Global Action Network for Sickle Cell and Other Inherited Blood Disorders

THE GLOBAL ACTION NETWORK FOR SICKLE CELL AND OTHER INHERITED BLOOD DISORDERS (GANSID) HOLDS A HIGH-LEVEL STAKEHOLDERS' MEETING.

AMPANG HOSPITAL, MALAYSIA
AUGUST 26-28, 2025

SPEAKERS:

Prof. Adekunle Adekile
Ms. Lanre Tunji-Ajayi, M.S.M

HEMOGLOBINOPATHIES

SPEAKER:

Prof. Adekunle Adekile

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OUTLINE

- **STRUCTURE & FUNCTION OF HEMOGLOBIN**
- **GENETICS**
  - **Inheritance**
  - **Human globin genes**
    - Structure
- **GENE ACTION AND GLOBIN SYNTHESIS**
- **HB SWITCHING**
- **MOLECULAR PATHOLOGY OF HB DISORDERS**
- **α -THALASSEMIA**
- **β -THALASSEMIA**
- **SICKLE CELL ANEMIA**

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INTRODUCTION

Hemoglobinopathies are the commonest monogenic diseases in the world

Inherited as autosomal recessive traits

>5% of world population carry genes for clinically-significant disorders of Hb

Cause significant morbidity

Human globin genes were the first to be cloned; therefore they constitute the first “molecular disease’

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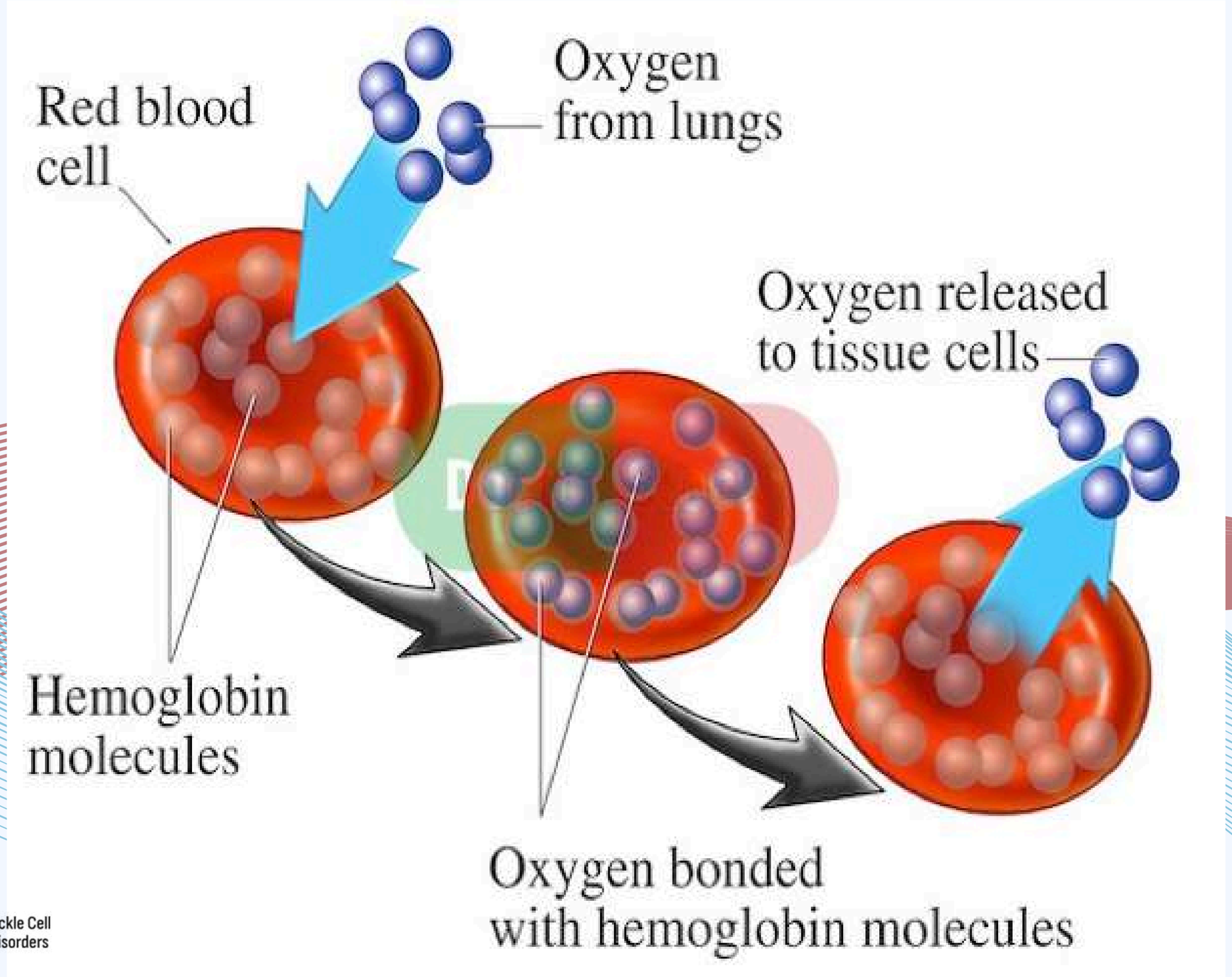
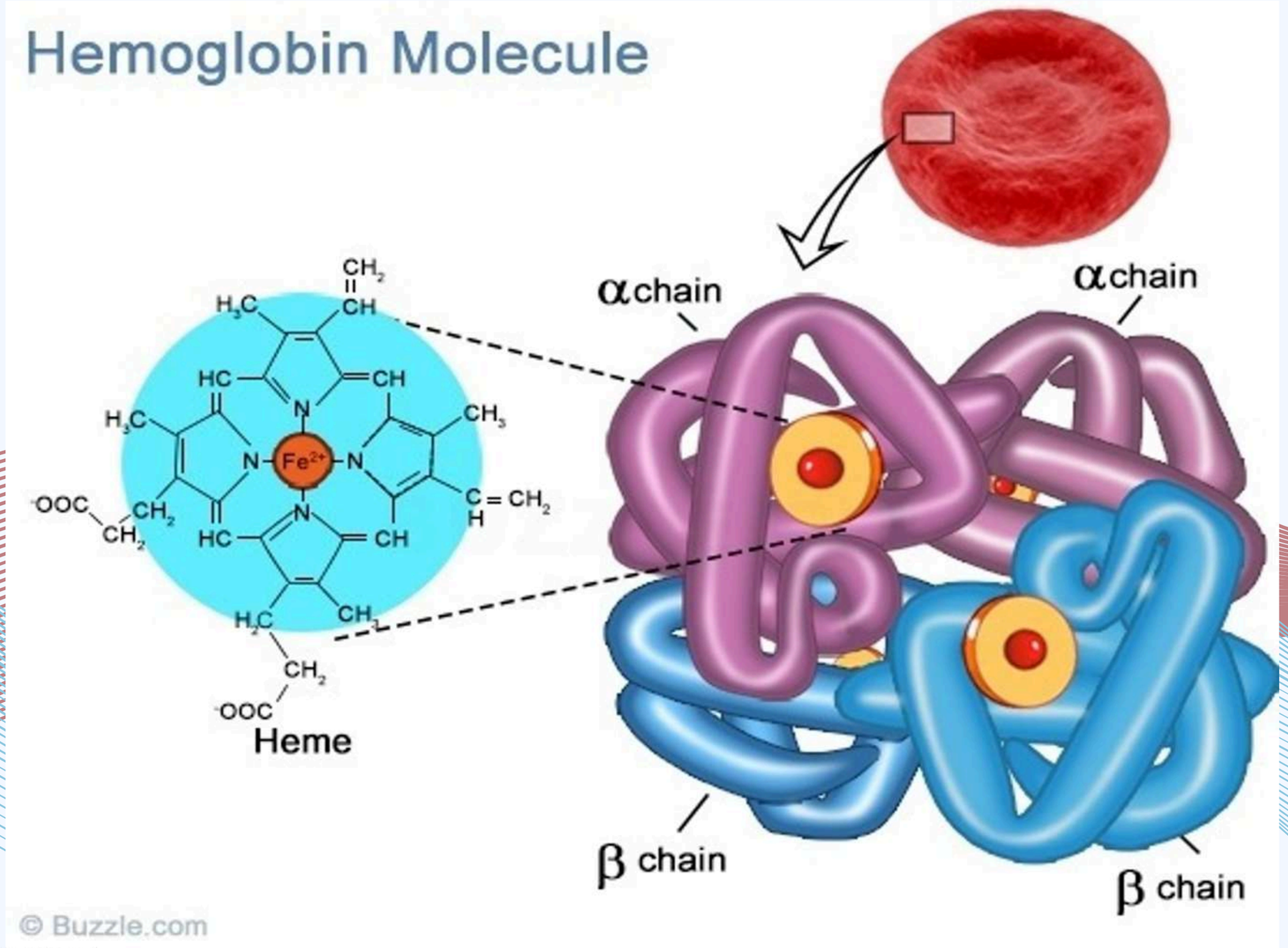

