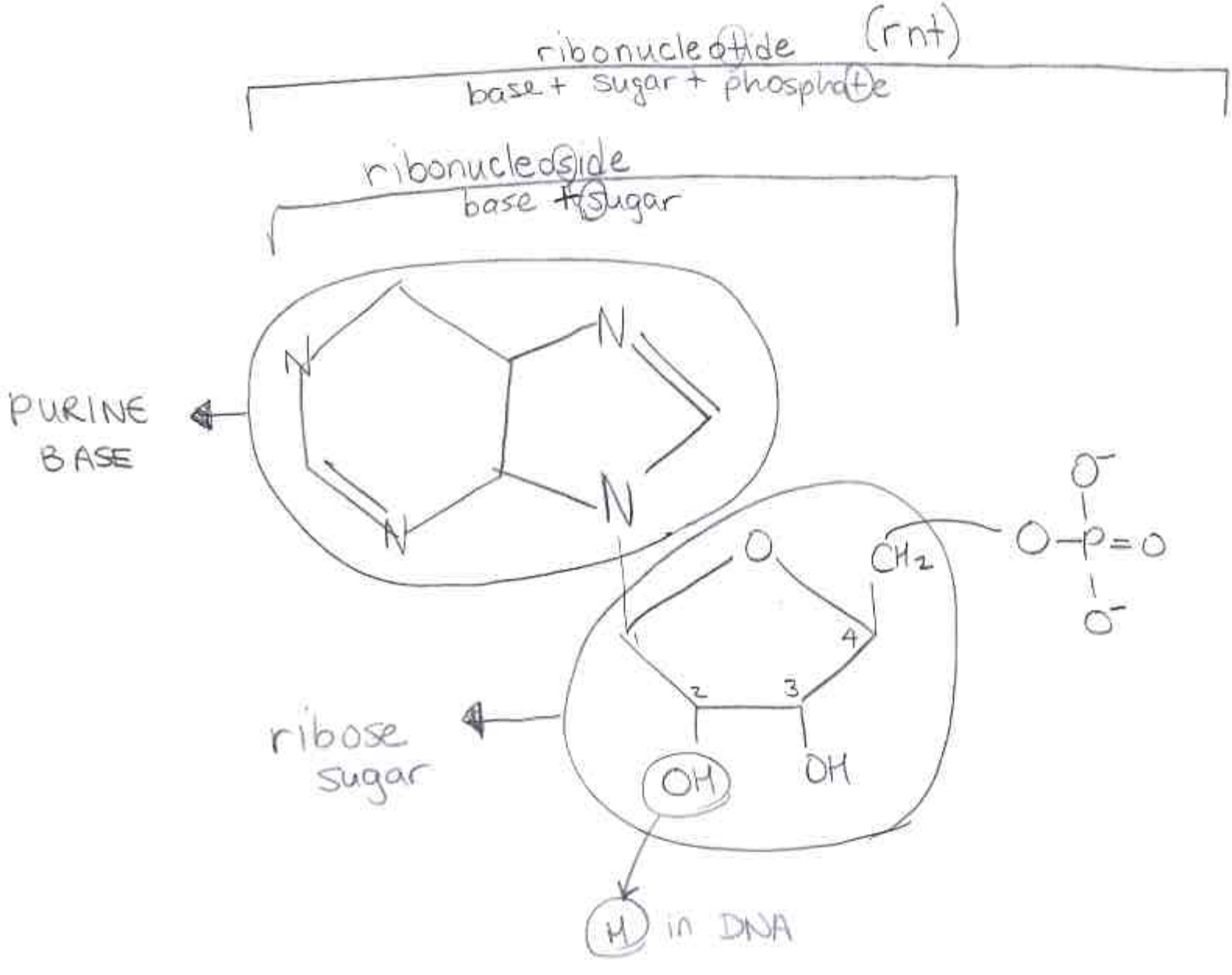

ribonucleotide (rnt)
base + sugar + phosphate
ribonucleoside
base + sugar
PURINE BASE
N
N
N
N
O
CH2
O
O-P=O
O-
1
2
3
4
ribose sugar
OH
OH
H in DNA

Why Important?

