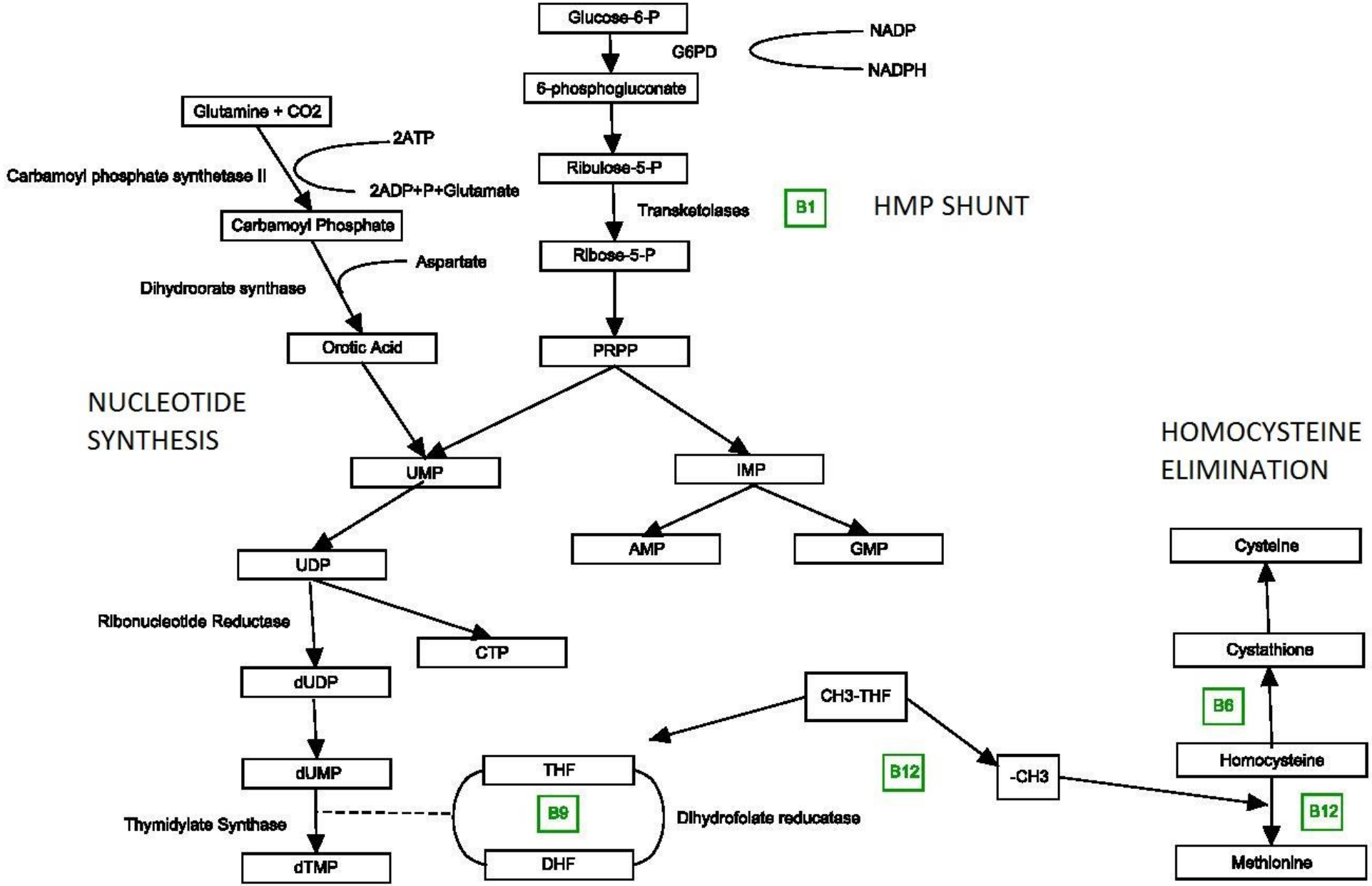
BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