Red blood cell
Oxygen from lungs
Oxygen released to tissue cells
Hemoglobin molecules
Oxygen bonded with hemoglobin molecules

STRUCTURE AND FUNCTION OF HB

- Hb is the O_2-carrying molecule in vertebrate red blood cells
- Contains 4 subunits – 2 α and 2 β chains
  - Each is composed of a polypeptide chain, globin and a prosthetic group, heme, which is an Fe-containing pigment that combines reversibly with O_2

Hemoglobin Molecule



STRUCTURE AND FUNCTION OF HB (CONT.)

- O_2 requirements vary during embryonic, fetal and adult life
- This is reflected in the different Hbs synthesized at different developmental stages
- Adult and fetal Hbs:
  - HbA, $\alpha_2\beta_2$; Hb A_2, $\alpha_2\delta_2$; Hb F, $\alpha_2\gamma_2$
- Embryonic Hbs:
  - Hb Portland, $\zeta_2\gamma_2$; Hb Gower 1, $\zeta_2\varepsilon_2$; Hb Gower 2, $\alpha_2\varepsilon_2$

STRUCTURE AND FUNCTION OF HB (CONT.)

- α-globin (and α-like) chain consists of 141 amino acids, while β and β-like chains have 146
- They are similar both in amino acid sequence (primary structure) and in 3-dimensional configuration (tertiary structure)
- The α and the β chains are encoded by genes on different loci

HUMAN GLOBIN GENES

- The α-like globin genes form a linked cluster located on chromosome 16:
    - 5’ -ζ-ψζ-ψα1-α2-α1-3’
- The β-like genes are located in a cluster on chromosome 11:
    - 5’ -ε-^{G}γ-^{A}γ-ψβ-δ-β-3’
- The ψζ, ψα1 and ψβ are pseudo genes and have no known coding function

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GENE STRUCTURE CONTD

- The α- and the β-like genes consist of 3 coding regions (exons) and 2 intervening sequences (introns)
- These, together with short non-coding sequences at the 5’ and 3’ ends of the genes form the major functional regions of the particular genes
- Additional important regulatory sequences lie outside the genes themselves

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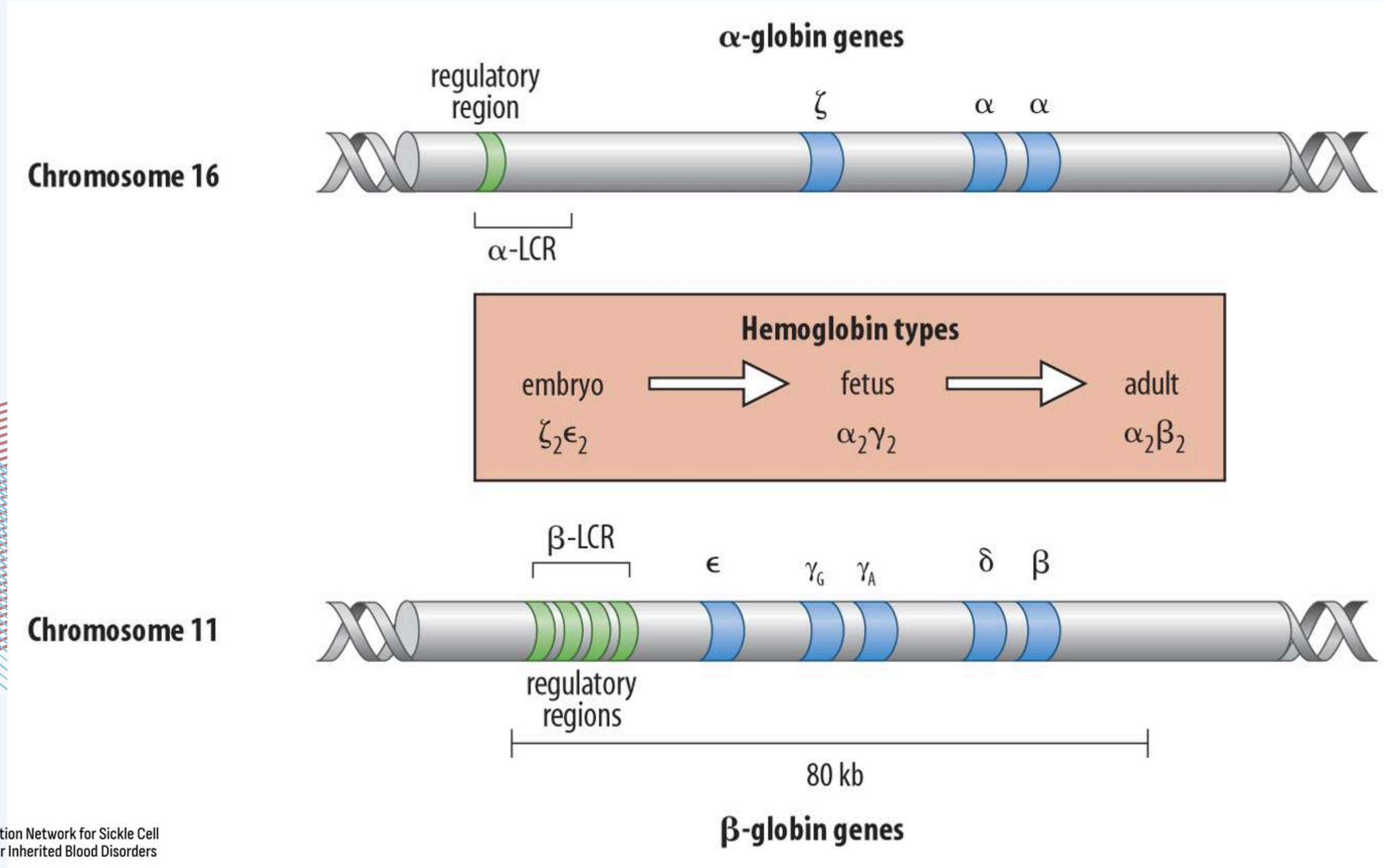

