مصادر المحاضرة ٧

Sources of Lecture 7

(Metabolism in mature erythrocyte & Genetic Deficiences)

1- Supplement from Marks on Erythrocyte metabolism (2 pages) will be supplied

2- slides :- will be supplied

3- Lippincot [chapter, Pentose phosphate Pathway (chap 13)]

V- Glucose-6-P Dehydrogenase deficiency

Pages 152 - 154

4. Pyruvate kinas Deficiency

chapter 8 (Glycolysis)

Pages 102 - 103

Please note, the slides that appear v. dark after photo copy are all from your book Lippincot. You can see them clearly in the book.

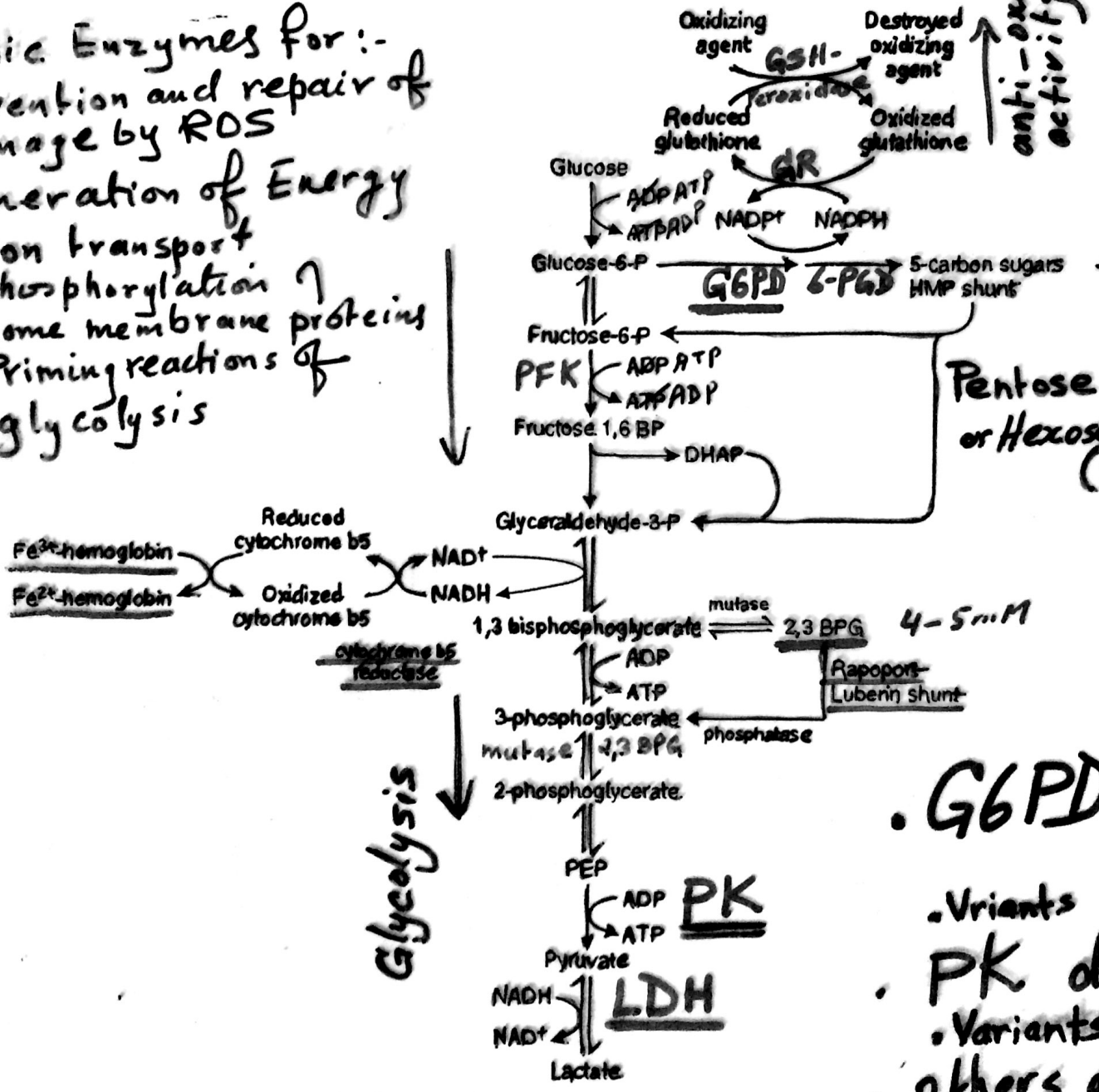
Erythrocyte Metabolism

Metabolic Enzymes for :-

1- Prevention and repair of damage by ROS

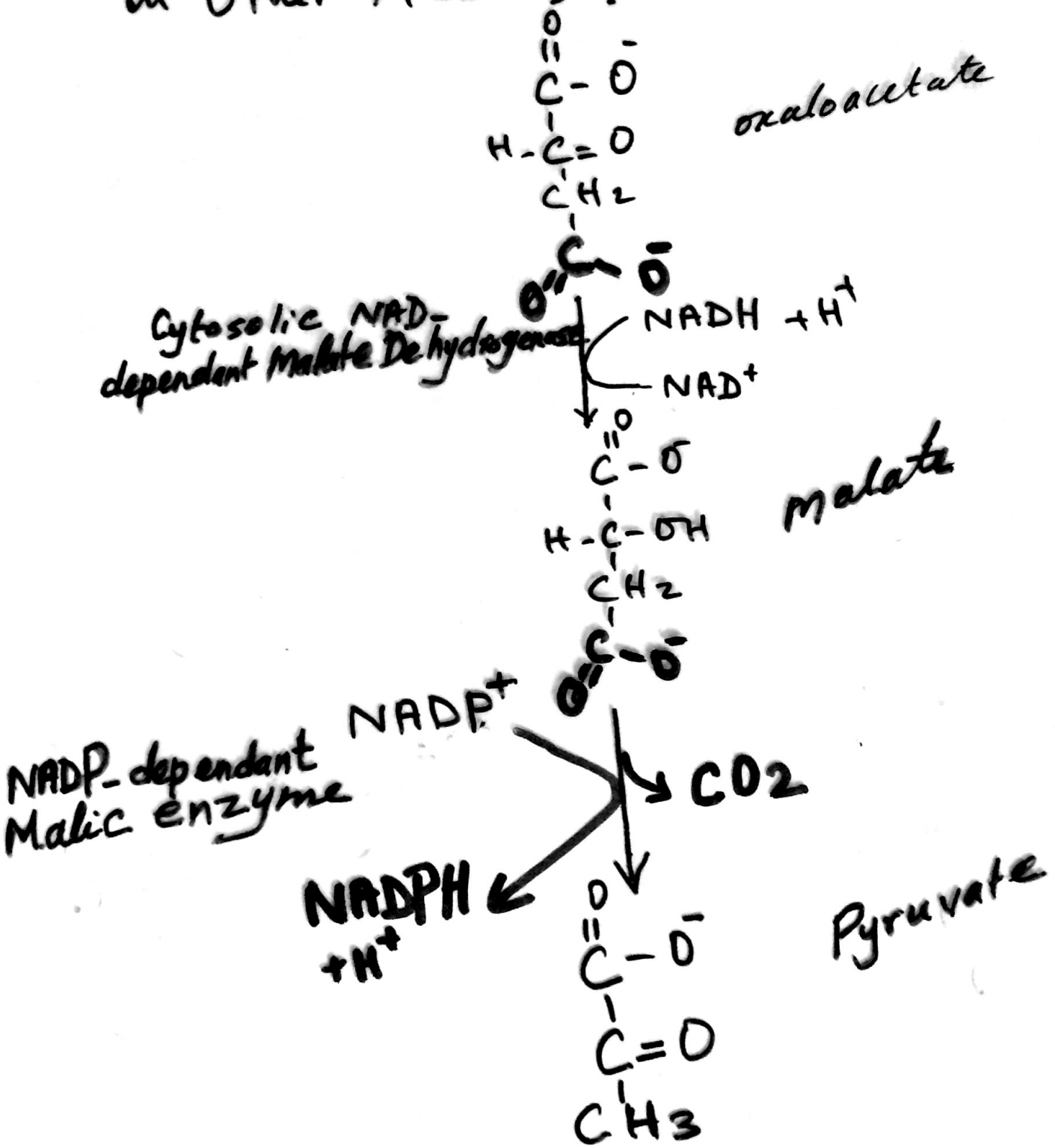
2- Generation of Energy

- Ion transport
- phosphorylation of some membrane proteins
- Priming reactions of glycolysis