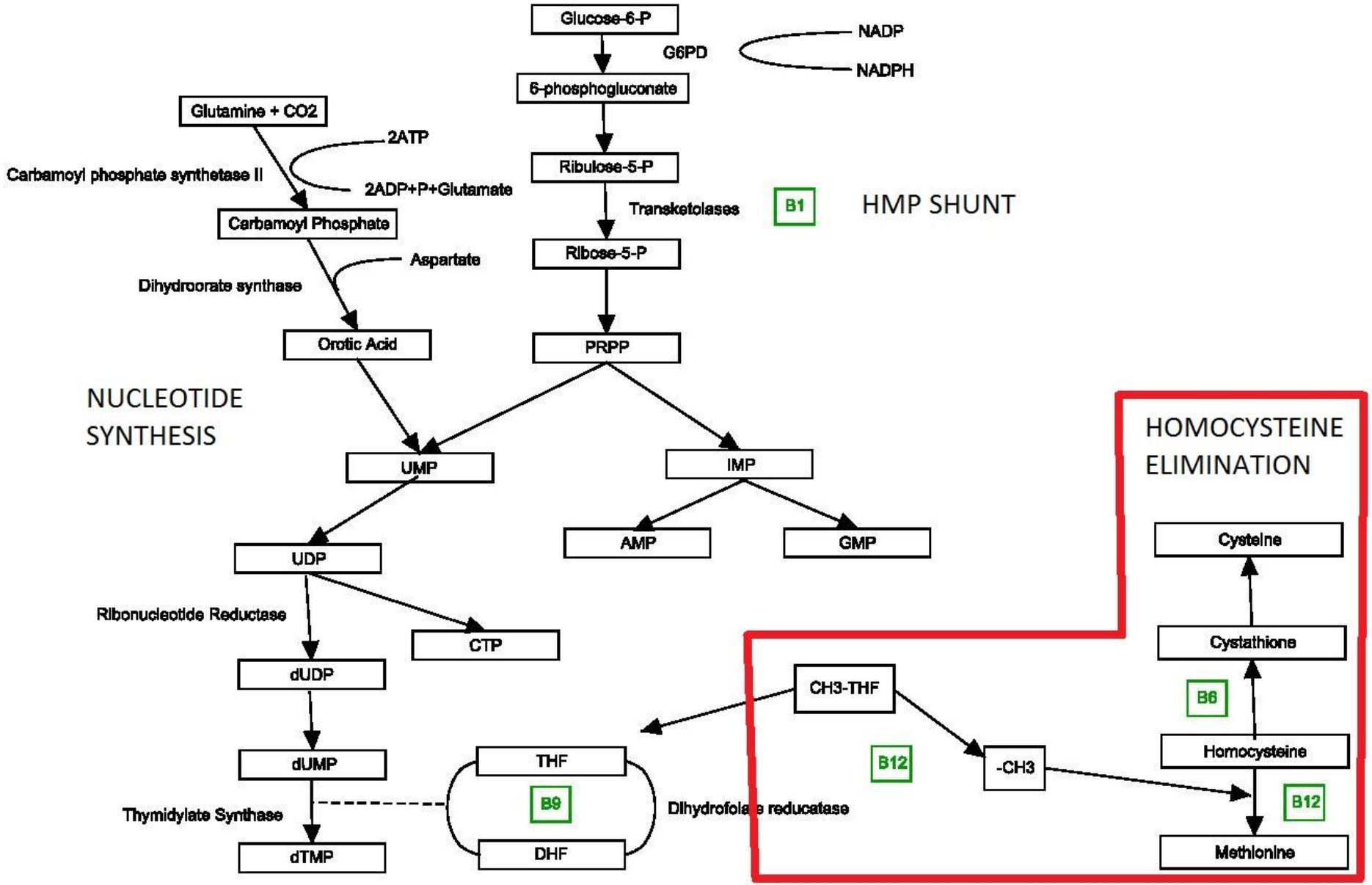
For each pathway:

- Where do we start?
- Where do we end?
- What are the goals of the pathway?
- What key enzymes will get us from start to end, and what do they need to function?
- Key disorders related to these pathways
- How do they all come together?

Homocysteine Metabolism

- **Start** with homocysteine **end** with cysteine or methionine
- **Goal** is to generate cysteine and methionine, get rid of homocysteine
- Key enzymes: homocysteine methyltransferase, cystathione synthase
- Disorders: homocystinuria (hereditary vs vitamin deficiency)
- Fits into pathways for folate, B12, and nucleotide synthesis


