→ Causes of DNA damage

(1) Endogenous : oxidation of base
Alkylation of base - 7 Methylguanosine
Hydrolysis of base - Deamination
Depurination
Depyrimidination
Adduct formation
Mismatch of base due to replication error
Monoadduct damage

(2) Exogenous → ultraviolet light.
Ionizing radiation - γ rays
Elevated temperature
Chemical - like vinyl chloride
He
Aromatic hydrocarbon

Replication Error

→ Types :-

(1) Single base alteration - Depurination
- Deamination of Cytosine to uracil
- Deamination of adenine to hypoxanthine
- Alkylation of base
- Base analog incorporation

(2) Two base alteration -
Bifunctional alkylating agent cross linkage
UV light induced thymine - thymine dimer

(3) Chain breaks -
Ionizing radiation
Radioactive disintegration of backbone element
oxidative free radical formation

(4) Cross linkage
- Between bases in same or opposite strands
- Between DNA & protein molecule (Histone)

* Cell cycle

→ DNA repair mechanism :

occur outside of S phase

(1) Mismatch repair :- Done by group of protein - mut protein

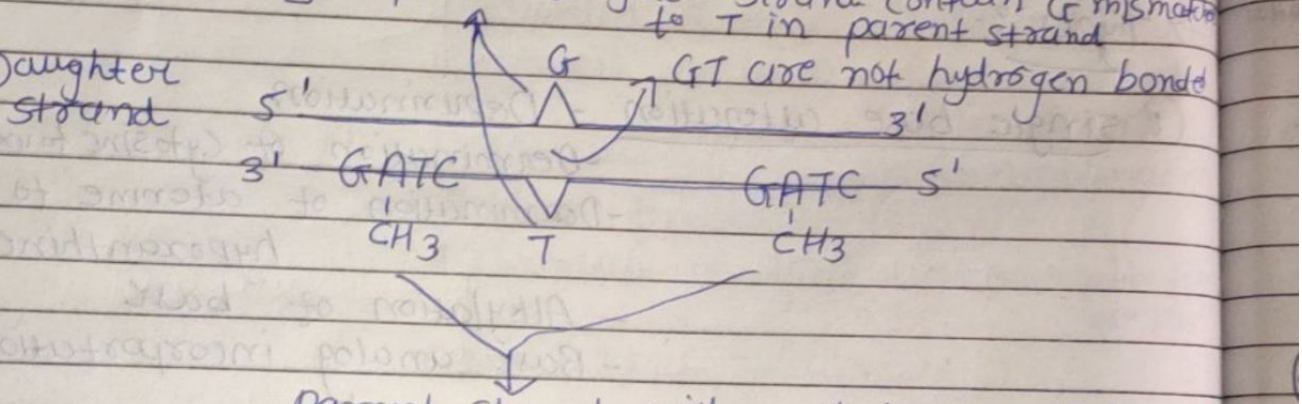
→ Mismatched strand identification :

↓

done by mut protein.

e.g. In prokaryotes E. coli

newly replicated daughter strand contain G mismatch to T in parent strand



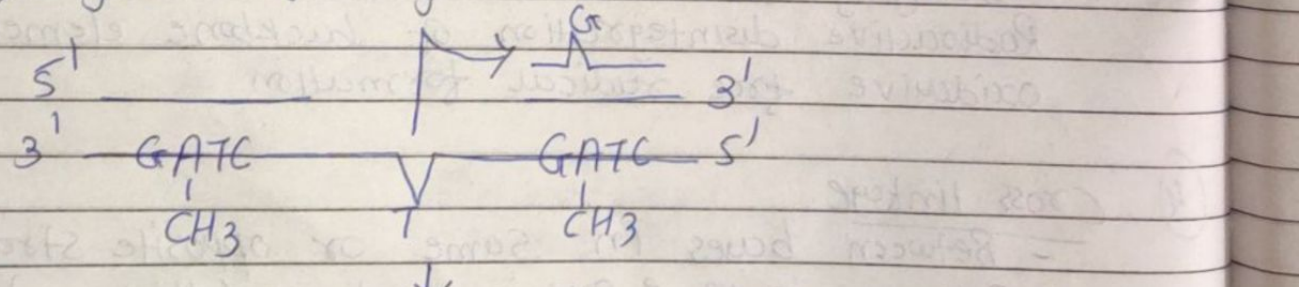
parent strand with methylated adenine

↓

(1) mut protein recognize mismatch, identify methylated (parent) strand, & cleave parent strand