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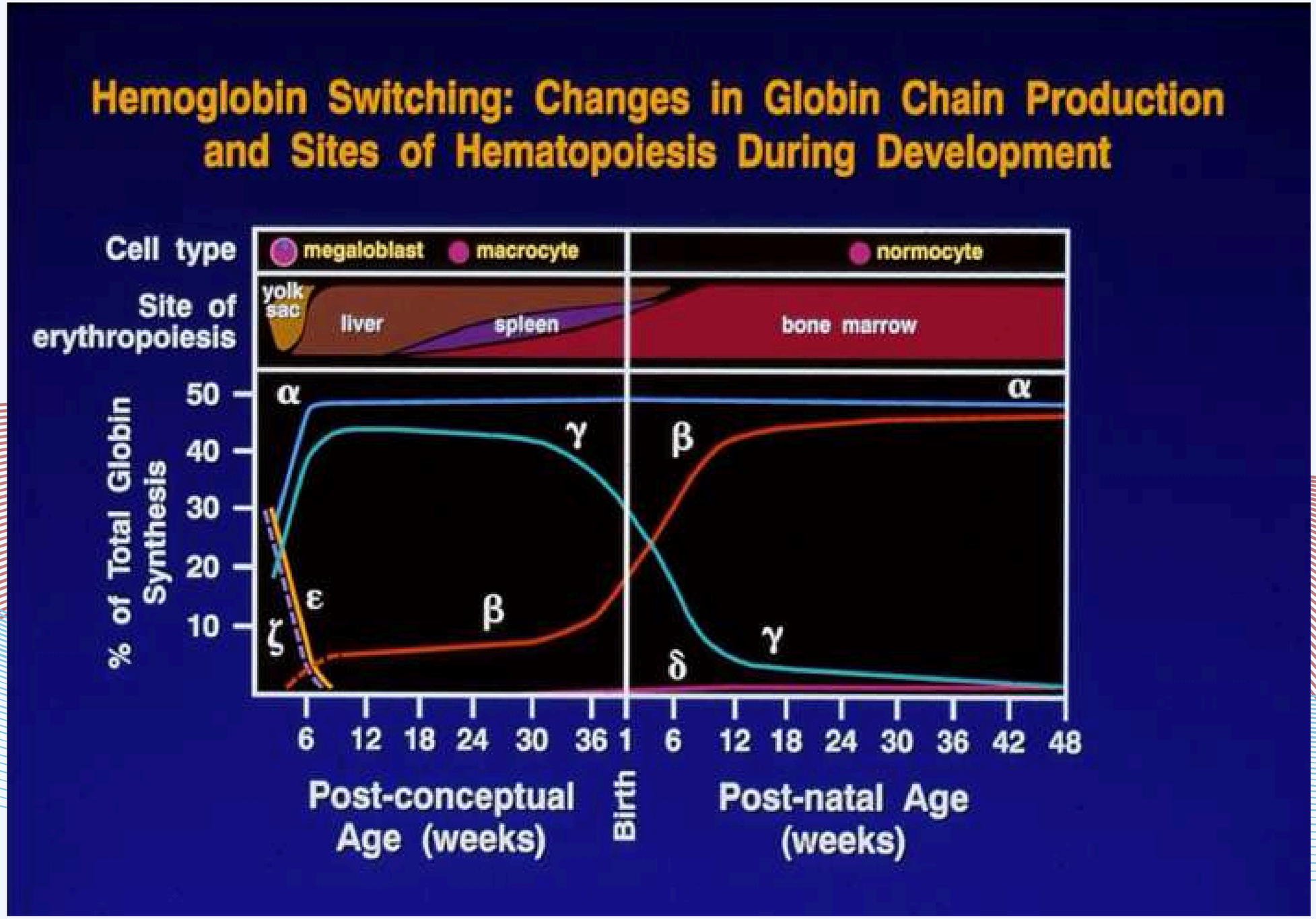
Hemoglobin Switching: Changes in Globin Chain Production and Sites of Hematopoiesis During Development