Glucose-6-P
G6PD
NADP
NADPH
6-phosphogluconate
Glutamine + CO2
2ATP
Carbamoyl phosphate synthetase II
2ADP+P+Glutamate
Ribulose-5-P
Transketolases
B1
HMP SHUNT
Carbamoyl Phosphate
Ribose-5-P
Aspartate
Dihydroorate synthase
Orotic Acid
PRPP
NUCLEOTIDE SYNTHESIS
HOMOCYSTEINE ELIMINATION
UMP
IMP
AMP
GMP
UDP
Ribonucleotide Reductase
CTP
dUDP
dUMP
Thymidylate Synthase
dTMP
THF
B9
DHF
Dihydrofolate reducatase
CH3-THF
B12
-CH3
Cysteine
Cystathione
B6
Homocysteine
B12
Methionine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-CH3
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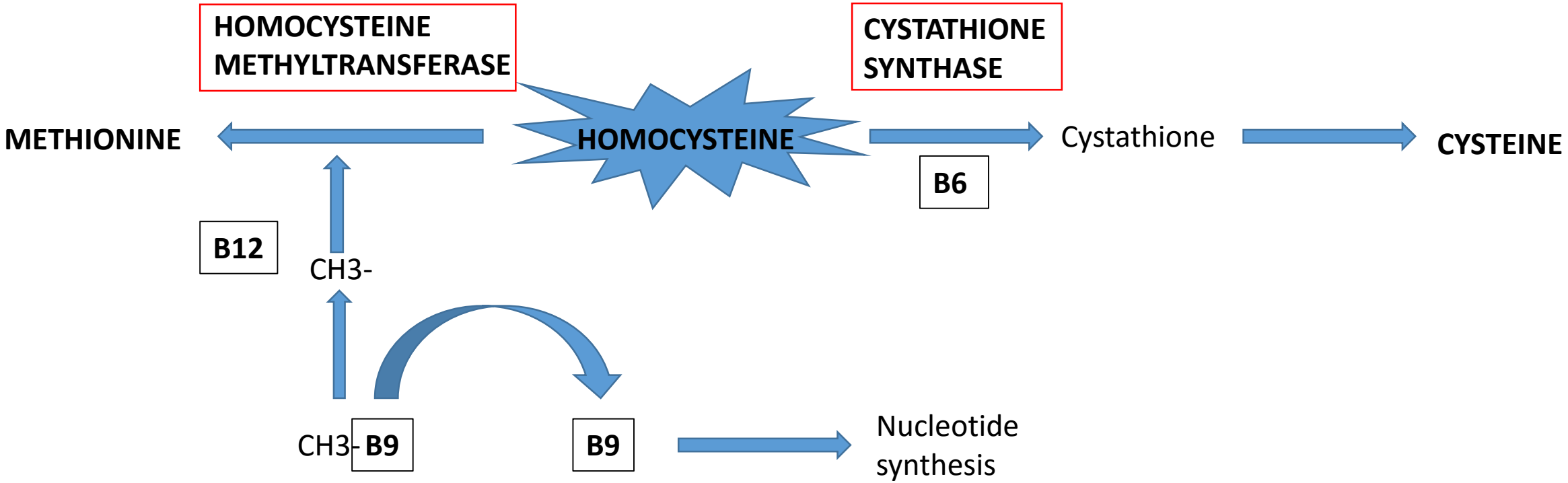
Cystathione
B6
Homocysteine
B12
Methionine

WRITING OUT THE PATHWAY



So what's the point?

- Generate cysteine and methionine, but this isn't necessarily the biggest problem when this pathway goes wrong
- The biggest issues with dysfunction of this pathway are from **excess homocysteine**, which is can result in developmental delay, osteoporosis, ocular abnormalities, thromboembolic disease, and **severe, premature atherosclerosis**

So what goes wrong and how does it present?

- Pathway dysfunction can be caused by severe vitamin deficiency (B6, B12, or B9), or from congenital deficiency of any of the enzymes
- For purposes of the boards, focus on presentation in children with congenital deficiency → all forms are autosomal recessive
- Children present with signs of **excess homocysteine**:
  - Severe, premature atherosclerotic disease (usually before age 20): stroke, MI, etc
  - Lens sublexion (vision problems)
  - May or may not have marfanoid habitus, but this is a major clue
  - Basically, though, if you hear about someone <20 having a stroke or MI put this on your radar

How to think about treatment

- Basically you have a pathway that goes in two directions, and one is being cut off by either an enzyme deficiency or a vitamin deficiency
- Treat by giving back what you lose on the cut-off pathway and “push” homocysteine down the open pathway to prevent buildup…..