① metabolic regulators

e.g. adenosine, caffeine, cAMP

ATP = phosphoryl donor (kinase rxns)

② ATP (+GTP) = universal currency of energy

③ $NTP_s \longrightarrow RNA$

$dNTP_s \longrightarrow DNA$

④ Coenzymes

eg. FAD, NAD, CoA

2 Paths

Salvage

activ. ribose PRPP
+
base
(1 step)

de Novo

PRPP

small molecules
ATP
(12 steps)

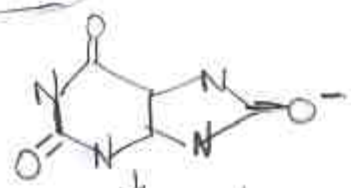
purine ribonucleotide (rnt.) ⟺ RNA

⟹ Cofactors etc

degradation ↓

deoxy-rnt ⟺ DNA

urate / uric acid



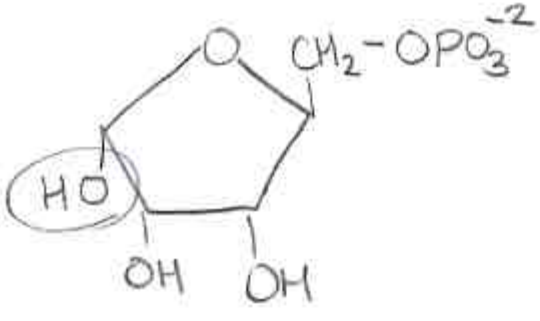
↓

excreted in urine

PRPP Synthesis

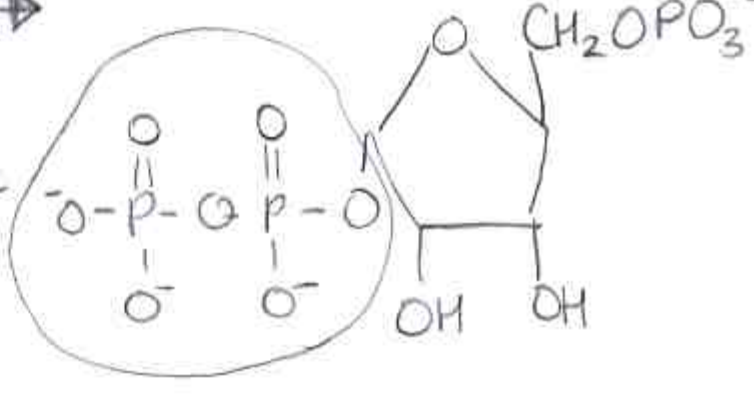
Ribose - 5Ⓟ

- from pentose Ⓟ pathway



ATP → AMP

addition of pyrophosphate



pur
pyr
his
trp

PRPP

5phospho ribosyl 1 pyrophosphate

Salvage

PRPP + preformed base ⟶ rnt

↑ (diet, DNA/RNA breakdown, DNA repair)

---

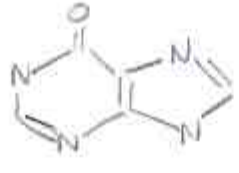
2 enzymes

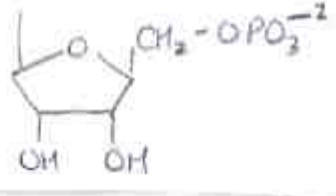
① PRPP + adenine (A) —(adenine (A) phosphoribosyl transferase)→ adenylate (AMP) + PP_i

② PRPP + guanine (G) or hypoxanthine (H) —(HG: Hypoxanthine-guanine phosphoribosyl transferase (HGPRT))→ guanylate (GMP) + PP_i

PRPP + hypoxanthine (H) ⟶ inosinate (IMP) + PP_i

IMP → GMP
IMP → AMP





Why important?

- Saves NRG = NO ATP spent!

How do we know its important? Lesch-Nyhan Syndrome

Lesch-Nyhan Syndrome

- Inborn error of metabolism, X-linked recessive (males)
- mutation in salvage pathway → ↓ activity of HGPRT

(A) neurological problems
- mental deficiency
- aggressive behavior
- compulsive self-destructive behavior

cause?: certain brain cells require salvage pathway (no de novo)

(B) high levels of urate in serum → kidney stones
→ gout (painful joint disease)

cause: ↓HGPRT → high [PRPP] → ↑ de novo pur. syn → urate overproduct (purine breakdown product)

- HOPE = Gene therapy

CONCLUSION!
1. salvage = important
2. absence of 1 enzyme → huge effect on health/behavior

De Novo (outline)

PRPP

10 Steps (0 → 9)

Lots of ATP
- ~~2~~ NH_3 (← 2 gln)
- 1 glycine
- 2 formyls (THF-C(=O)-H cofactor)
- 1 bicarbonate
- 1 NH_2 (← asp)

