much less mutagenic than the same dose given rapidly. This is because mice have a mechanism for repairing the damage caused by x-ray "energy particles", but Drosophila do not. If the damage is not repaired before the next mitosis, the errors tend to become permanent. Most humans can also repair radiation damage, but persons with Ataxia Telangiectasia cannot repair the damage suffer from very high rates of cancer.
Since repair is never 100% perfect, there is a natural concern over exposure to radioactivity and x-rays. There is a background level of "cosmic radiation, televisions emit small amounts of radioactivity and we often get medical and dental X-rays. One of the fears over using atomic radiation to produce electricity is that accidents will allow escape of radioactive gasses and that radioactive waste may end up in the environment to add significantly to our exposure. People who work with radioactivity often wear badges to measure exposure. Exposure in humans is measured in "rads" or "rems". A rad is the dose that will give absorption of 100 ergs/g of tissue, and a rem is the equivalent of 1 roentgen in biological effects (for example, the dose that would cause 3% lethals in Drosophila). The two measures are generally considered equivalent.

Average background exposure in humans in the US averages 0.1 to 0.2 rads per year, where 5/yr is considered "safe". Most diagnostic medical procedures expose the patient to 0.1 per x-ray, but a barium enema and fluoroscopy could expose to 3 rems per minute. Cancer treatments can target specific tissues with very high doses, 10-25 rems per treatment. With respect to inducing mutations, radiation of dividing cells is much more serious than non-dividing cells. Whole body radiation of a fetus can be very damaging; If a woman receives abdominal radiation of 10 rads or more at 32 days into a pregnancy, a therapeutic abortion will be recommended, since abnormal development is certain. From data collected years ago when expectant mother's were x-rayed in the first trimester just to see how the baby was developing, it is estimated that
childhood leukemia, lymphosarcomas and cerebral tumors increased by 50%.

A continuous study of Japanese exposed to the atomic bomb blasts also shows a dramatic increase in leukemia and other cancers. Surprisingly to many, the children of those exposed have not shown a significant risk for "detectable" mutations, such as chromosomal aberrations, visible mutations, or electrophoretic variant proteins. These observations suggest that repair may be more efficient in gonads than in somatic cells.

Another surprise concerning exposure to atomic radiation came not so long ago. Around 1990, it was realized that most of our exposure comes from radon, a natural occurring gas that can come from terrestial sources including granite etc. Thus, there are some locations around the country that have higher levels of natural radiation than others. The gas often accumulates in basements and granite buildings where exposure can accumulate over time. The problem is enhanced by smoking. Kits are available to determine the levels of radon in houses, wells etc.

**UV light**

Ultraviolet light at the wavelength of 254 nm is another energy-related mutagen. Light at this wavelength is absorbed by pyrimidines, especially thymine. When the energy is absorbed, the ring structure becomes unstable and often leads to the formation of thymine-thymine dimers. If the thymines are in opposite strands, the chromosomes will brake when trying to replicate, but more often the thymine dimers form from adjacent thymines in the same strand. The T:T dimers do not have
normal base pairing properties, so when DNA tries to replicate, the wrong base may be inserted.

UV light is a much safer mutagen to use than ionizing radiation, since it will only penetrate about one cell layer. Thus it is a good mutagen to use for bacteria and fungi, but not for complex organisms. As you should know, UV is a skin cancer risk for humans. As is the case for other mutagens, there are several enzymatic systems for repairing thymine dimers. Xeroderma pigmentosum is an inherited disease that shows the effects of defective UV repair.

X' X' normal
X' X highly freckled, rusty colored hair
X X highly freckled, rusty hair, skin cancer