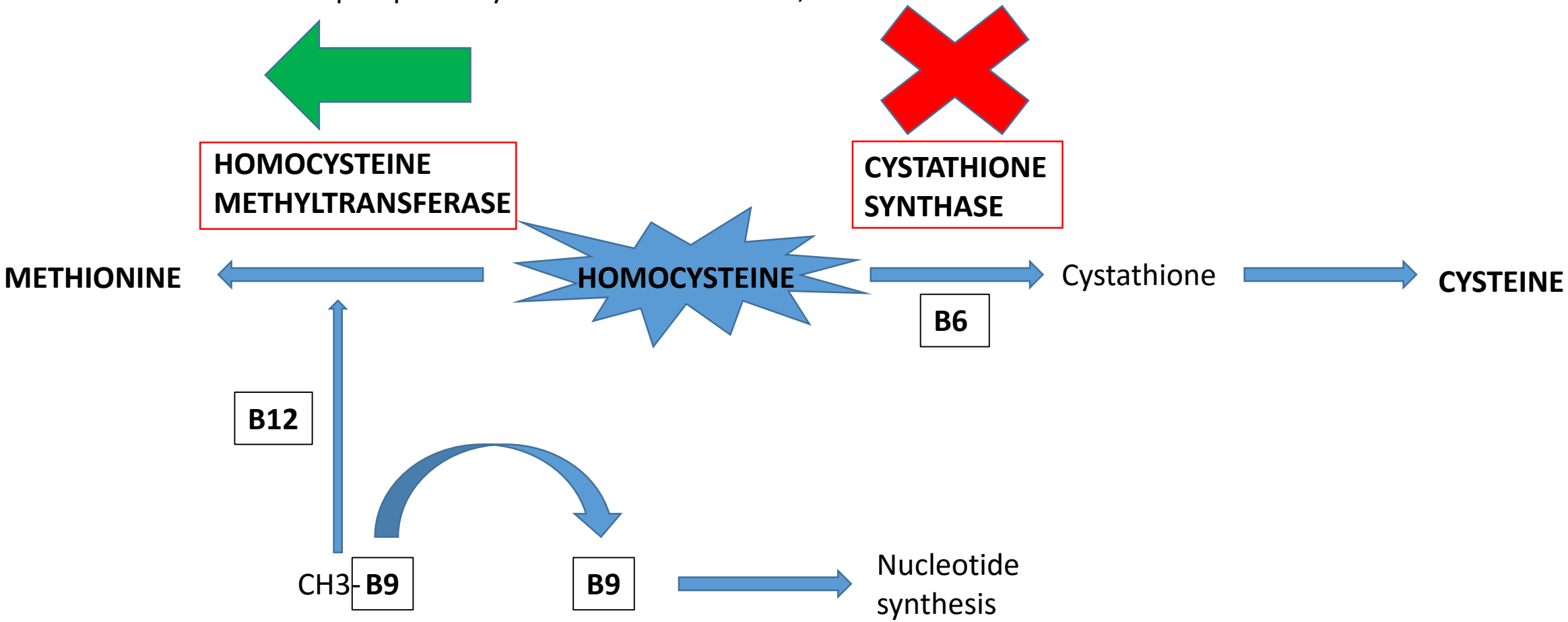
PROBLEM: Cystathione synthase deficiency

PRESENTATION: Symptoms related to elevated homocysteine, high methionine, low cysteine

SOLUTION:

-give back broken pathway: supplement cysteine

-"Push" down open pathway: decrease methionine, increase B12 and B9 in diet

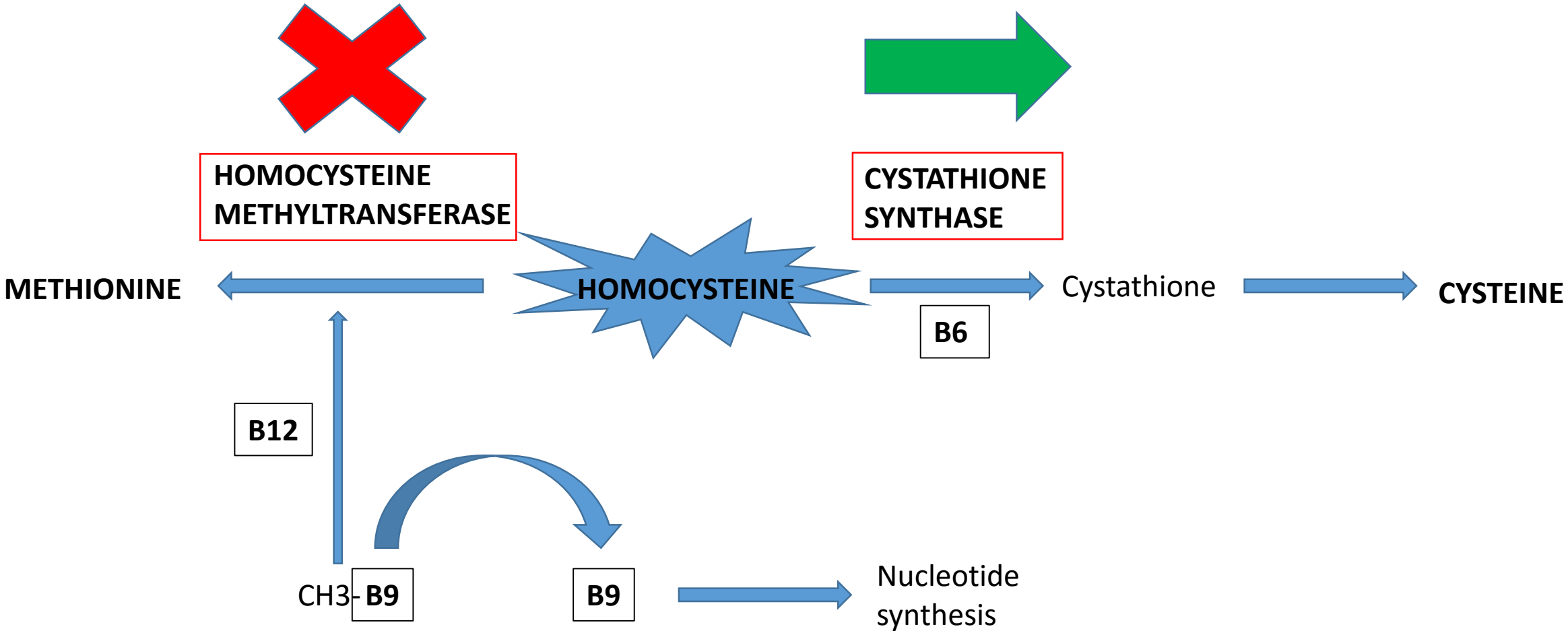


PROBLEM: Homocysteine methyltransferase deficiency

PRESENTATION: Symptoms related to elevated homocysteine, low methionine, high cysteine

