

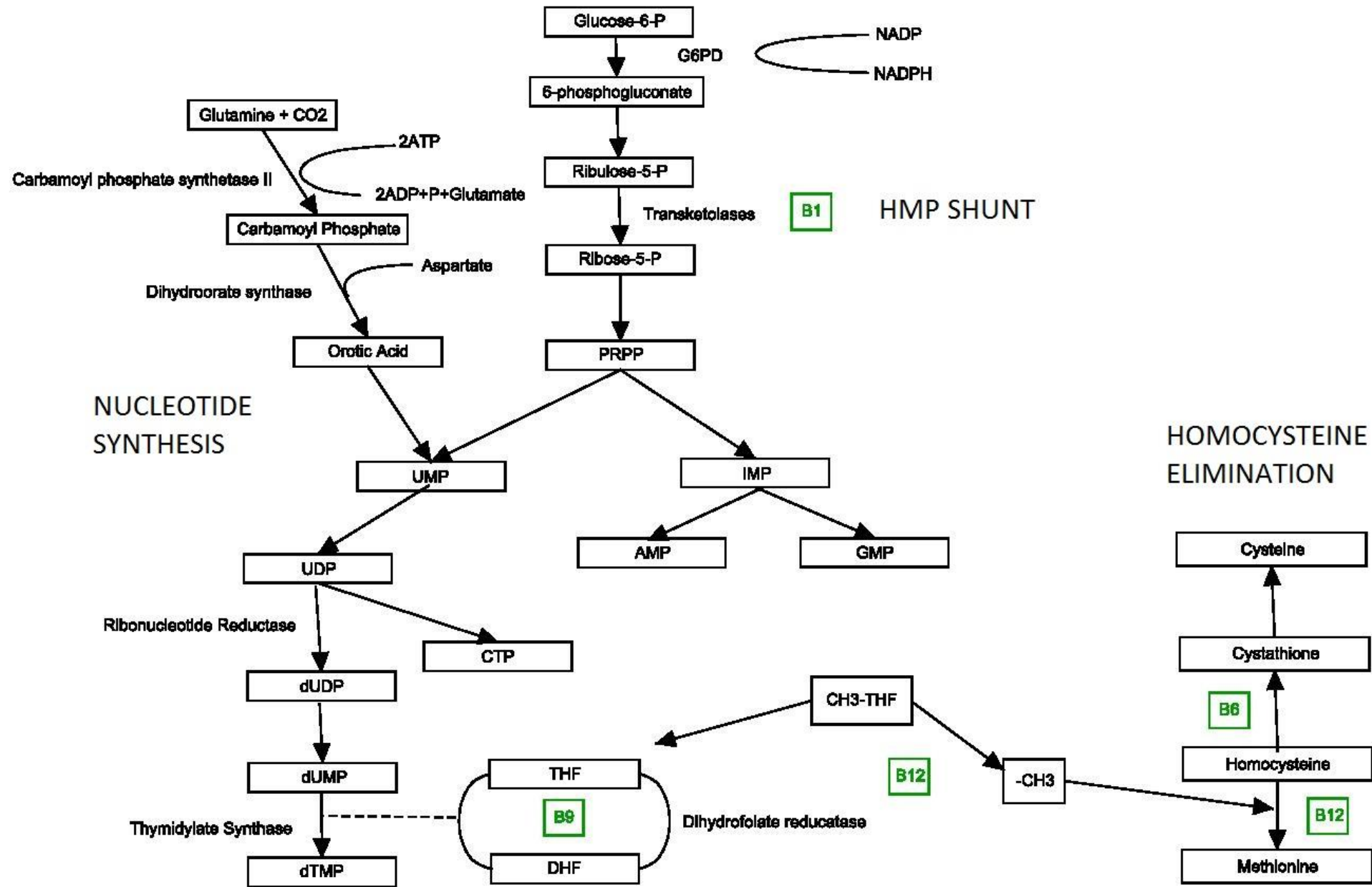
BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

