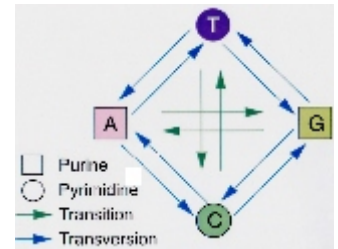


MECHANISMS OF MUTAGENESIS

rvsd 3/4/94, 3/8/95, 3/6/96, 3/11/98, 8 Mar 00, 14 Mar 01, 8 March 04, 10 March 08, 9Mar09, 8Mar10, 10Mar10, 7Mar11
 GMSLG 7th: P.496-519, 9th: 513-531

Mutations	transitions	most common, purine for a purine, pyrimidine for a pyrimidine
(p 515 for diag)	transversions	rare, purine for a pyrimidine, vice versa.
	frameshift	micro deletion or addition of one base, alters reading frame
	deletions	removes sections, stable, cannot revert.



SPONTANEOUS MUTATIONS

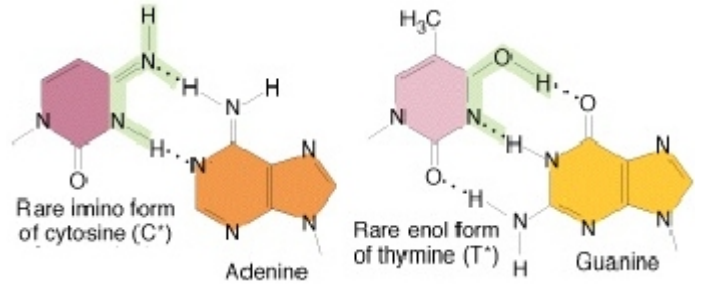
ERRORS IN REPLICATION

I. TAUTOMERIC SHIFTS, all transitions (project image on p 521)

tautomers ("same unit") of bases allow mispairing: usually **keto**, to **imino** or **enol** cause:

Tautomerization of guanine to enol form:
 (Lactam = cyclic amine with adjacent keto group)

imino	cytosine bonds with	adenine
enol	thymine bonds with	guanine
imino	adenine bonds with	cytosine
enol	guanine bonds with	thymine

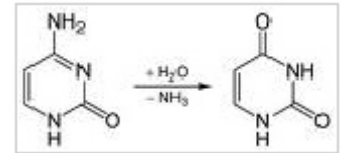


Phenotype of point mutations (can be silent: 1 & 2)

- 1) no change in AA (note wobble)
- 2) neutral (AA change has no effect)
- 3) missense or nonsense

II. SPONTANEOUS LESIONS

- 1) **depurination** (10,000 lost/20 hr cell cycle in mammalian cell) (p 522)
 Apurinic sites can cause 1/3 transitions, 2/3 transversions
- 2) **deamination**, esp of cytosine to yield uracil, causes GC to AT transition (p 523)
- 3) **Oxidation**: superoxide, H₂O₂, hydroxyl radicals can oxidize esp guanidine (makes 8-oxo-7-hydrodG), mispairs with A, causing G to T transversion. (p 500)



INDUCED MUTATIONS:

- 1) **base analogs**: (p 526-527) Analogs are less stringent in pairing, cause transitions
 - 5 BU inserted as T (Br in 5 position), ionizes to base compliments G
 - 5 FU inserted as T (F in 5 position), ionizes to base compliments G
 - 2 AP when protonated, pairs with cytosine



- 2) **Frameshift** mutation by intercalation, typically planar molecules (p 528)
 hot spots some addition of four base seq in tandem

intercalation: proflavin, acridine orange, ICR-191
Benzopyrene (p 510) (polycyclic aromatic hydrocarbons = PAHs)

- 3) **alkylating agents**: ethyl methane sulfonate, DES, Nitrosoguanidine add to bases, cause esp GC to AT.
 hydroxylamine: GC to AT transitions

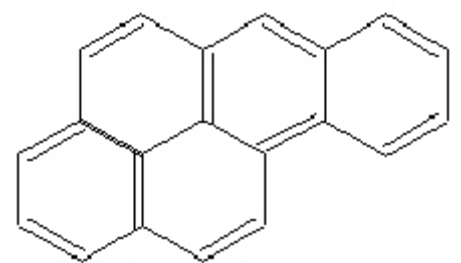
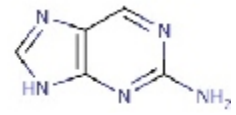
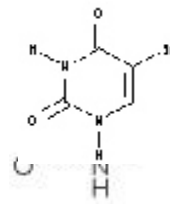
- 4) **nitrous acid**: causes transitions, converts C to U. Nitrites in foods become nitrous acid in stomach

- 5) **UV** (p. 529) shows structure of pyrimidine dimers (cyclobutane generated).

[**Aflatoxin, B1**: (p 531) bulky addition adds to guanine, caused removal of adjunct. Leads to apurinic sites]

SOS system: bypass serious DNA damage, prevents death of cell, but can cause mutations

Ames test for mutagens (p. 510): reversion of well



benzo(a) pyrene

characterized his⁻ mutant.