- G6PD deficiency ~ 200-400 millions
  - Vriants
- PK deficiency (rare)
  - Variants
- others are v. rare

Alternative Sources of NADPH in Other Tissues :-

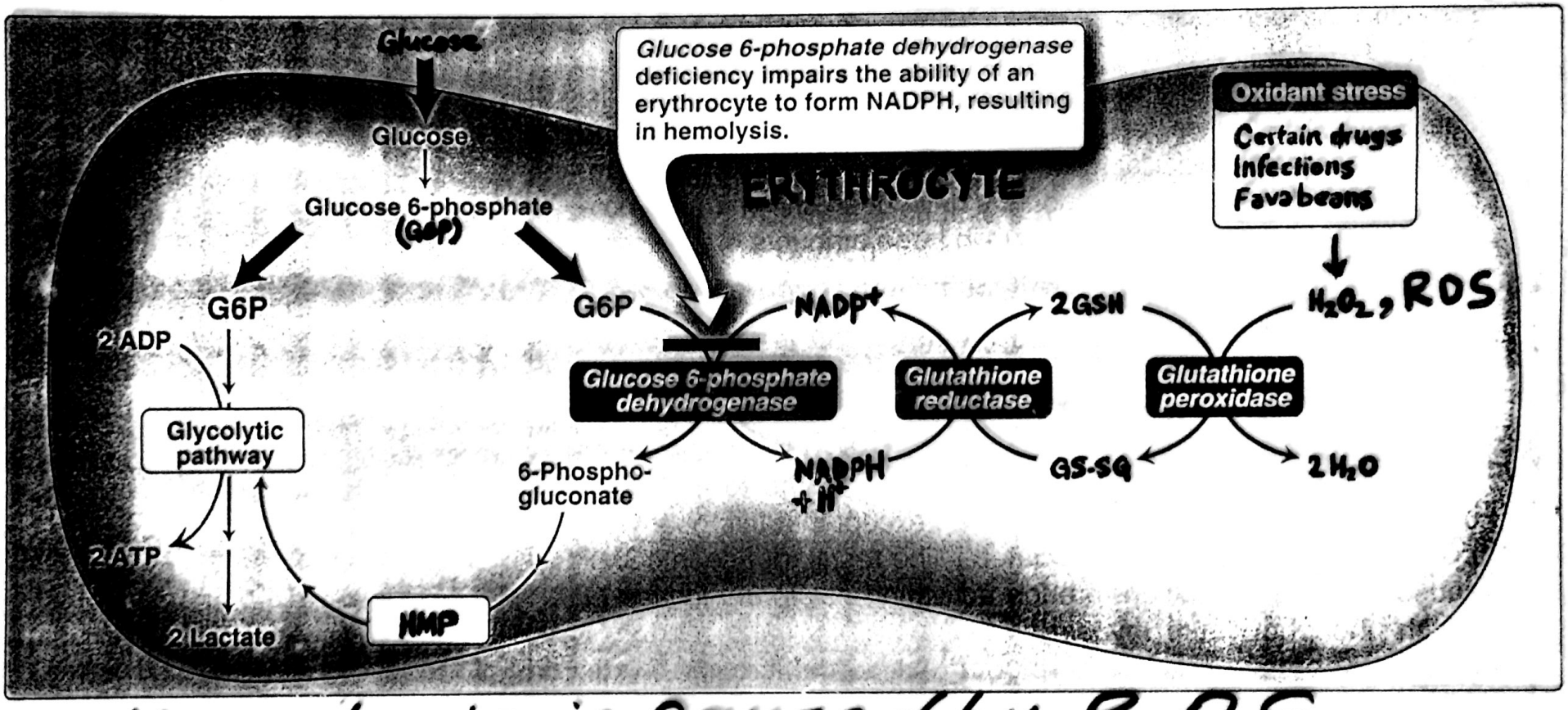


G6PD DEFICIENCY

- Introduction
  - location of the gene
- Geographic Prevelance of G6PD Deficiency
  - Middle East
  - Tropical Africa & Asia
  - Parts of Mediterranean
- Clinical Symptoms
  - Resistance to Malaria
- Role of G6PD in Red Blood Cells
  - $\Longrightarrow$ NADPH
    - Anti-oxidant
    - Heinz Bodies in deficiency
    - Oxd of membrane proteins $\longrightarrow$ rigid & nondeformable