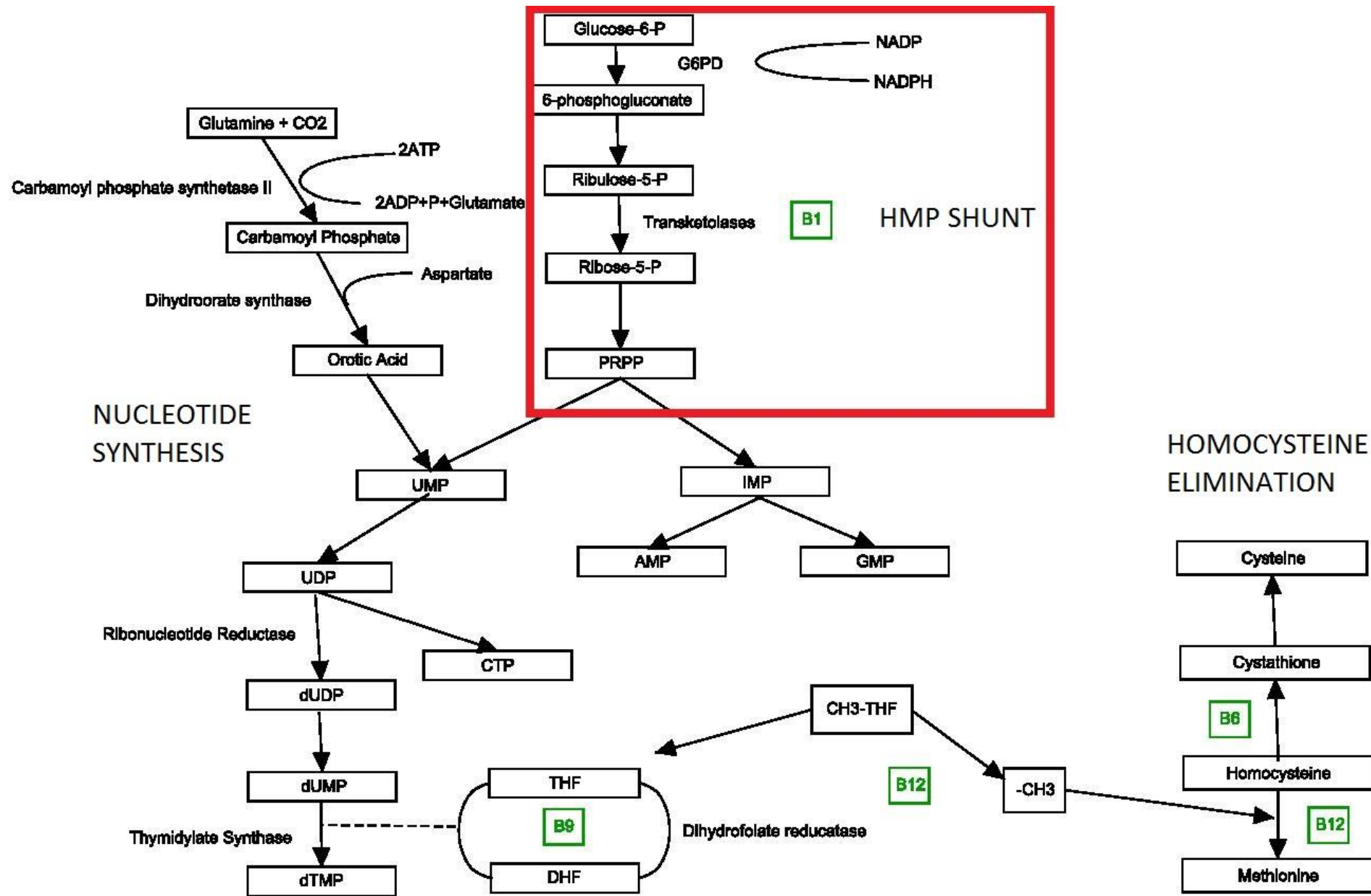
For each pathway:

- 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?