IMP

10a: 1 GTP, 1 NH_2 (asp)

10g: 1 ATP, 1 NH_3 (gln)

11a

11g

AMP

GMP

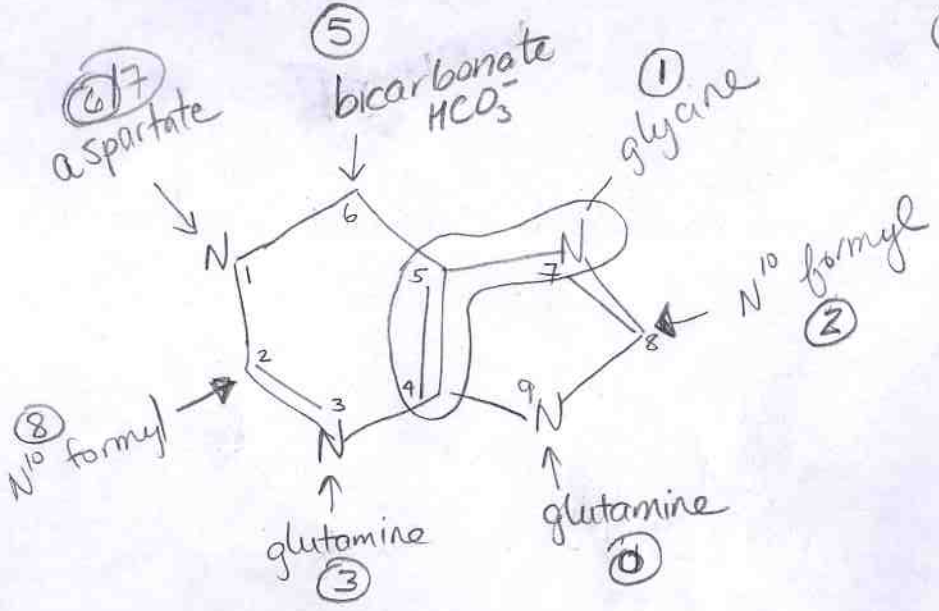
①

Imp. Concepts

1) scratch synth from small mol.
2) uses ATP
3) N incorp from amino acids (asp, gln, gly)
4) purine ring is built on ribose (PRPP)
5) conserved (E.c. → human)
6) highly regulated

②

③



④ Imidazole
⑨ ring closure

④

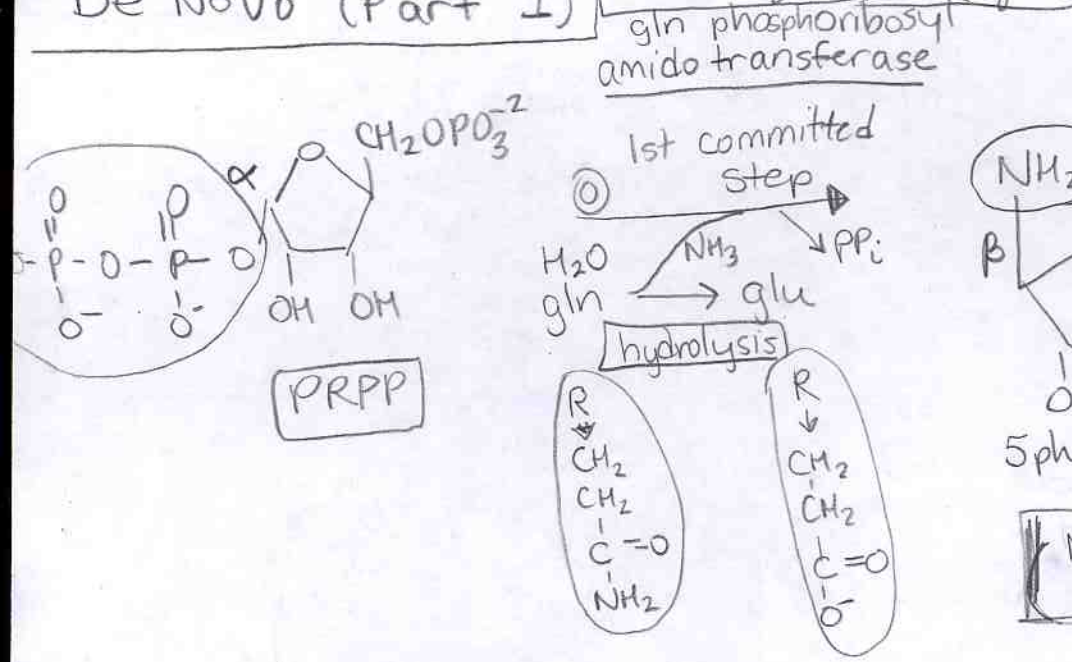
How did they figure it out?