G6PD Deficiency

Pathways of G6P metabolism in the erythrocyte

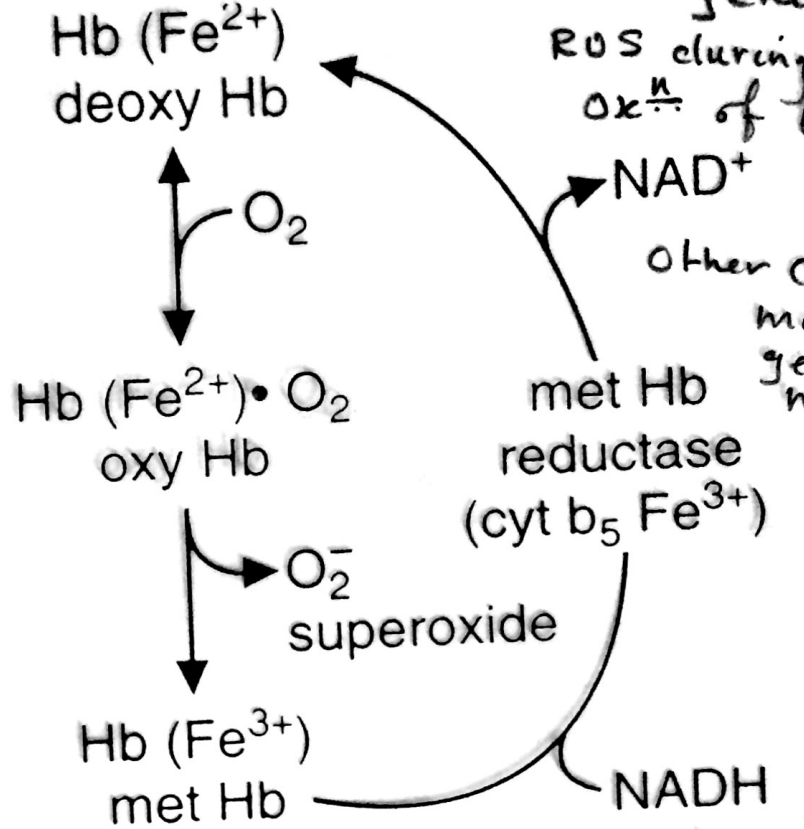


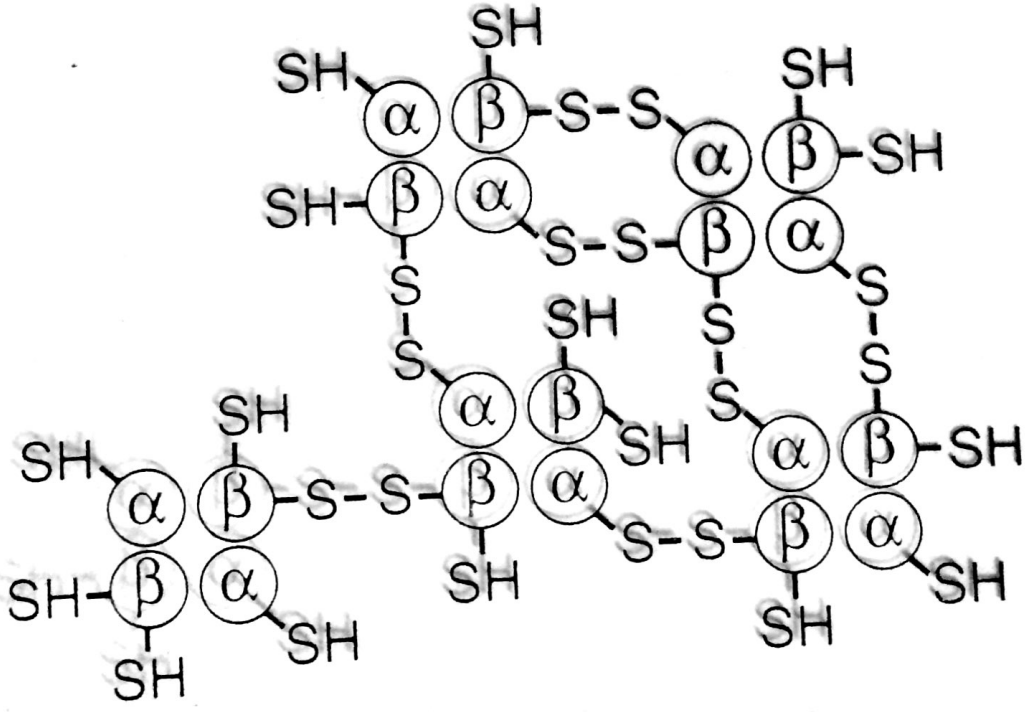
Hemolysis is caused by ROS

Formation of Heinz-bodies in red blood cell

rbc generates O_2^- and ROS during non-enzymatic ox^n of Hb → Met Hb

Other cells :- most ROS is generated in mitochondria





Cross-linked hemoglobin in Heinz bodies

- Precipitating Factors in G6PD Deficiency :-

1- Oxidant Drugs

AAA

A: antibiotic e.g. sulfamethoxazole, chloramphenicol

A: Antimalaria primaquine

A: Antipyretics

Acetanalid, but not acetaminophen

2- **Favisim** — Fava beans → Contain the glycosides: vicine + convicine