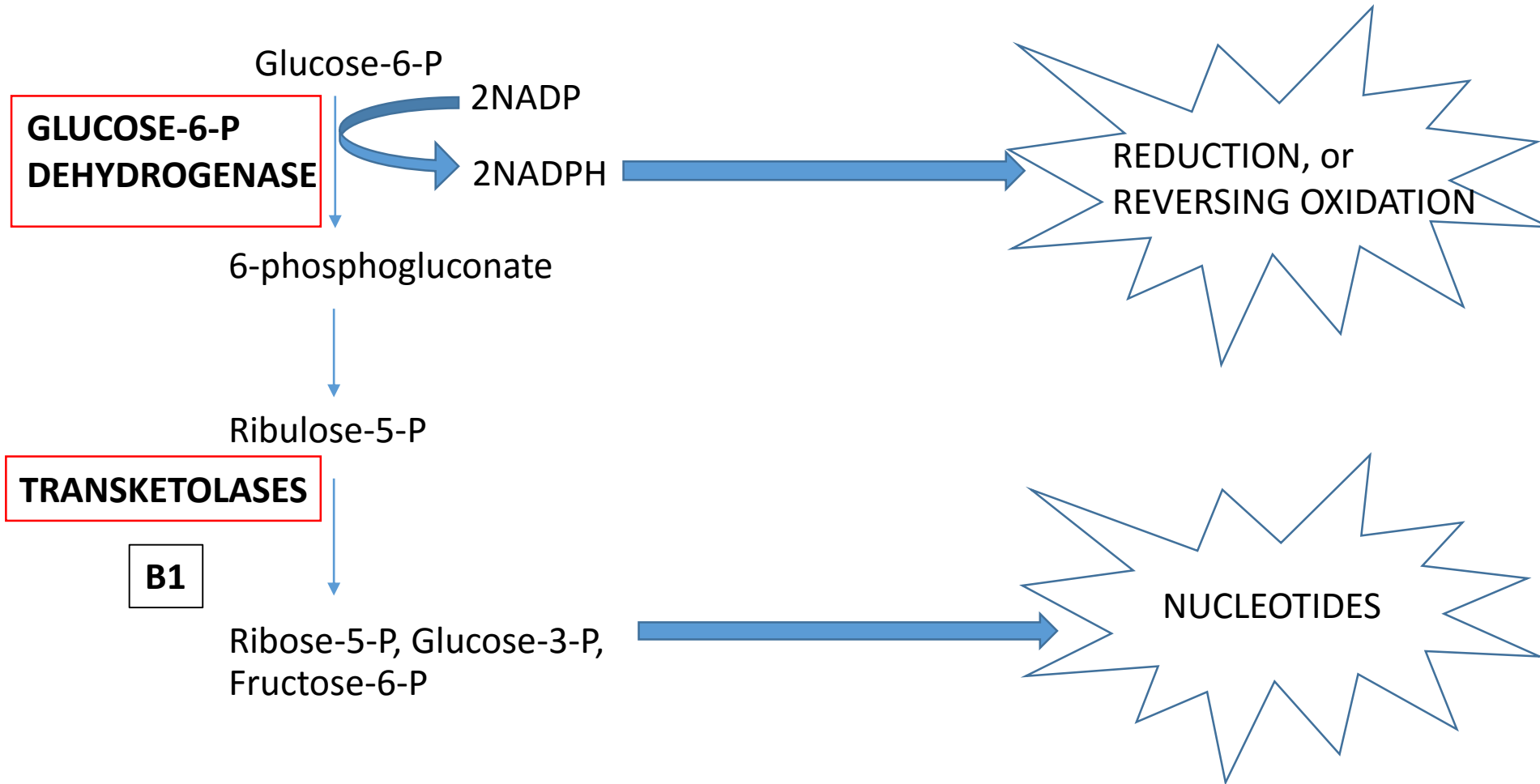
HMP SHUNT (aka Pentose phosphate pathway)

- **Start** with glucose-6-P, **end** with Ribose-5-P, NADPH, and Fructose-6-p
- **Goal** is to generate NADPH for reductive reactions (i.e **PREVENT** oxidative damage) and to make precursors for nucleotides
- Key enzymes: Glucose-6-phosphate dehydrogenase (G6PD) and Transketolases, requires vitamin B1
- Disorders: G6PD deficiency, Vitamin B1 deficiency
- Fits into pathways for glucose metabolism and nucleotide synthesis





WRITING OUT THE PATHWAY



Why NADPH? Why reduce??