Fed Radiolabelled precursers (like glycine $^{\oplus}H_3N\text{-}CH_2\text{-}{}^{13}COO^{\ominus}$) to pigeons.

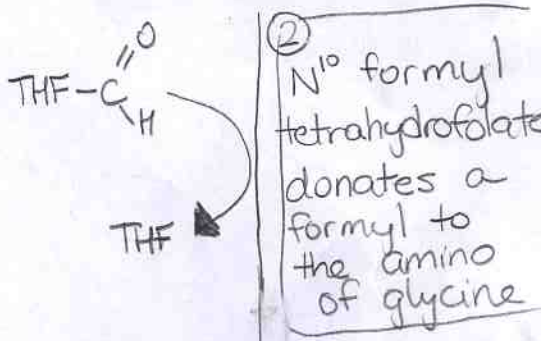
Collected poop (uric acid) Chemically degraded to determine the positions of the labeled atoms

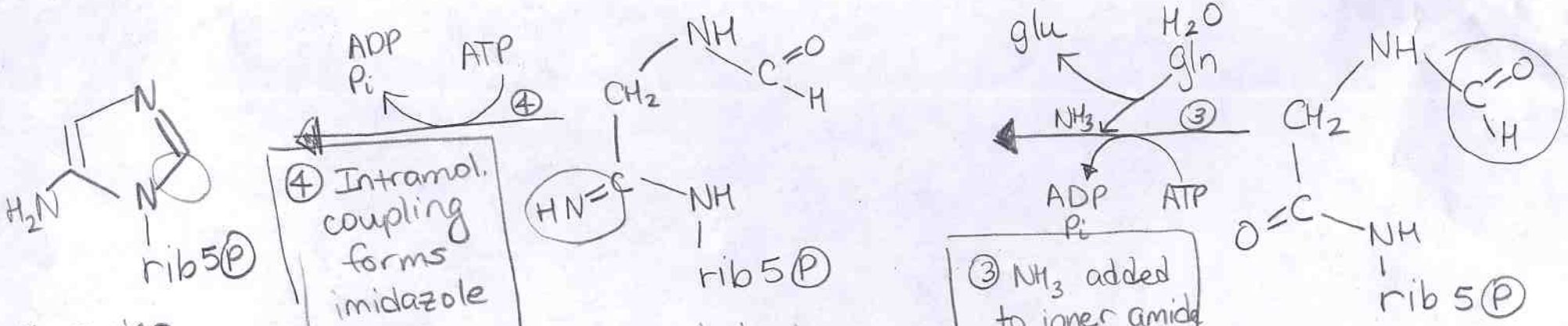
De Novo (Part I)