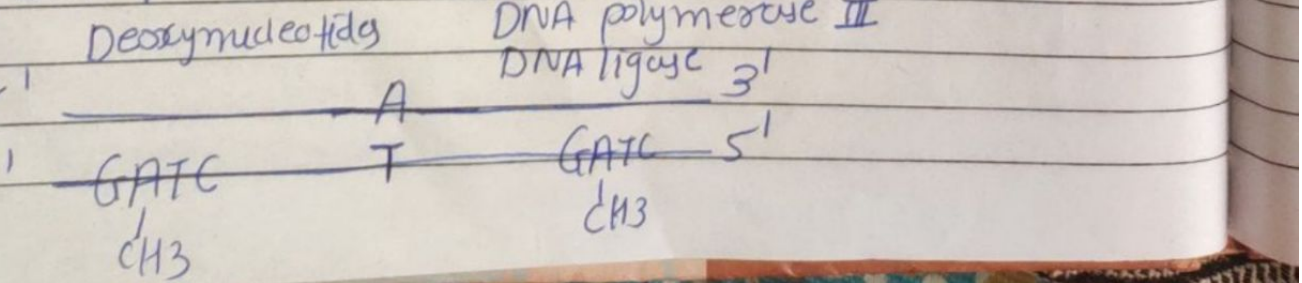
↓

(2) Segment of daughter strand is released.



↓

(3) polymerase III gap & ligases join newly synthesized DNA pieces to original strand.



Mutation to protein involved in mismatch repair in human associated with hereditary nonpolyposis Colorectal cancer / Lynch syndrome

→ Mut protein identify ~~mutation~~ mismatch on daughter cell

↓

Endonuclease nicks the strand

↓

Exonuclease remove mismatched nucleotide

↓

additional nucleotide at 5'- & 3'-end of mismatch are also removed.

↓

gap filled by DNA polymerase III, using sister strand as template

↓

DNA ligase join - ~~5'-phosphate of~~ 3'-OH of newly synthesized DNA with 5'-phosphate of remaining stretch of original DNA strand.

(2) Nucleotide excision repair :-

→ occurs throughout cell cycle

UV radiation

↓

Covalent joining of two adjacent pyrimidines.