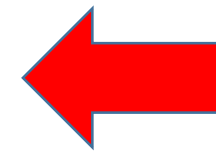
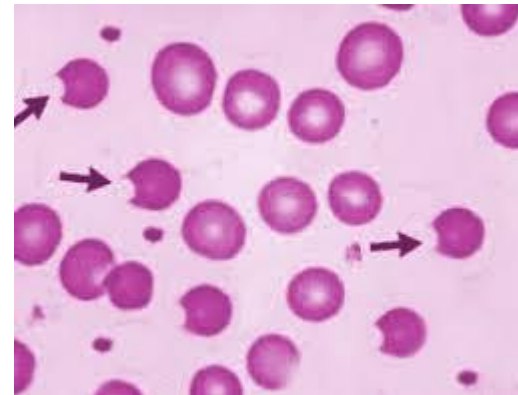
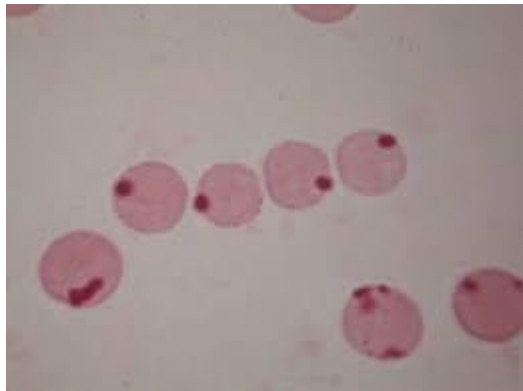
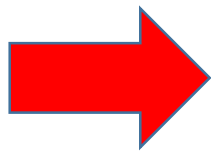
- Remember that reduction is essentially the opposite of oxidation
- Need reduction to make stuff: fatty acids, sterols, etc (we care less about this)
- Free oxygen radicals are bad for our cells, they damage our proteins and do all kinds of bad stuff (we care more about this)
- Mainly done by “recharging” glutathione reductase, cell’s go-to guy for dealing with free oxygen radicals
- So what causes oxidative stress?
 - Oxidizing agents: Sulfonamides, Primaquine, anti-TB drugs, FAVA BEANS
 - Infection, causes oxidative stress via inflammatory reaction

SO what goes wrong? Aka what are they likely to ask me about?

- May ask you about role of transketolases, role of vitamin B1
- Most high yield aspect of this pathway is G6PD deficiency

G6PD Deficiency:

- X-linked enzyme deficiency, most common among African Americans
- Most common human enzyme deficiency
- Essentially, RBC's can't generate enough NADPH to reverse oxidative stress from drugs, infection, fava beans, etc
- Leads to formation of reactive oxygen species within cells that denature hemoglobin, forming **HEINZ BODIES** on smear. Phagocytes don't like RBC's with Heinz bodies, so they eat them, leading to formation of **BITE CELLS**



How will they ask about this?

Patient (usually African American) will present with signs of RBC destruction (jaundice, pallor, dark urine) and falling blood counts shortly after exposure to oxidative stress

- DRUGS: antimalarials, sulfonamides, TB meds

- INFECTION

- BEANS (new recipe, “African bean”, travel with new foods)