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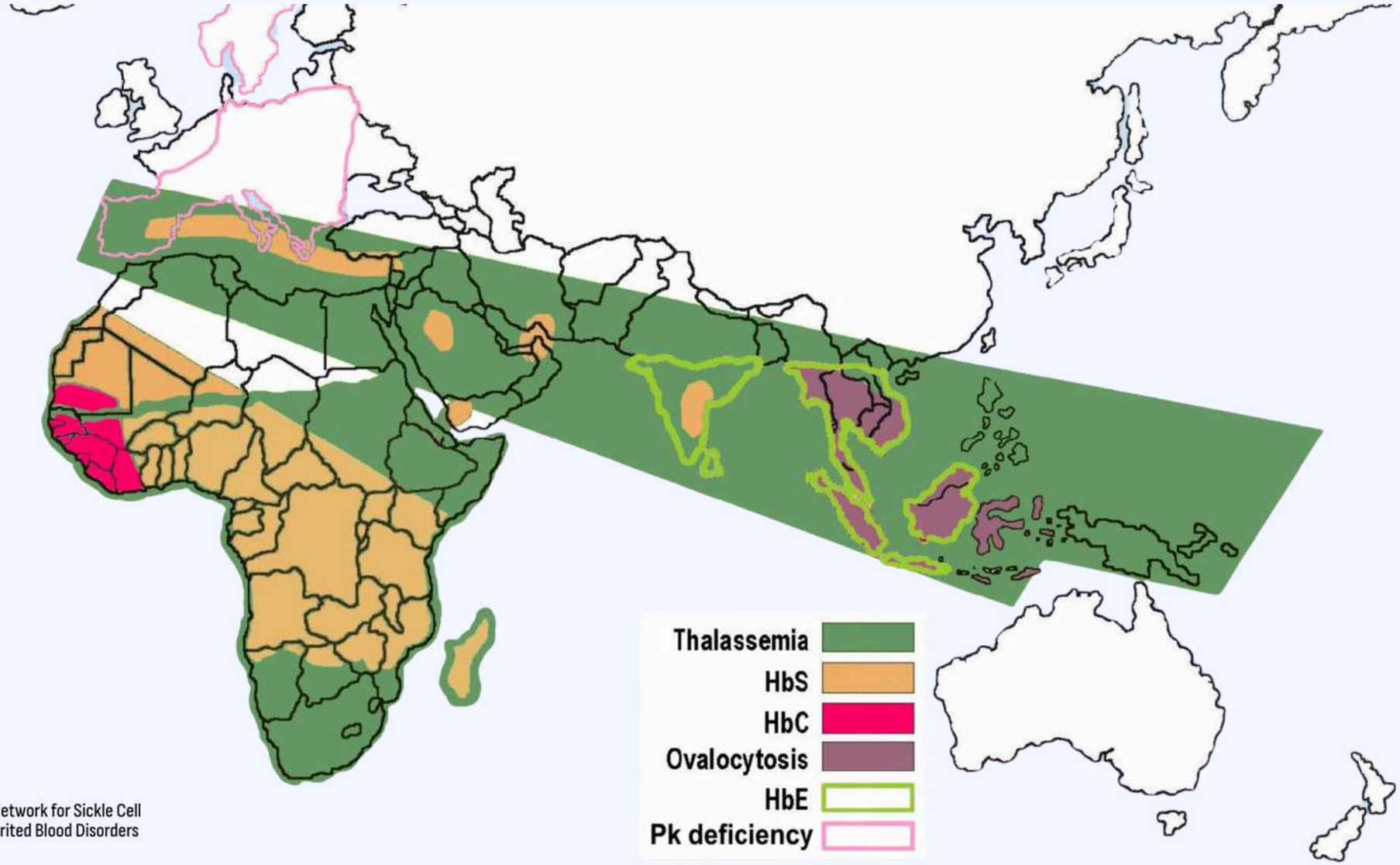
MOLECULAR PATHOLOGY OF HEMOGLOBIN DISORDERS

- Inherited disorders may be:
  - Reduced output of one or other globin genes
    - Thalassemia
  - Production of structurally abnormal globin chains
    - Type of disease depends on how this alteration affects Hb stability or function
  - Structural Hb variants may be synthesized at reduced rate (e.g. Hb E)
  - Disturbed transition from fetal to adult Hb
    - Hereditary persistence of fetal Hb (HPFH)

DISTRIBUTION OF SOME CLINICALLY SIGNIFICANT HB VARIANTS



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MOLECULAR PATHOLOGY OF THE α THALASSEMIAS

- Normal α-globin genotype
  - αα/αα
- Two major types of α-thalassemia
  - α^{+}
    - One of the linked α genes is lost through deletion (-) or mutation (T)
    - Heterozygous is -α/αα or α^{T}α/αα respectively
    - Homozygous is -α/-α or α^{T}α/α^{T}α respectively
  - α^{0}
    - Loss of the two genes usually results from a deletion
    - Heterozygote is --/αα
      - In populations where a specific deletion is common, add a superscript: $--^{SEA}$/αα or $--^{MED}$/αα for Southeast Asia and Mediterranean respectively
    - Homozygote is --/--; results in hydrops fetalis

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ALPHA-GLOBIN GENOTYPES AND CLINICAL SYNDROMES

Genotype	Clinical Syndrome
-a/aa	Silent carrier or alpha thal minor; a+ thal trait *(mild microcytic, hypochromic anemia)*
-a/-a --/aa	Homozygous a+ thal or a0 thal trait (*mild – moderate anemia*)
--/-a	Hemoglobin H disease *(moderate to severe anemia)*
--/--	Hydrops fetalis or homozygous alpha thalassemia; Barts hemoglobin *(incompatible with life)*

THE β THALASSEMIAS

- There are 2 main classes:
  - β^0 thalassemia
    - Absence of β-globin chain
  - β^+ thalassemia
    - Variable reduction in production of β-globin chain
- Mutations in the β-globin gene may cause reduced synthesis at the level of:
  - Transcription or mRNA processing
  - Translation
  - Stability of globin gene product

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DEFECTIVE β-GLOBIN GENE TRANSCRIPTION

- Mechanisms:
  - Complete or partial deletion
    - Not common except for 619 bp del found in Indians
  - Mutations in the TATA box area close to transcription start site or in the proximal or distal promoter elements
    - Usually associated with mild thalassemia

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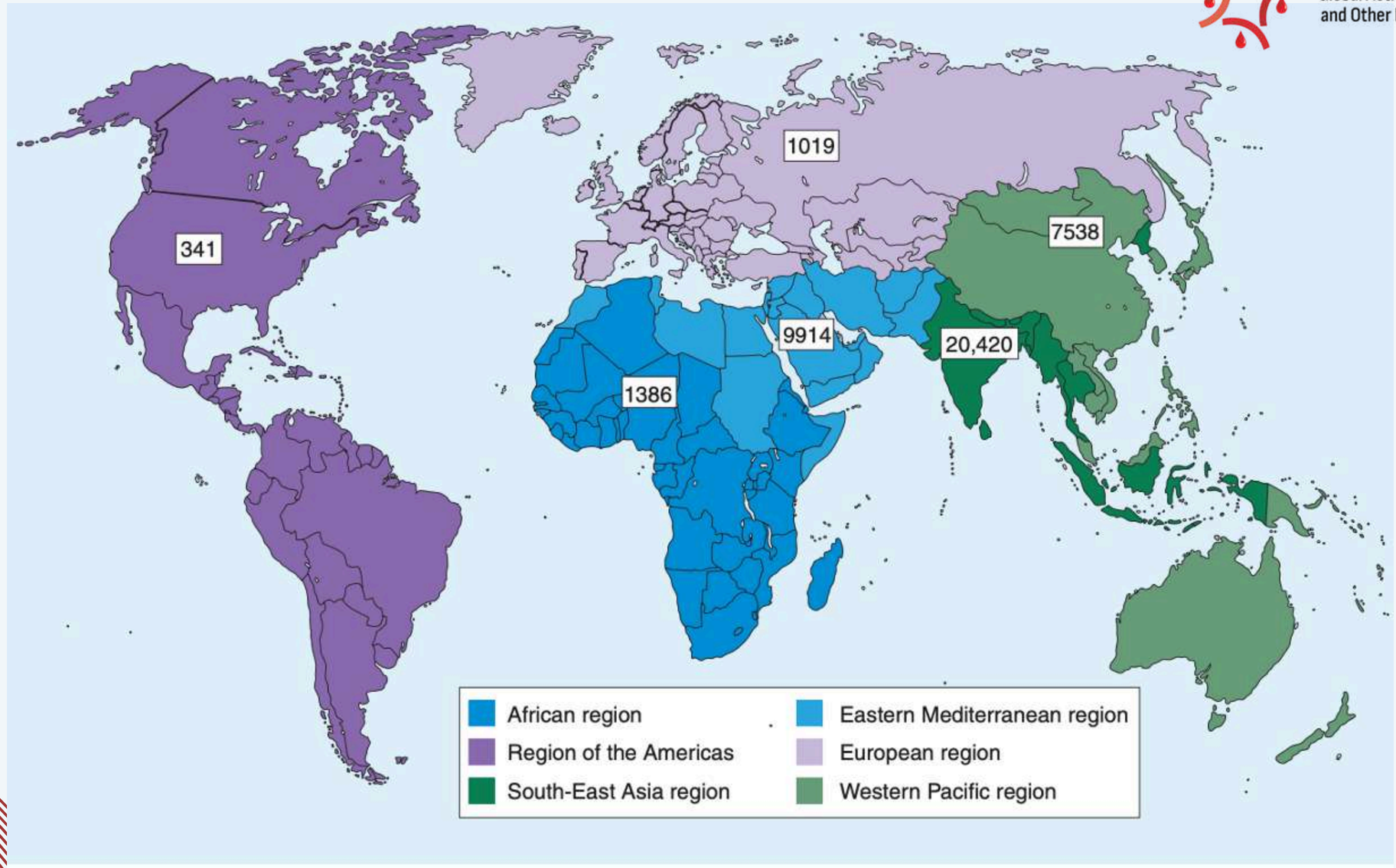