↓

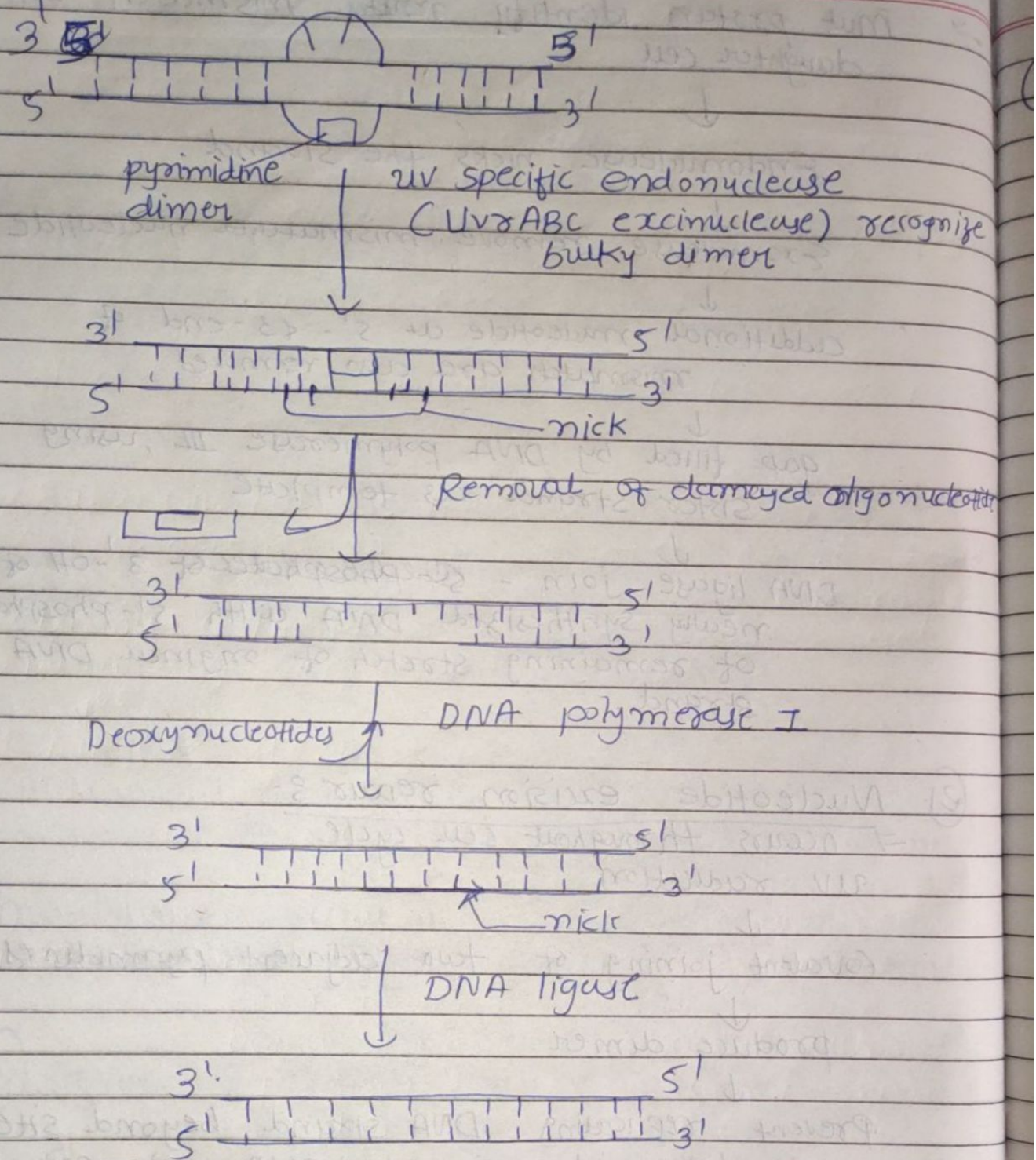
produce dimer

↓

Prevent replicating DNA strand beyond site of dimer formation by DNA polymerase.

→ Can formed in skin cell exposed to UV radiation in unfiltered sunlight.

→ Xeroderma pigmentosum - genetic disease
- Cell can not repair DNA damage
- So extensive accumulation of mutation
- Early & numerous skin Cancer.