- may give you a family history

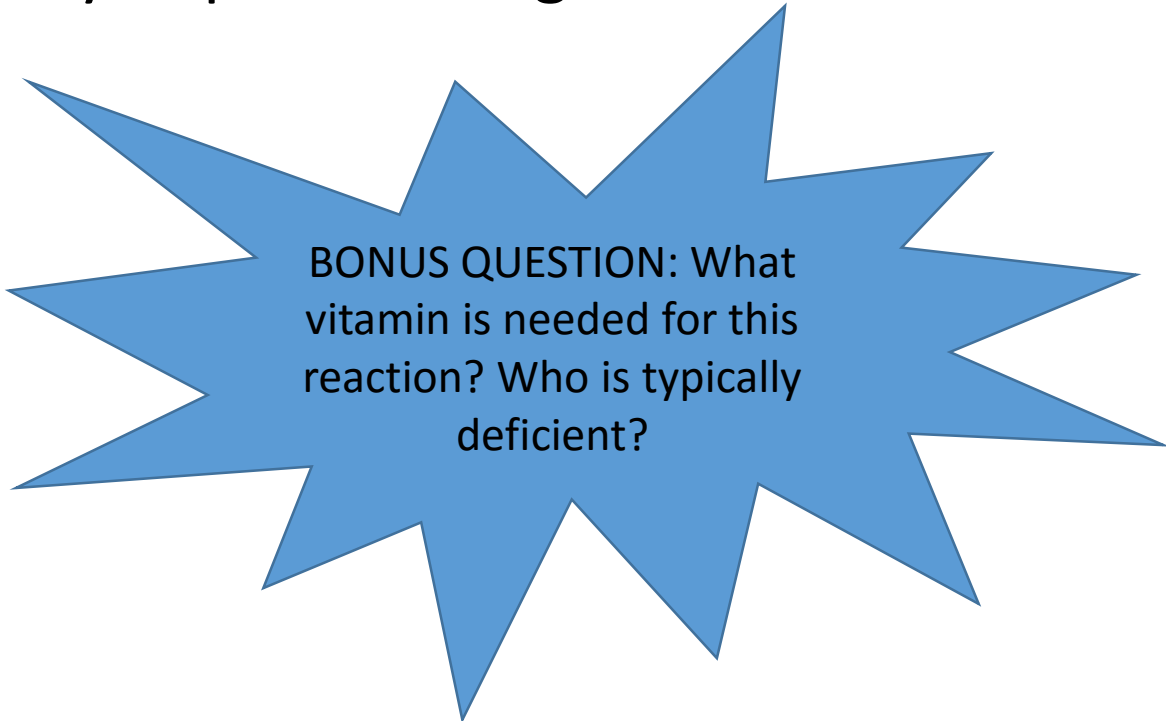
- may give you bite cells, Heinz bodies



SAMPLE QUESTIONS FOR HMP SHUNT

Researchers are studying a pathway in cultured human cells that is responsible for combatting oxidative stress through generation of NADPH as well as ribose-5-phosphate, a substrate for nucleotide synthesis. What enzyme is most directly implicated in generation of ribose-5-phosphate?

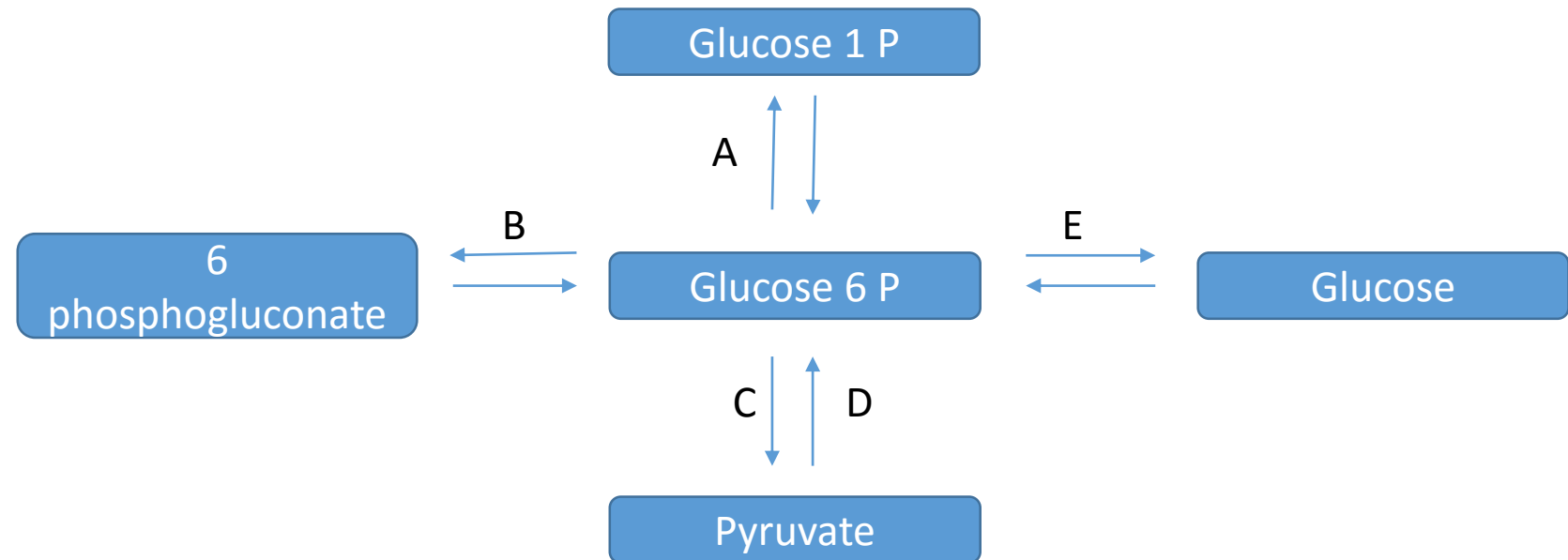
- A) Glucose-6-P dehydrogenase
- B) Transketolases
- C) Glutathione reductase
- D) Enolase
- E) Aconitase