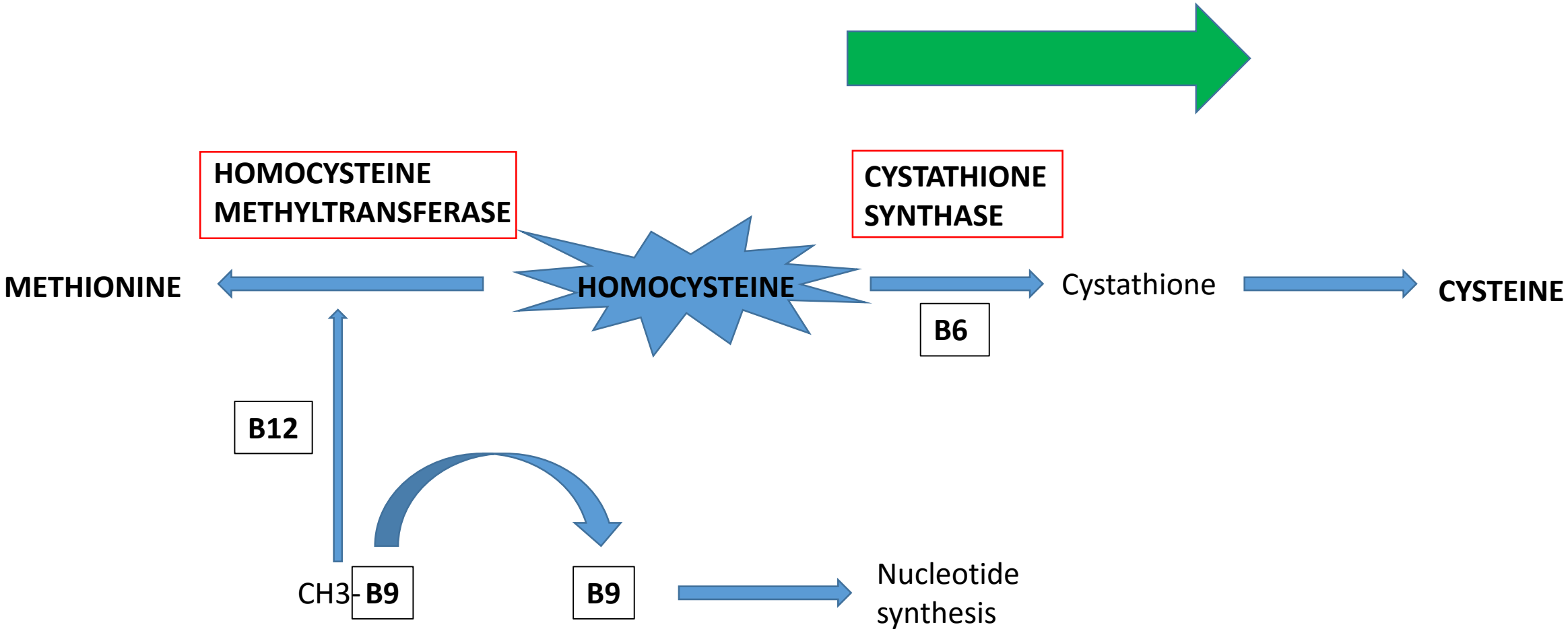
-give back broken pathway: supplement methionine

-"Push" down open pathway: supplement vitamin B6



PROBLEM: Decreaed affinity of cystathione synthase for B6
PRESENTATION: Symptoms related to elevated homocysteine, high low cysteine
SOLUTION:

-give back broken pathway: supplement cysteine and B6

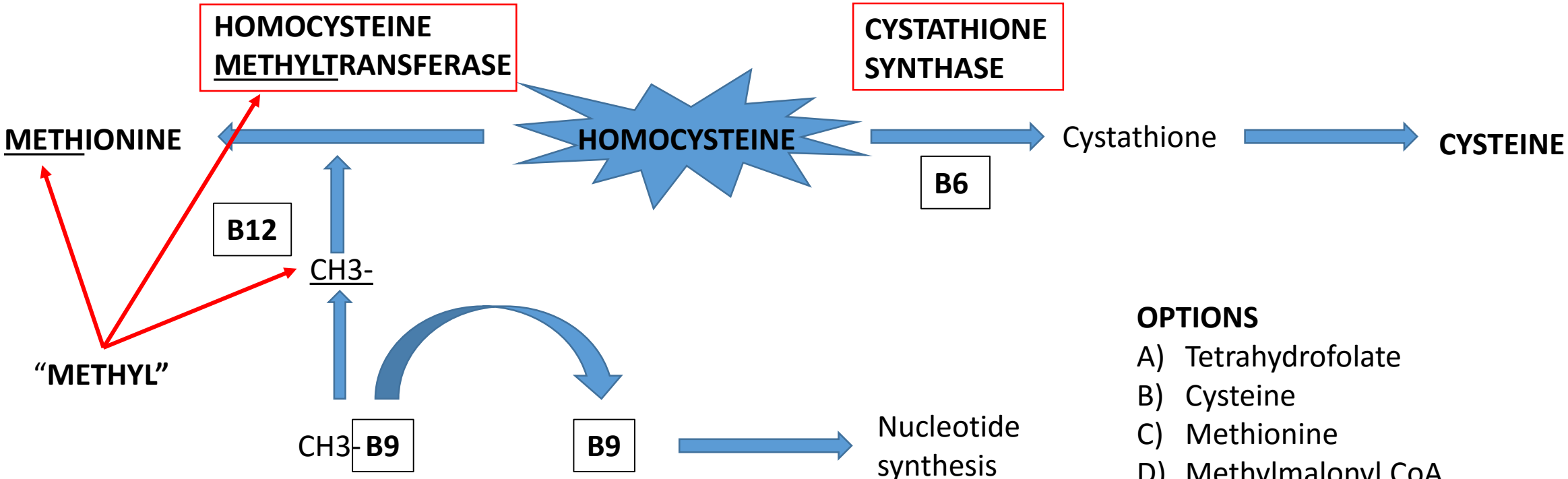


SAMPLE QUESTIONS FOR HOMOCYSTEINE

A 35 year old man presents to the Emergency Department with approximately 20 minutes of crushing substernal chest pain that began while jogging. In the ED his EKG showed prominent ST elevation in leads II, III, and aVF, prompting a diagnosis of acute inferior STEMI. After immediate stabilization a lipid panel is sent that revealed total cholesterol, HDL, and LDL levels within normal limits. Further investigation reveals a serum homocysteine level of almost double the normal limit.

Genetic testing reveals a mutation affecting activity of homocysteine methyltransferase that leads to a decrease in function. This leads to impaired ability to convert homocysteine to what end product?

A) Tetrahydrofolate
B) Cysteine
C) Methionine
D) Methylmalonyl CoA
E) Acetyl CoA



OPTIONS

A) Tetrahydrofolate
B) Cysteine
C) Methionine
D) Methylmalonyl CoA
E) Acetyl CoA

A 15 year old boy is brought to the emergency department with crushing chest pain that developed while playing soccer. Physical examination shows a tall, slender boy with elongated digits and mild kyphosis. EKG reveals ST elevation in leads V1-V4 and he is diagnosed with acute STEMI. Studies performed after immediate catheterization and stabilization show marked elevation of serum homocysteine and methionine with decreased levels of cysteine. Further evaluation shows a complete loss of function mutation in cystathione synthase. In addition to cysteine supplementation, long term management would involved increased what in the diet?

A) Methionine
B) Folate and B12
C) Tryptophan
D) Vitamin B6
E) Acetyl CoA

PROBLEM: Cystathione synthase deficiency

PRESENTATION: Symptoms related to elevated homocysteine, high methionine, low cysteine

SOLUTION:

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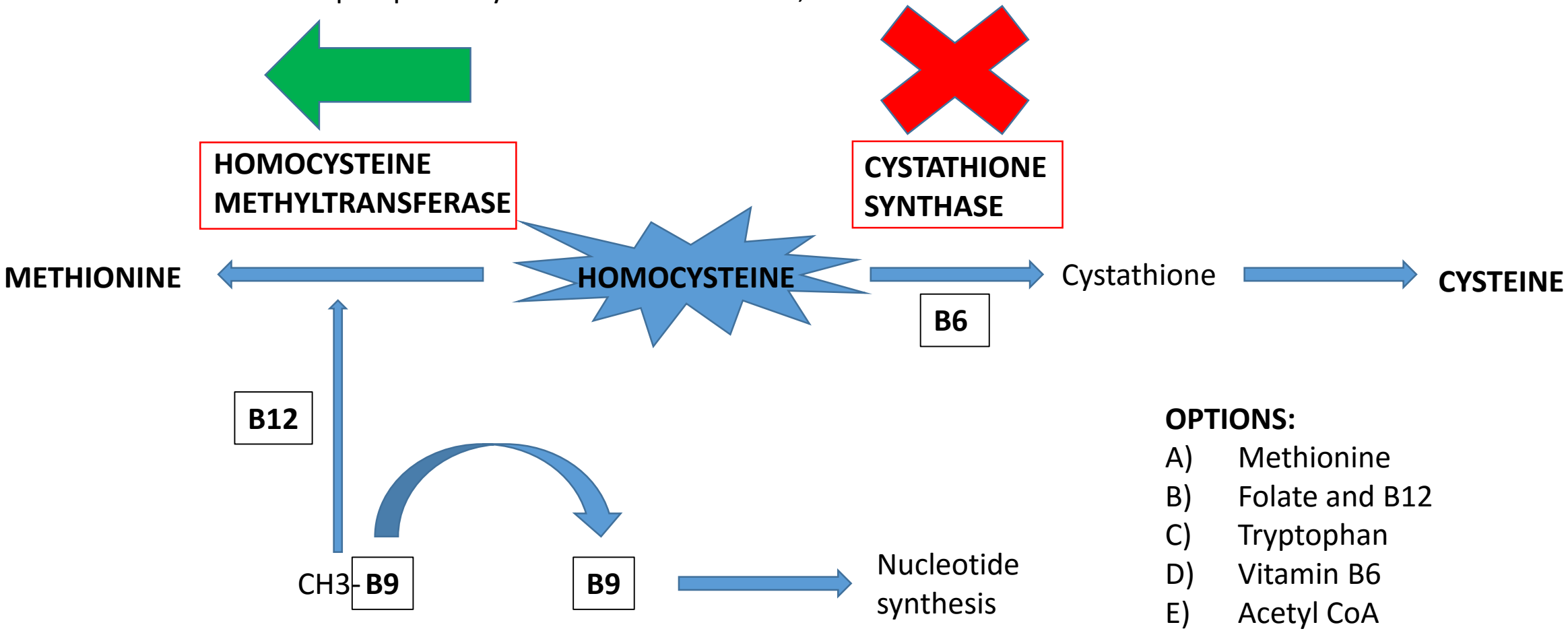
-"Push" down open pathway: decrease methionine, increase B12 and B9 in diet



OPTIONS:

A) Methionine
B) Folate and B12
C) Tryptophan
D) Vitamin B6
E) Acetyl CoA

A 7 year old boy is brought to the office for a routine physical exam. On exam you note a tall, thin boy with elongated digits. He has been having trouble in school, which he attributes to not being able to see the board. Further examination shows bilateral lens sublexion. The following year your office gets a call from the hospital stating that the same boy has been admitted and treated for multiple, diffuse pulmonary emboli and that Doppler venography of the head shows almost 70% occlusion of the MCA on the right side. After a thorough workup the patient is likely to be discharged with which of the following supplements?

A) Pyridoxine
B) Acetyl CoA
C) Homocysteine
D) Ascorbic Acid
E) Iron

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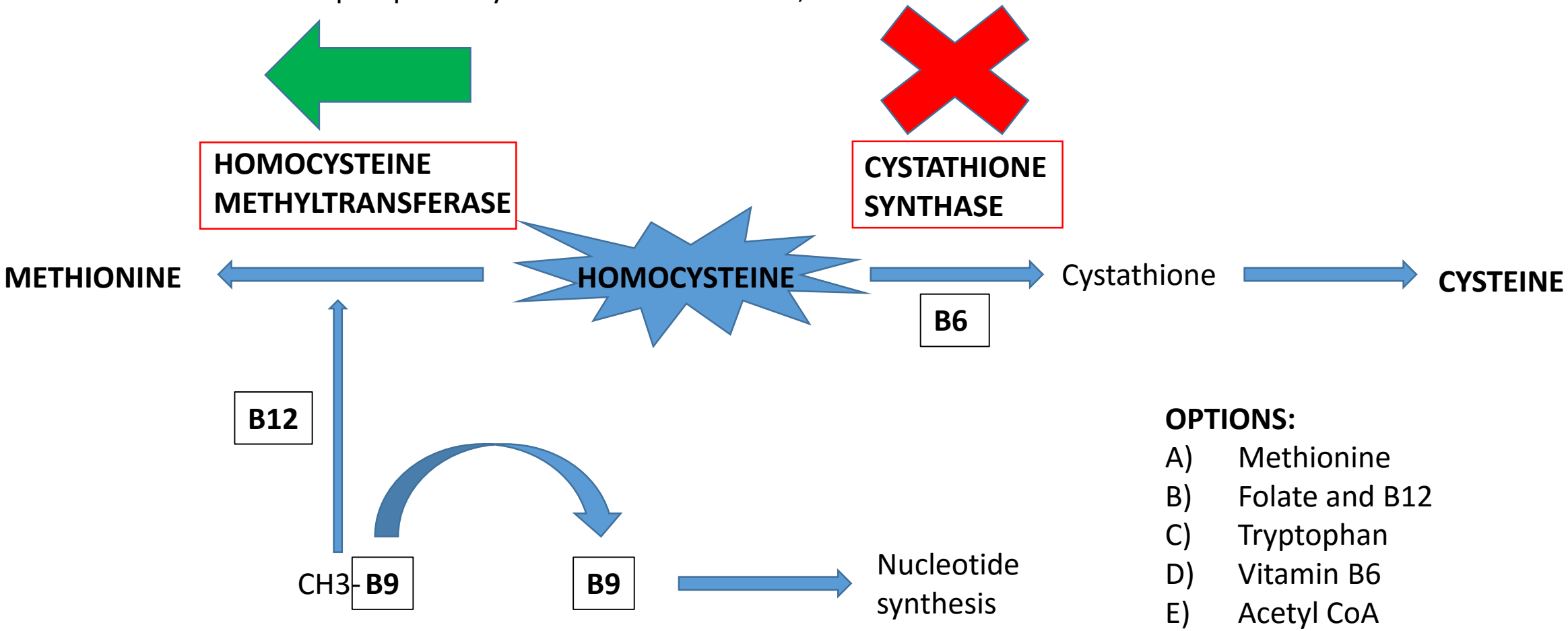