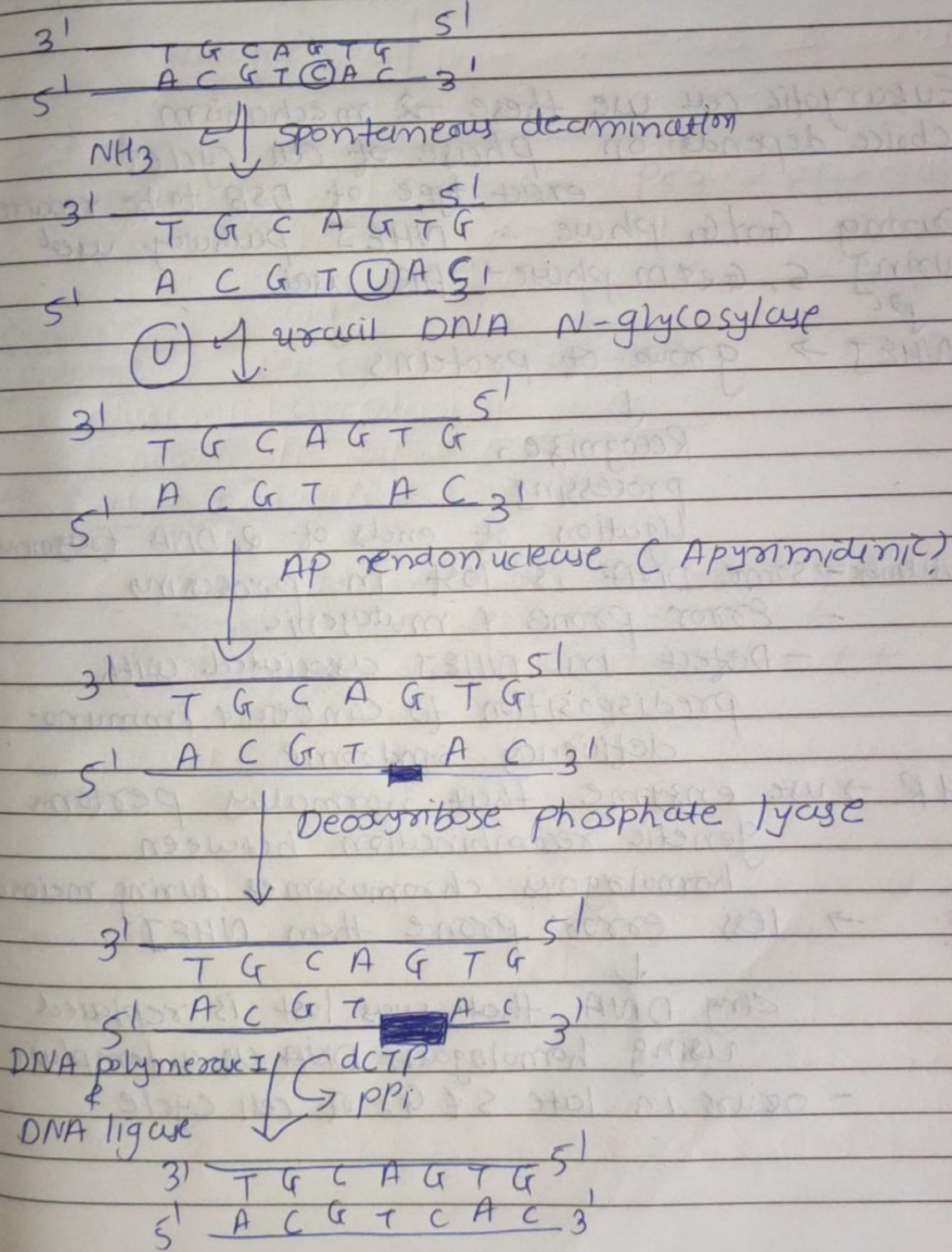

3'
5'
5'
3'
pyrimidine dimer
UV specific endonuclease (UvrABC excinuclease) recognize bulky dimer
3'
5'
5'
3'
nick
Removal of damaged oligonucleotide
3'
5'
5'
3'
Deoxynucleotides
DNA polymerase I
3'
5'
5'
3'
nick
DNA ligase
3'
5'
5'
3'

③ Base excision repair

- Base alteration - spontaneous, deaminating or alkylating compound

e.g. Cytosine $\xrightarrow{NH_3}$ uracil

e.g. Nitrous acid from nitrates.
Hypoxanthine → adenine
guanine → Xanthine



Mutation to protein BRCA1 / BRCA2, involved in HR → ↑ risk for developing breast & ovarian cancer.

(4) Double strand break repair

Caused by - Ionizing radiation
Chemotherapeutic agent like doxorubicin
Oxidative free radicals

→ 2 system required - (1) Non homologous end joining (NHEJ)
Disadvantage - Error prone & mutagenic