Figure 1. Estimated annual affected births of children with β-thalassemia.
These figures are from estimates calculated in [16].

Colah et al: Expert Rev. Hematol. 3(1), 103–117 (2010)

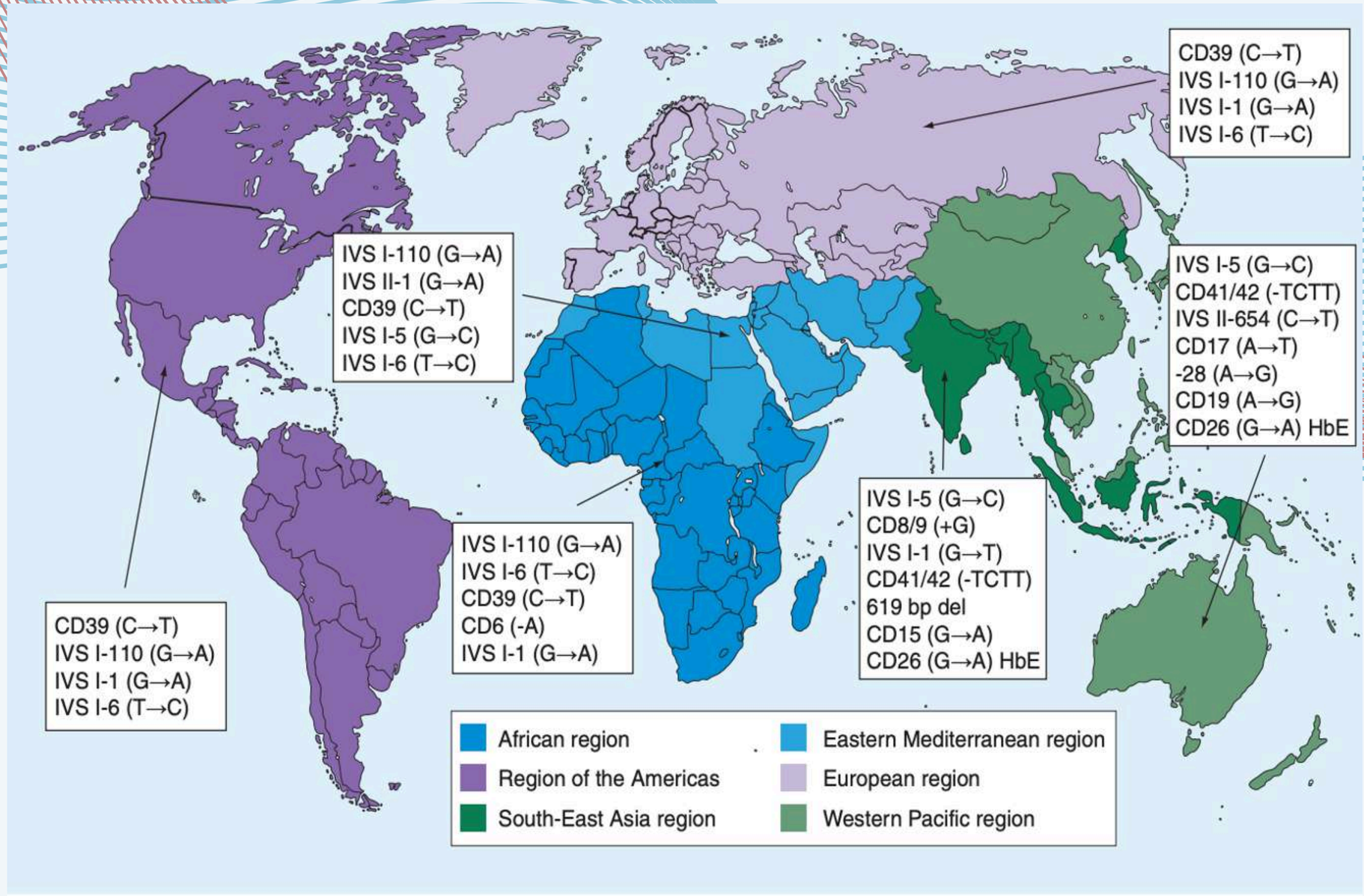

Figure 3. Common β-thalassemia mutations in different regions of the world.