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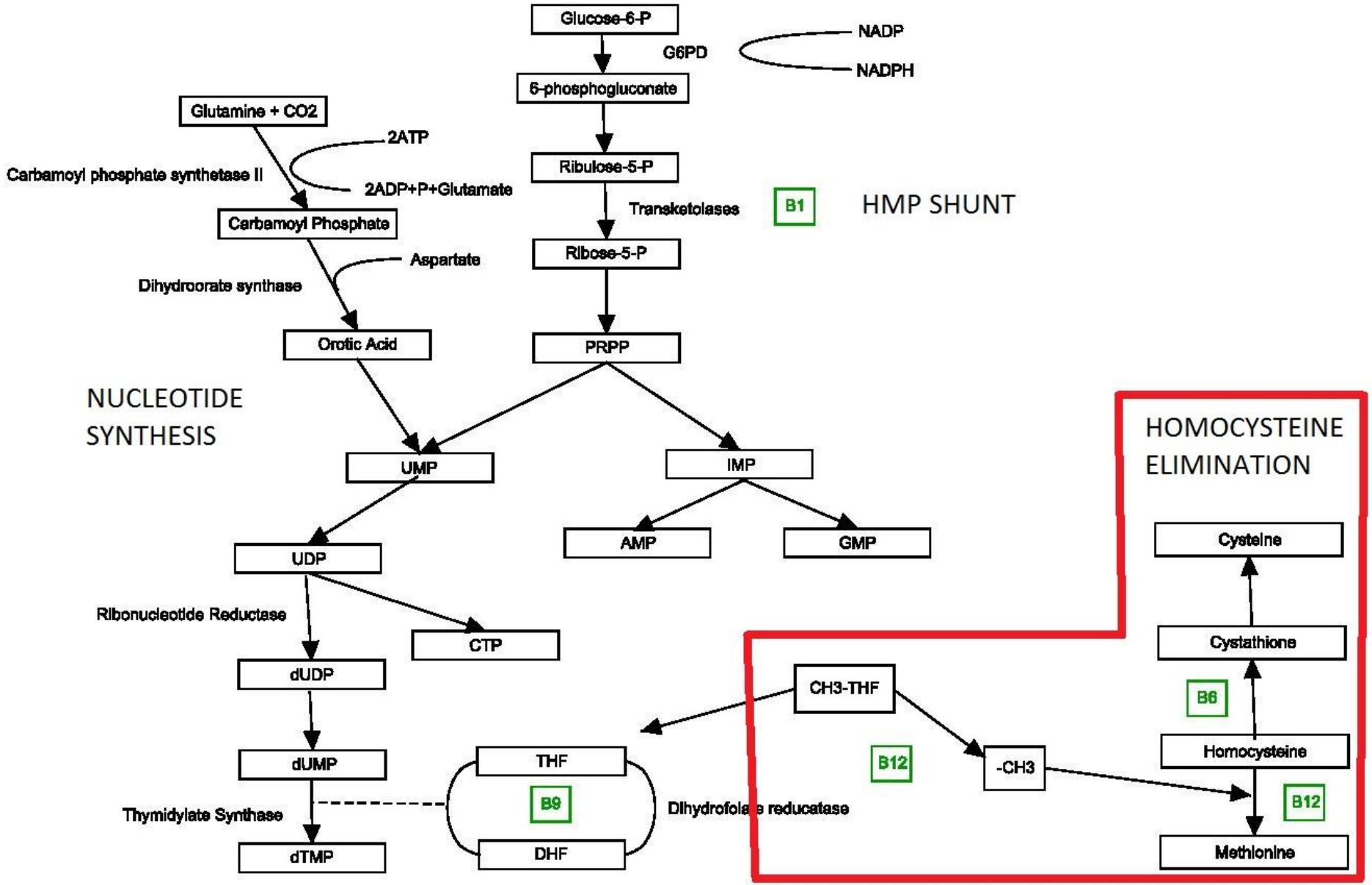
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