Produce → dericine ×

the aglycones → isouramil ×

3- **Infection** × oxidants cause rapid decline in GSH

4- **Neonatal jaundice**

- Properties of the Variant Enzymes

- Molecular Biology of G6PD

Majority missense mutation → Point mutations

Large deletions or frameshift mutations → not observed

(B) Med. 563 C → T 188 ser → phe

A^+ → 376 A → G, 126 Asn → Asp

A^- → 376 A → G + 202 G → A, 126 Asn → Asp, 68 Val → Met

Properties of the G6PD Variant Enzymes

1- Classification of G6PD Variants

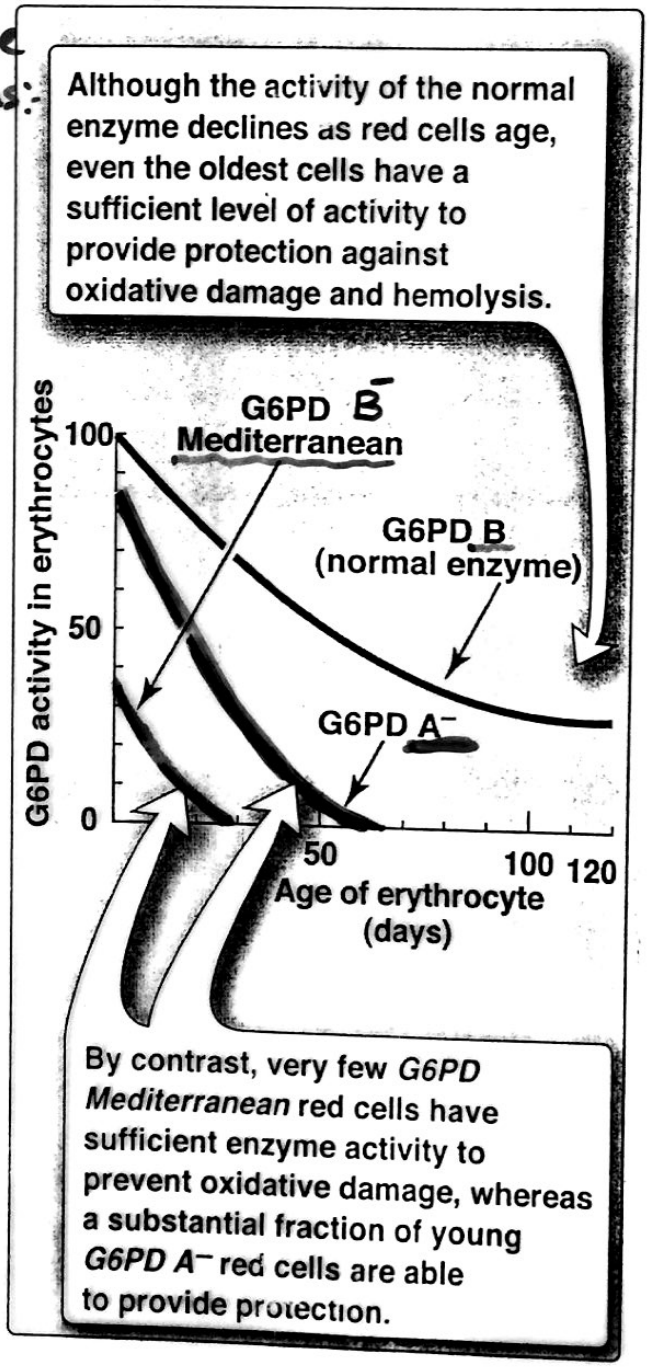
Class	Clinical symptoms	Residual enzyme activity
I	Very severe	<2%
II	Severe	<10%
III	Moderate	10–50%
IV	None	60–150%