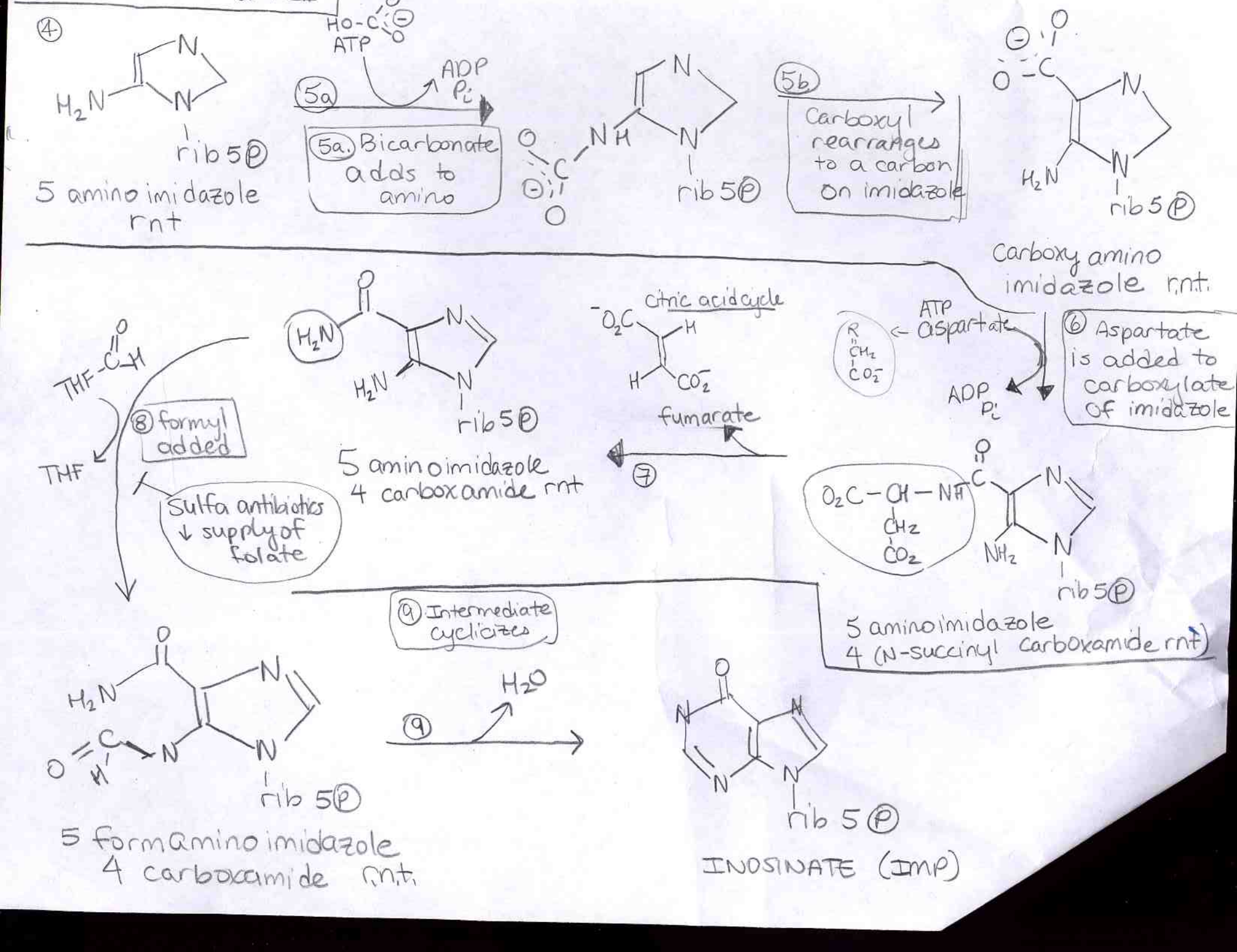
gln phosphoribosyl amidotransferase



glycinamide rnt

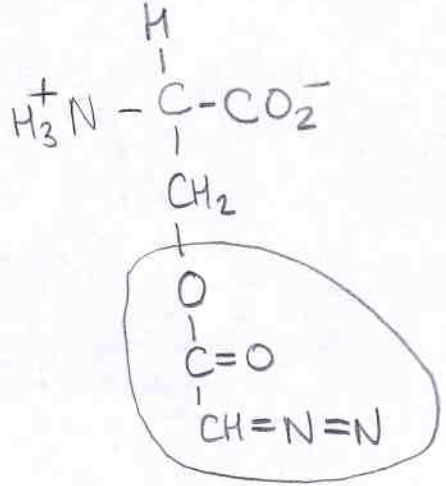




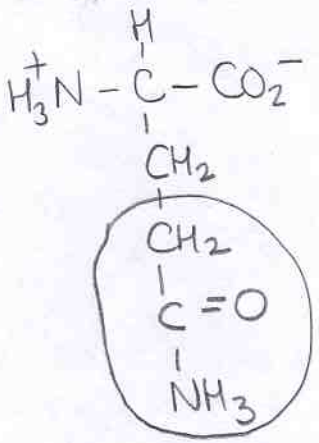

④
HO-C(=O)-O⊖
ATP
ADP
P_i
5a
5a. Bicarbonate adds to amino
5b
Carboxyl rearranges to a carbon on imidazole
5 amino imidazole rnt
rib 5Ⓟ
Carboxy amino imidazole r.n.t.
⑥ Aspartate is added to carboxylate of imidazole
ATP
aspartate
ADP
P_i
citric acid cycle
fumarate
⑦
⑧ formyl added
THF
Sulfa antibiotics ↓ supply of folate
5 amino imidazole 4 carboxamide rnt
⑨ Intermediate cyclizes
H_2O
5 formamino imidazole 4 carboxamide r.n.t.
5 amino imidazole 4 (N-succinyl carboxamide rnt)
INOSINATE (IMP)