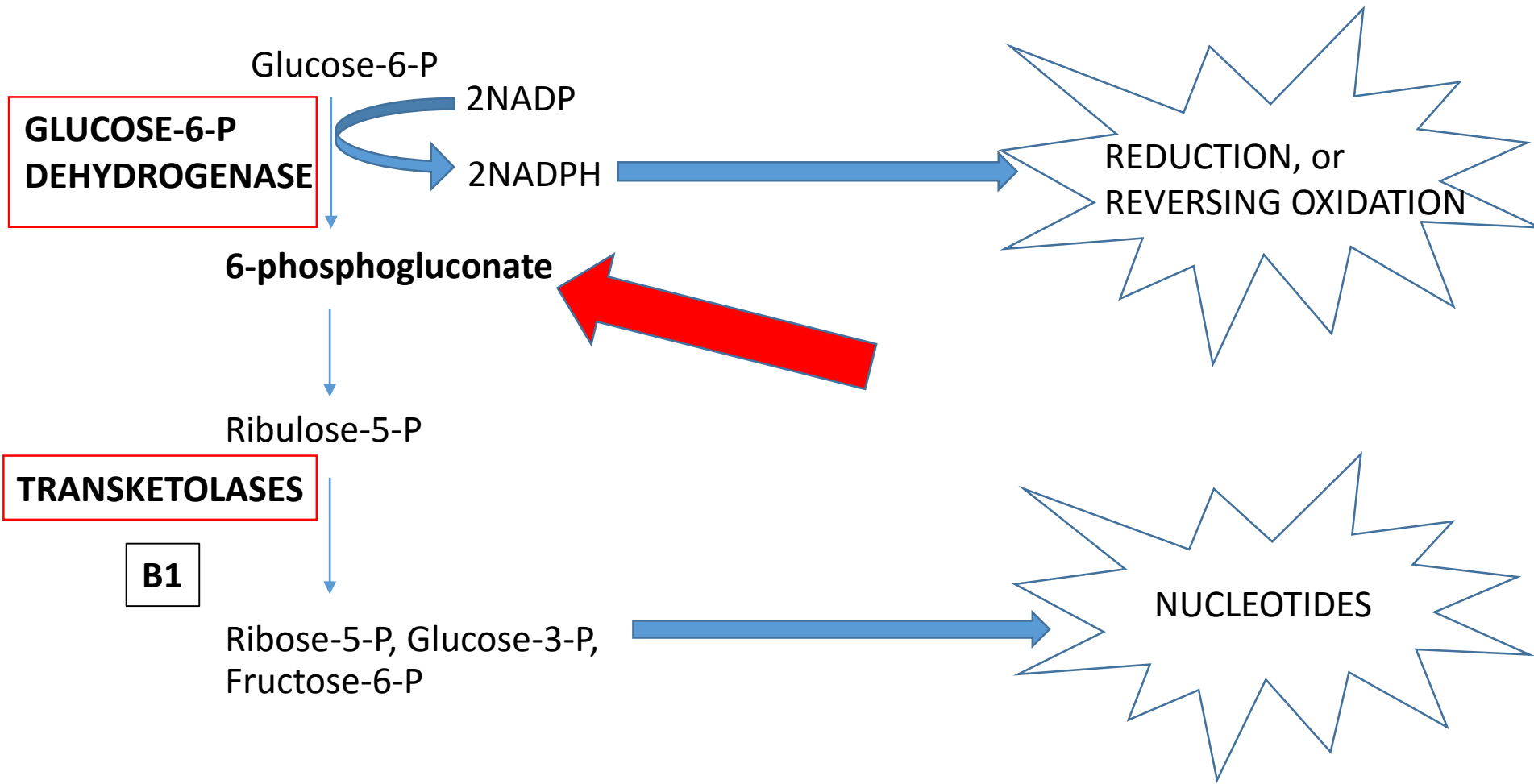


BONUS QUESTION: What vitamin is needed for this reaction? Who is typically deficient?