→ (2) Homologous recombination (HR) - less error prone

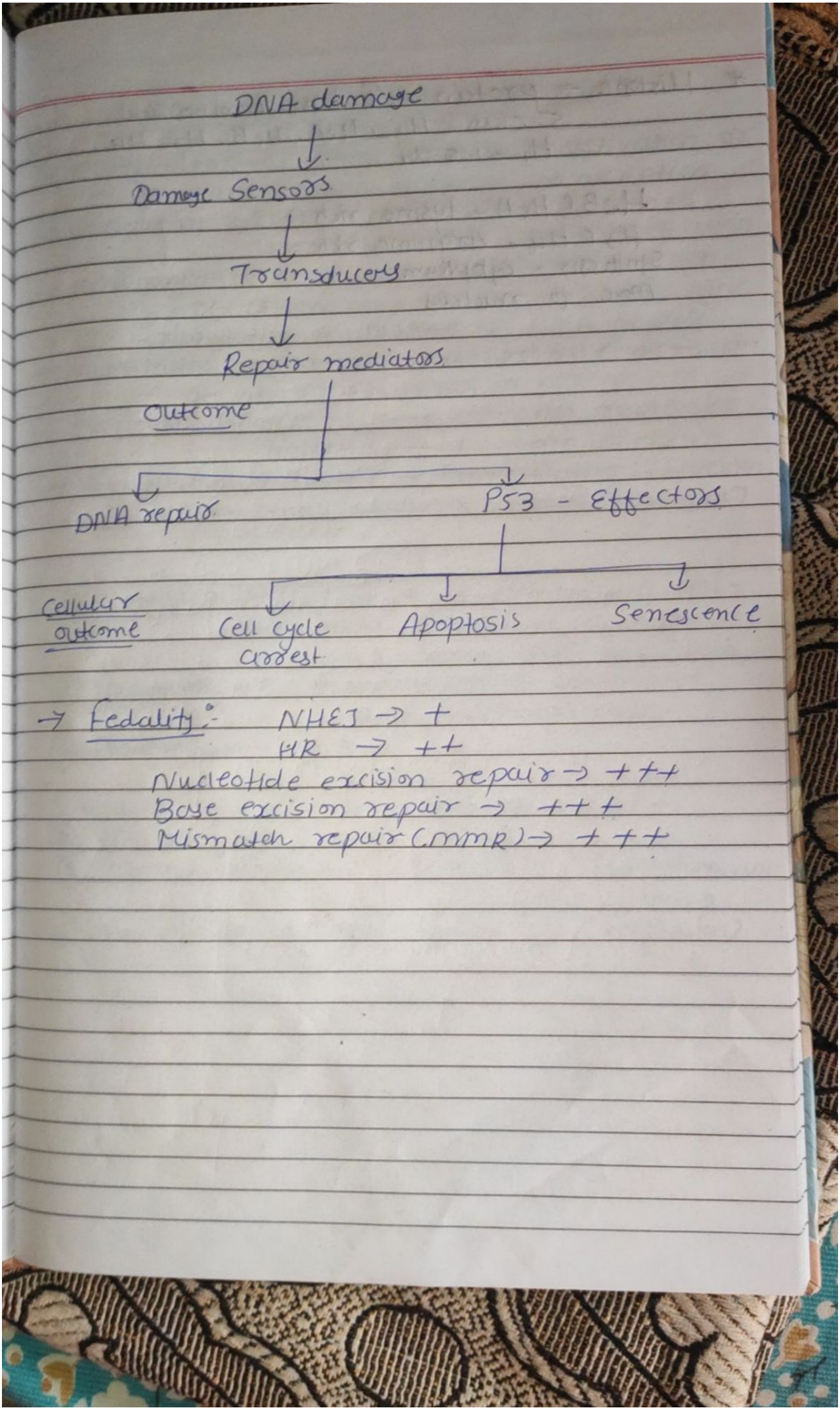
→ Eukaryotic cell use these 2 mechanism
→ choice depends on phase of cell cycle & exact type of DSB to be repaired
→ During G0/G1 phase - NHEJ pathway used
→ During S, G2 & M phase - HR used

(1) NHEJ → group of proteins
↓
Recognize,
processing
ligation of ends of 2 DNA fragments

Disadvantage → some DNA is lost in processing
- Error prone & mutagenic
- Defect in NHEJ associated with predisposition to cancer & immuno-deficiency syndrome.

(2) HR → we enzyme that normally perform genetic recombination between homologous chromosomes during meiosis

Adv. → less error prone than NHEJ
↓
any DNA that was lost is replaced using homologous DNA as a template
- occurs in late S & G2 of cell cycle



→ Fedality:- NHEJ → +
HR → ++
Nucleotide excision repair → +++
Base excision repair → +++
Mismatch repair (MMR) → +++