Azaserine

- an antibiotic that inhibits purine biosyn
- suicide inhibitor of gln amidotransferases (covalently binds active site of enzymes that catalyze ATP-dep. amido transfer of gln → to acceptor
- gln analog



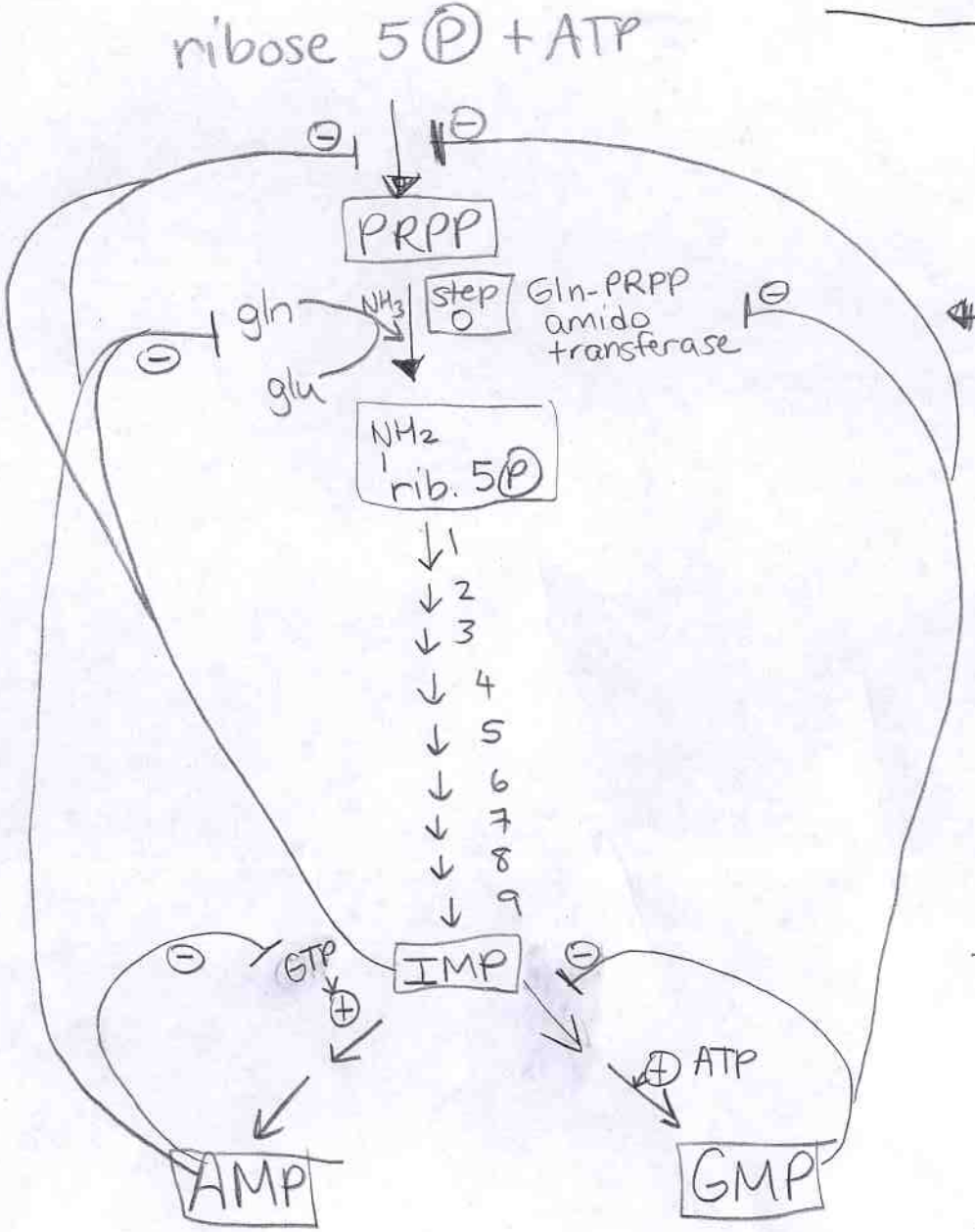
gln



Question: What steps will be inhibited?
Which intermediate(s) will accumulate?

Regulation of Purine Biosynthesis

FEEDBACK INHIBITION



AMP + GMP synergistically inhibit this step. ①

Reciprocal use of r.nt. helps balance AMP/GMP syn. rates