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Colah et al: Expert Rev. Hematol. 3(1), 103–117 (2010)

β THALASSEMIA TRAIT

- Heterozygosity for β^0 or β^+ Thalassemia
- Clinically asymptomatic
- Mild anemia in some cases (Hb 10-11 g/dl)
- Elevated Hb A_2 (~5%)
- Mildly elevated Hb F in some cases (1-5%)
- α/non-α ratio (~2.0)

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β THALASSEMIA INTERMEDIA

- Moderately severe anemia with variable transfusion requirement
- Hepatosplenomegaly with development of hypersplenism
- Skeletal deformities/abnormalities
- Extramedullary hematopoiesis
- Survival into adulthood

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β THALASSEMIA MAJOR

- Homozygosity or compound heterozygosity for various β^0 and β^+ thalassemia mutations
- Severe transfusion-dependent anemia at an early age (~3 months)
- Liver and spleen enlargement, growth retardation, delayed puberty, bony abnormalities
- Iron overload
- Death in second decade from intractable arrhythmias/CHF (untreated or undertreated cases)

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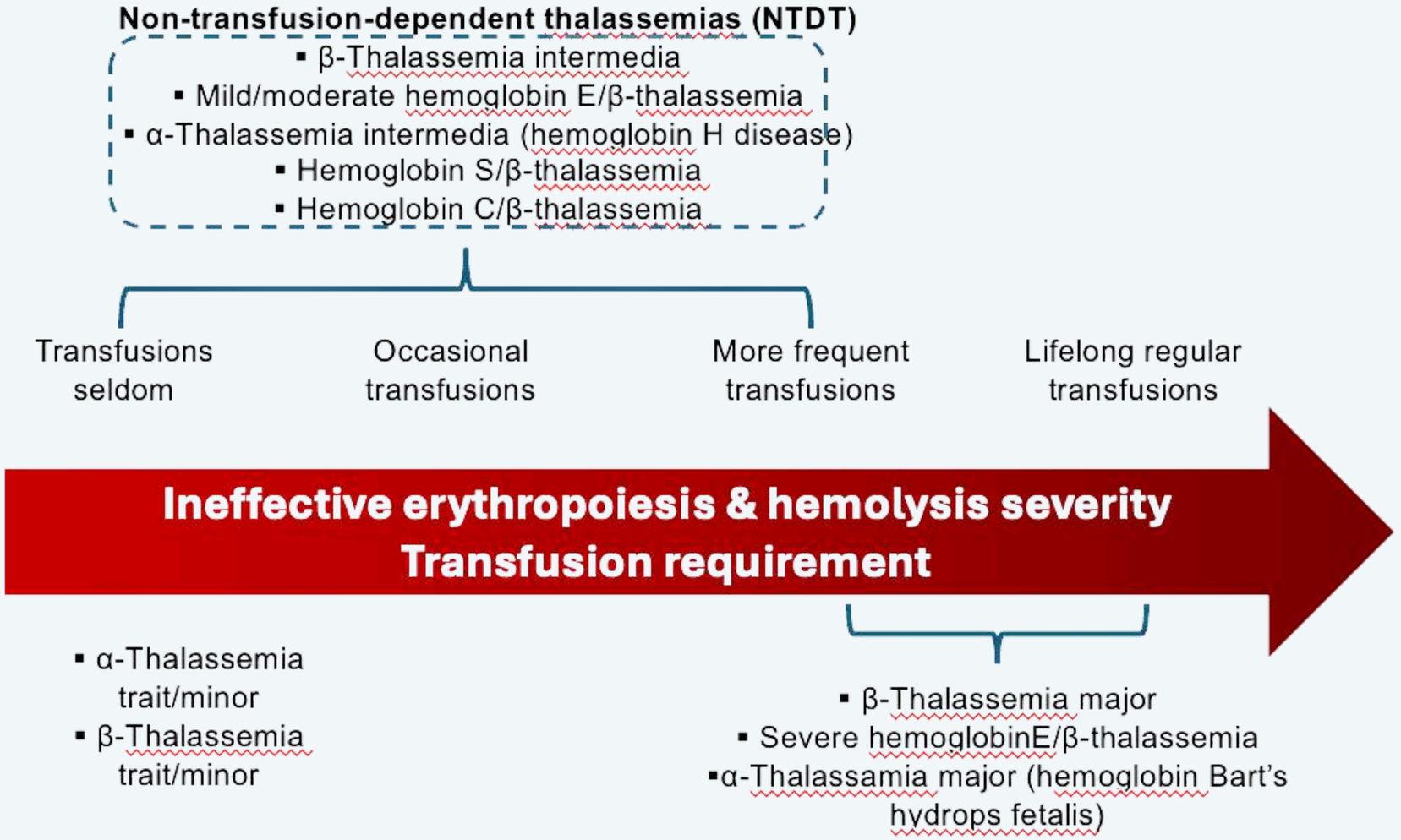
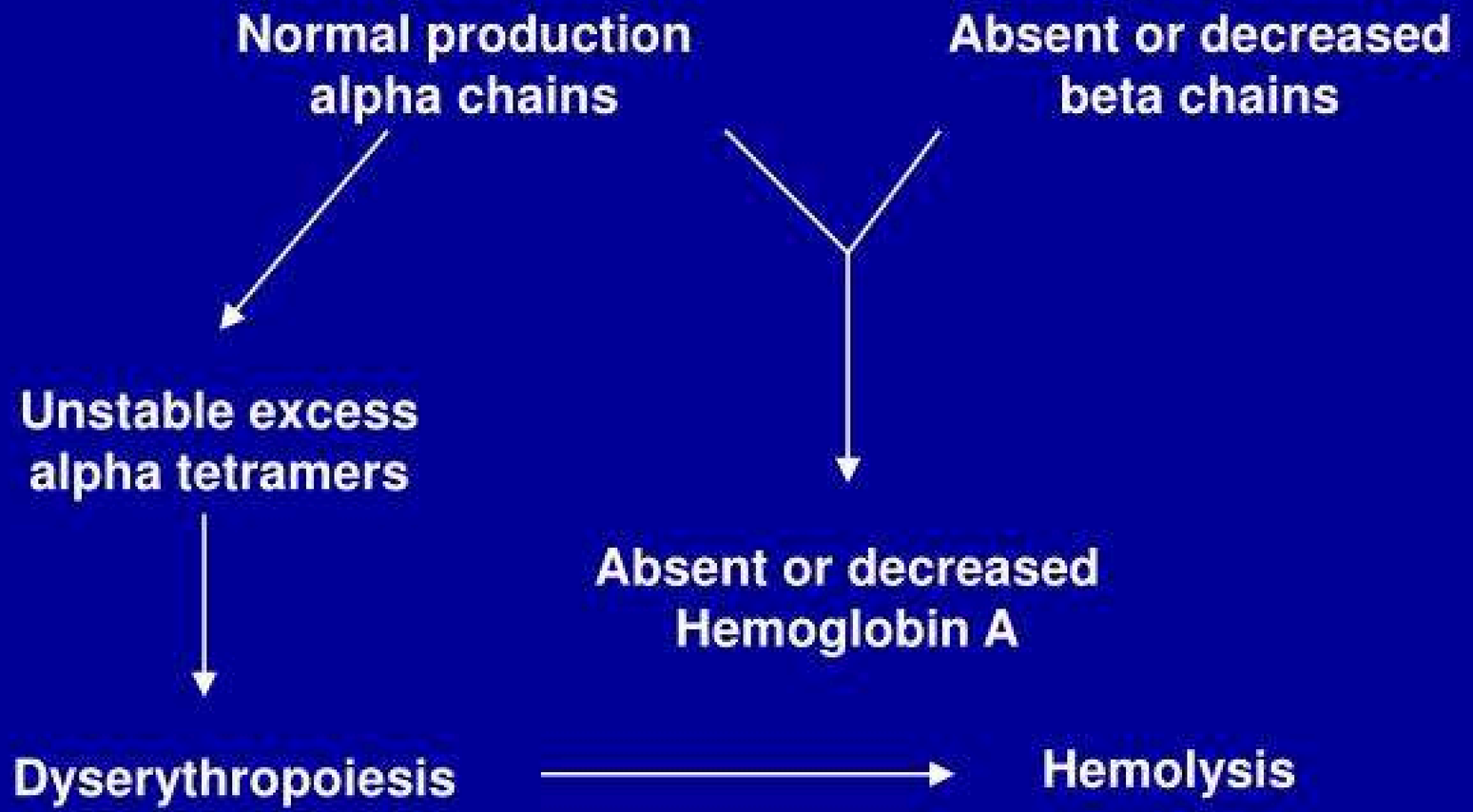
SPECTRUM OF TRANSFUSION REQUIREMENTS IN THE THALASSEMIAS