→ Chronic nonspherocytic hemolytic anemia CNSHA

e.g. → Med. Variant B⁻

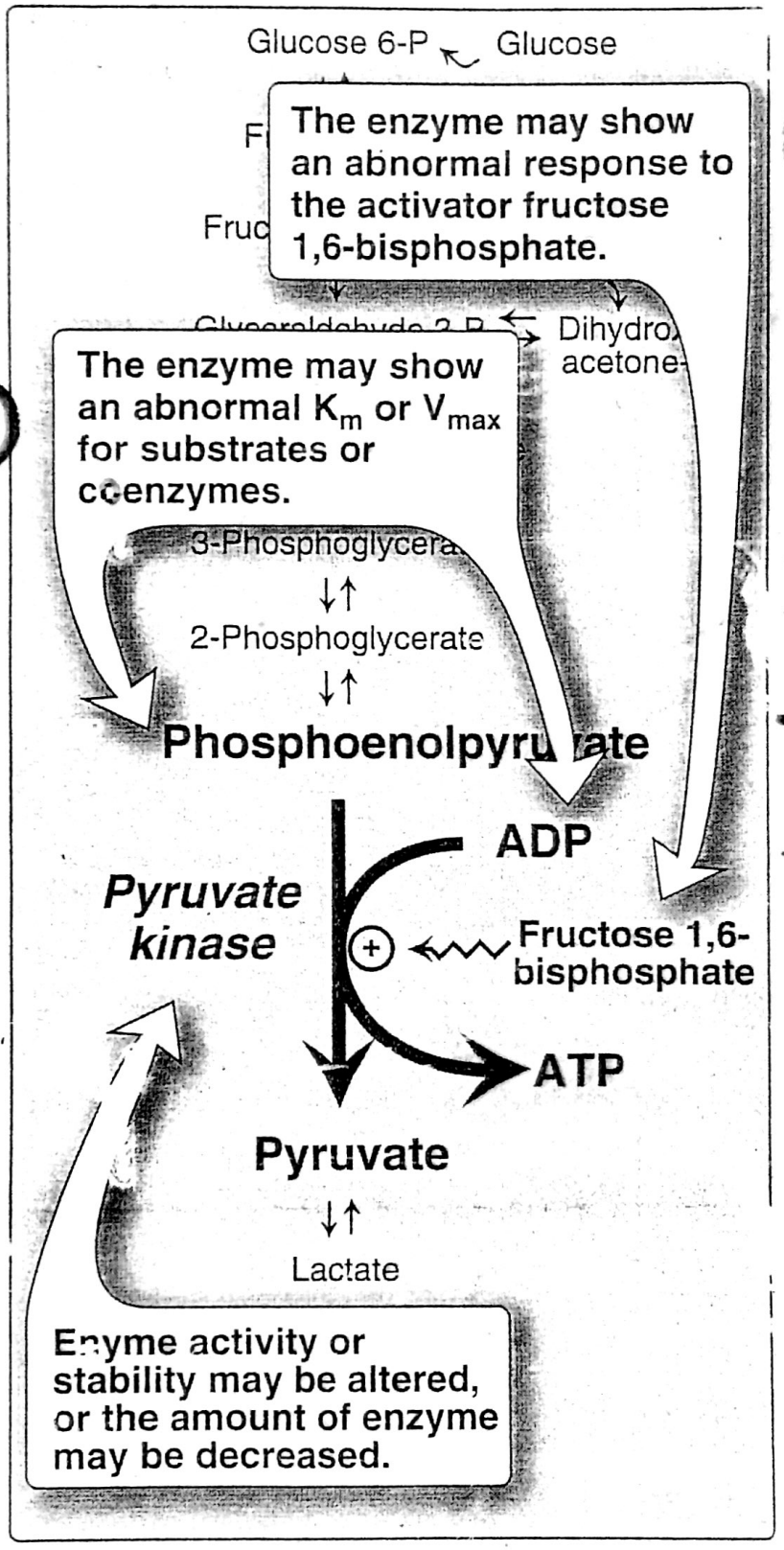
→ e.g. A⁻ (African)

2- Decline of erythrocyte G6PD activity with cell age for three most common forms:



- Pyruvate Kinase Deficiency

95% of glycolytic enz deficiency cases



- Severe deficiency requires blood transfusion

→↑ 2,3-BPG

→↓ ATP

- PGI (4% of glycolytic cases)

Prenatal Detection of HbS

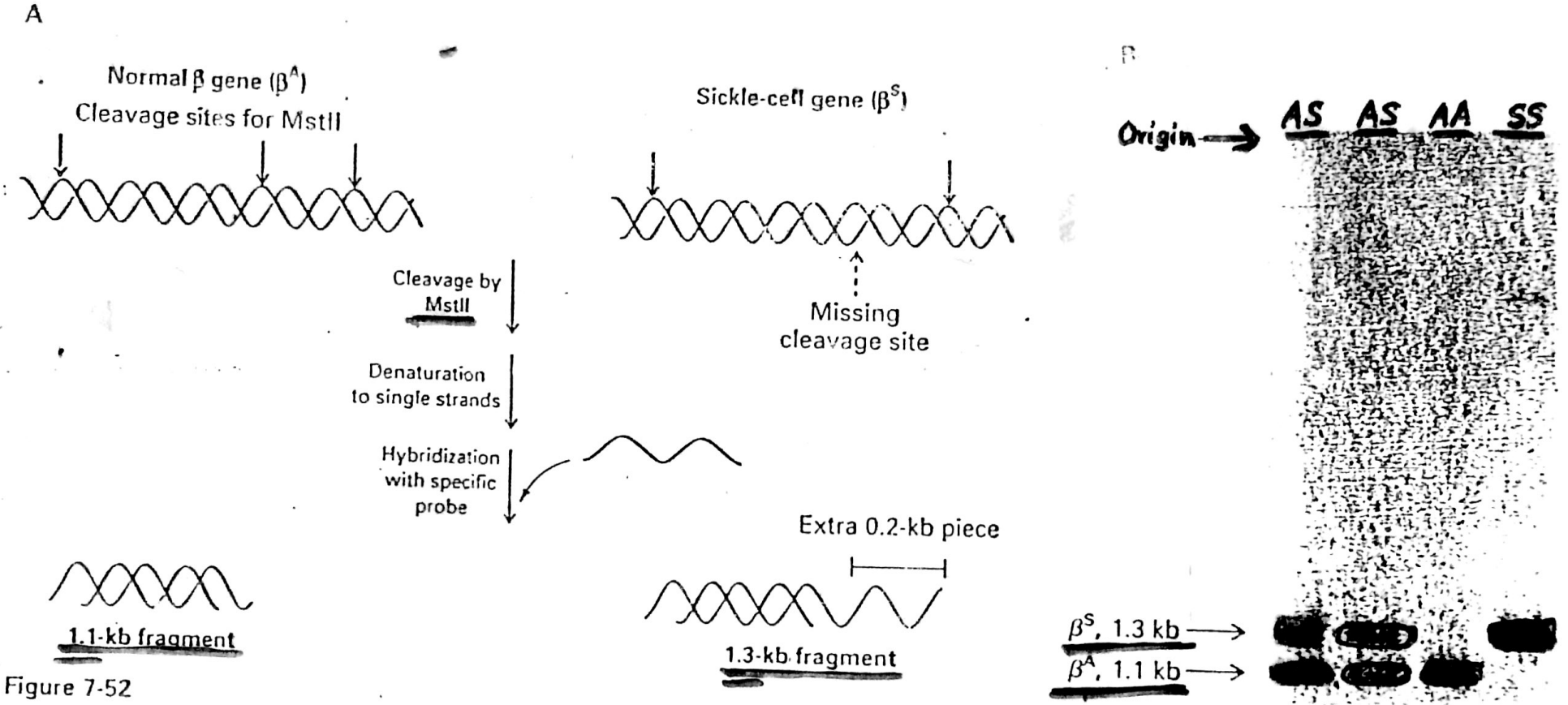


Figure 7-52
Restriction endonuclease method for detecting the sickle-cell gene. (A) Target site in the gene and fragments produced by digestion. (B) Electrophoretic pattern of a digest from parents who are heterozygous for the gene (lanes labeled *AS*), a normal child (*AA*), and a child with sickle-cell anemia (*SS*). [Part B is from Y.-W. Kan. In *Medicine, Science, and Society*, K.J. Isselbacher, ed (Wiley, 1984), p. 297.]