A 35 year old man is diagnosed with a superficial skin infection and is prescribed antibiotics. His infection begins to clear, but three days later he returns to the office complaining of fatigue and dark urine. Labs reveal mildly decreased hemoglobin with elevated serum LDH. Peripheral smear shows abnormal red blood cells. Which of the following substrate pathways for Glucose-6-Phosphate is most likely abnormal in this patient?

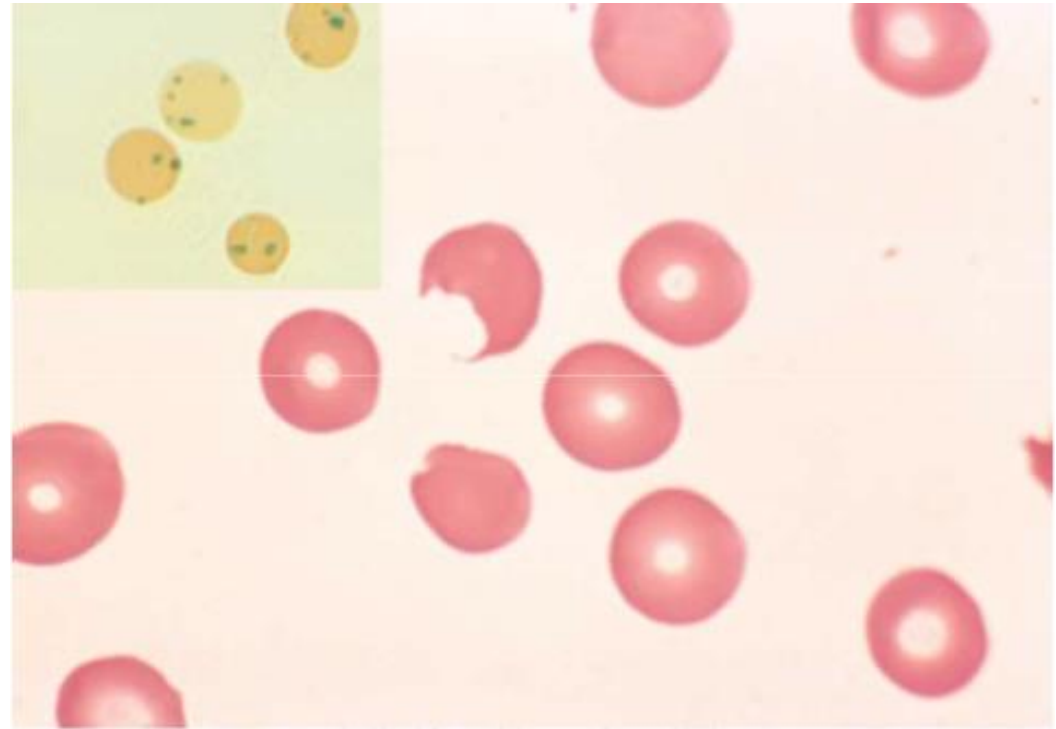
- A)
- B)
- C)
- D)
- E)





A man with recent travel to sub-Saharan Africa is diagnosed with malaria and started on the appropriate therapy. Shortly thereafter he begins to have complaints of intermittent fatigue and dark urine. Findings on peripheral blood smear are shown below. A loss of function mutation in what enzyme would produce similar results?

- A) Glucokinase
- B) Spectrin
- C) Glutathione reductase
- D) Pyruvate kinase
- E) Pyruvate dehydrogenase



A 35 year old Moroccan man presents to the emergency department complaining of 3 days of weakness. Mucosal pallor and mild scleral icterus are noted on physical exam. His wife recently returned from a trip to Ethiopia and the two have been sharing meals made with fruits, beans, and other vegetables that she brought back with her, though she currently reports no symptoms. Findings on peripheral blood smear are shown below. What accounts for the structures found within the patient's red blood cells, indicated by the arrow?

- A) Basophilic Stippling
- B) Excess iron in macrophages
- C) Mechanical hemolysis
- D) Functional asplenia
- E) Accumulation of denatured hemoglobin