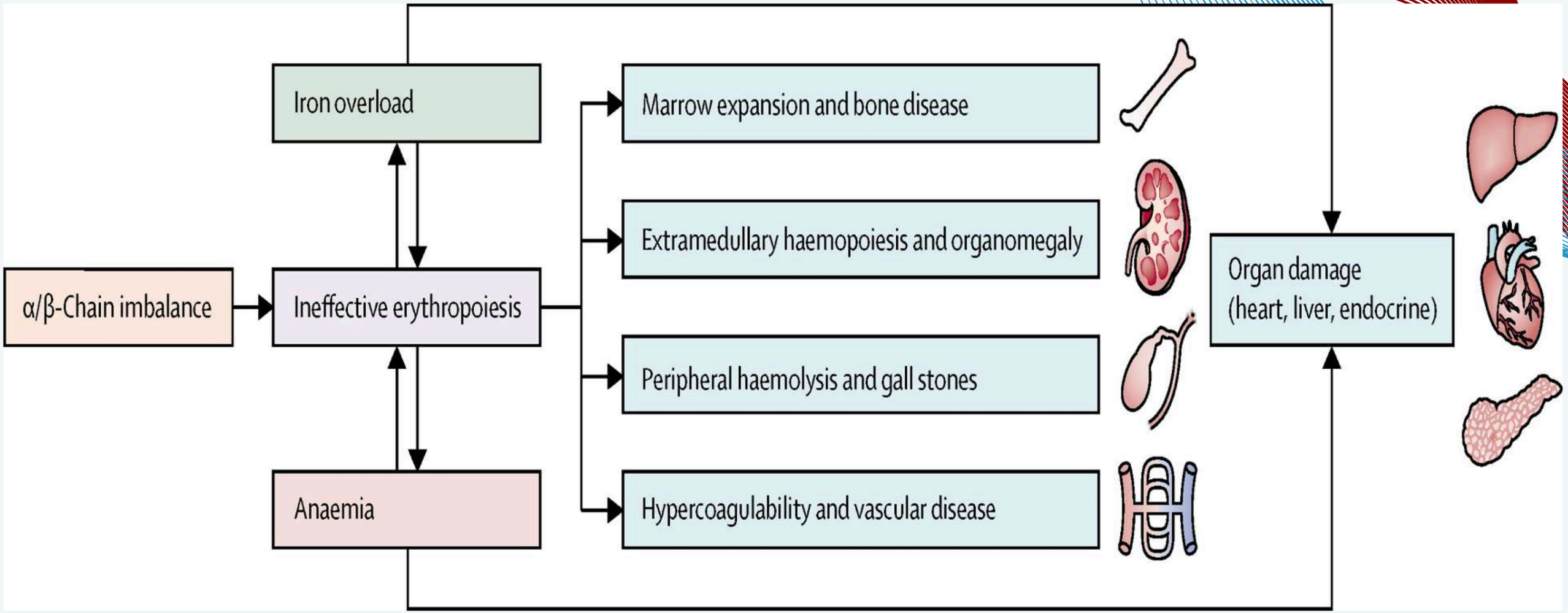
Musallam KM, et al. Haematologica. 2013;98:833-4.

Pathophysiology of Beta Thalassemia



Weatherall. *BMJ*. 1997;314:1675.
Olivieri et al. *N Engl J Med*. 1999;341:99.

PATHOPHYSIOLOGY



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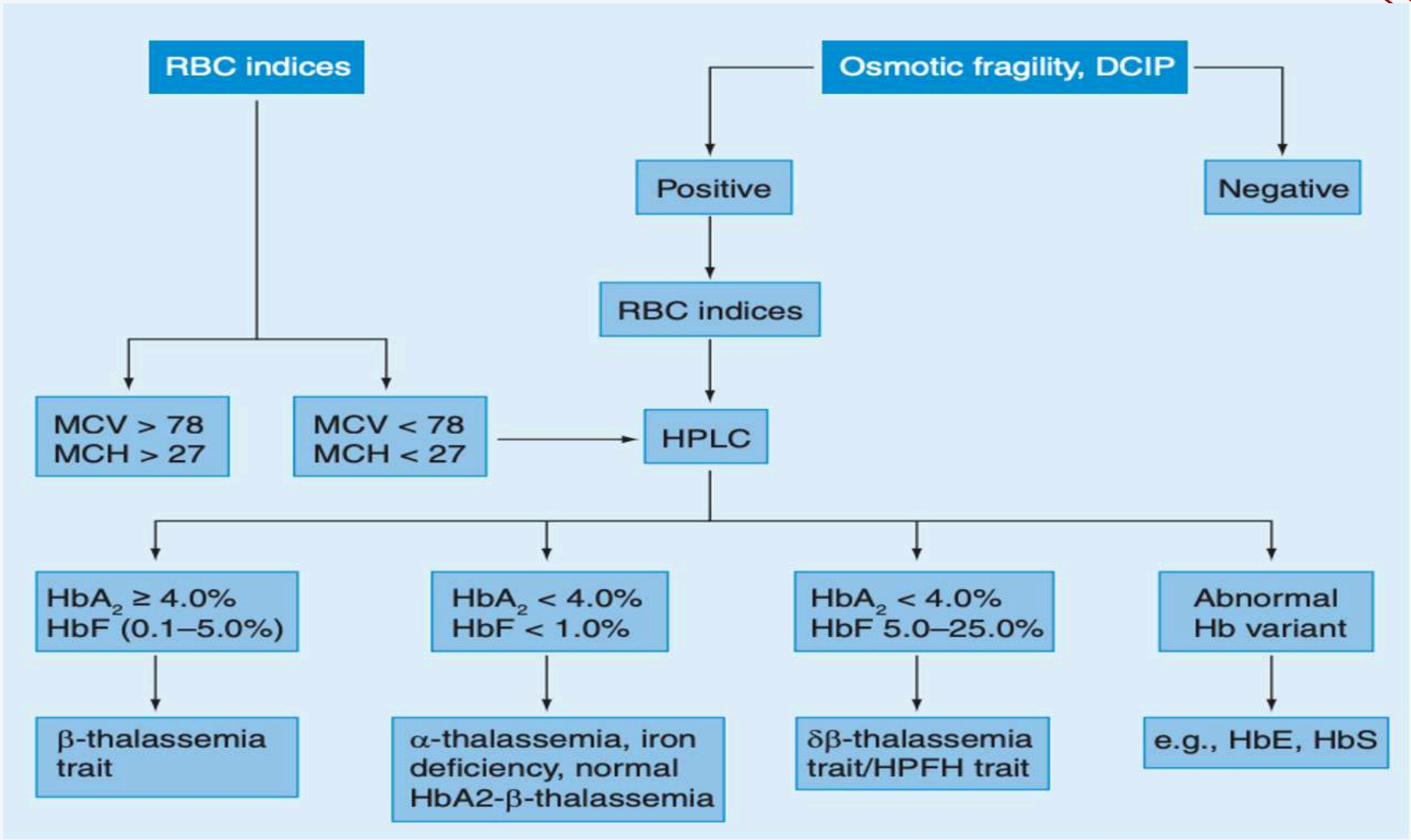

Figure 2. Flowchart for screening for carriers of the β-thalassemias.
DCIP: Dichlorophenol indophenol; Hb: Hemoglobin; HPFH: Hereditary persistence of fetal hemoglobin; HPLC: High-performance liquid chromatography; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; RBC: Red blood cell.

Colah et al: Expert Rev. Hematol. 3(1), 103–117 (2010)

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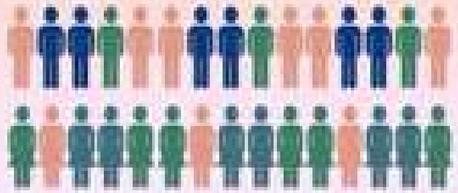
β-THALASSEMIA MAJOR-MANAGEMENT

- Chronic Transfusion Therapy
  - PRBC transfusions often monthly to maintain Hgb 10-12 g/dl
- Chelation Therapy
  - Binds free iron and reduces hemosiderin deposits
    - Desferrioxamine (Desferal)
    - Deferasirox (Exjade, Jadenu)
    - Deferiprone
- Luspatercept
- Splenectomy
  - Transfusion requirements increase 50% in 6mo
- Stem Cell Transplantation
- Genetic therapy
  - Casgevy
  - Beti-cel (Zynteglo®)

Safety and Efficacy of Luspatercept for the Treatment of Transfusion-Dependent Thalassemia Patients

Study design

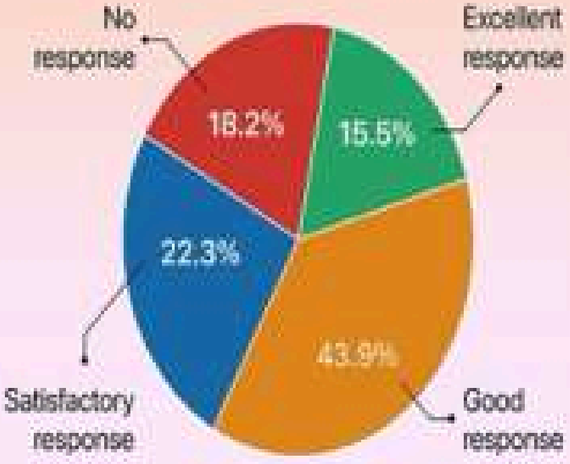
Largest real-world, multicenter, retrospective-prospective observational cohort study



Patients with transfusion-dependent thalassemia (N = 231)

Results

Response to luspatercept



Key response factors


Older patients

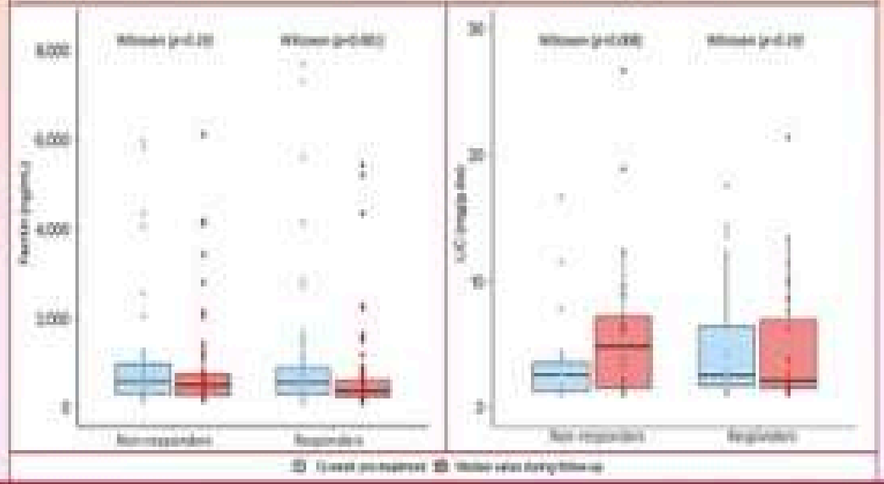

Splenectomy


Genotypes other than β⁺/β⁺


Late transfusions

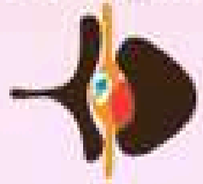
Effects on iron metabolism

Serum ferritin decreased and liver iron concentration (LIC) remained stable



Adverse events

Thromboembolic events observed in eight patients



Extramedullary masses observed in seven patients

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Origa et al. Am J Hem 2025; 100:1651–1655

MONITORING AND FOLLOW UP

- **Growth pattern, skeletal changes and organomegaly**
- **Iron status**
  - Serum ferritin
  - Liver and Heart MRI T2*
- **Screen for hepatitis and AIDS**
- **Liver function tests**
- **Hormonal assays**
  - Diabetes, hypothyroid, gonadotropin deficiency
- **Echocardiography**
- **BMD and Osteoporosis prevention**
  - Diet, exercise
  - Hormone supplementation
  - Osteoclast-inhibiting medications

SICKLE CELL ANEMIA

- Autosomal recessive inheritance (β6 Glu→Val; GAG→GTG)
- Heterozygote is a carrier or trait
- Homozygous state is SS or sickle cell anemia
- Associated with significant morbidity and mortality
- 8-12% of African-Americans carry trait
- In the Arabian Peninsula, varies from <1 to >25%
- Sub-Saharan Africa 20 – 30%
- Increased gene frequency in the “malaria belt” (Africa, Mediterranean, Middle East, India)

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INHERITANCE OF SICKLE CELL DISEASE

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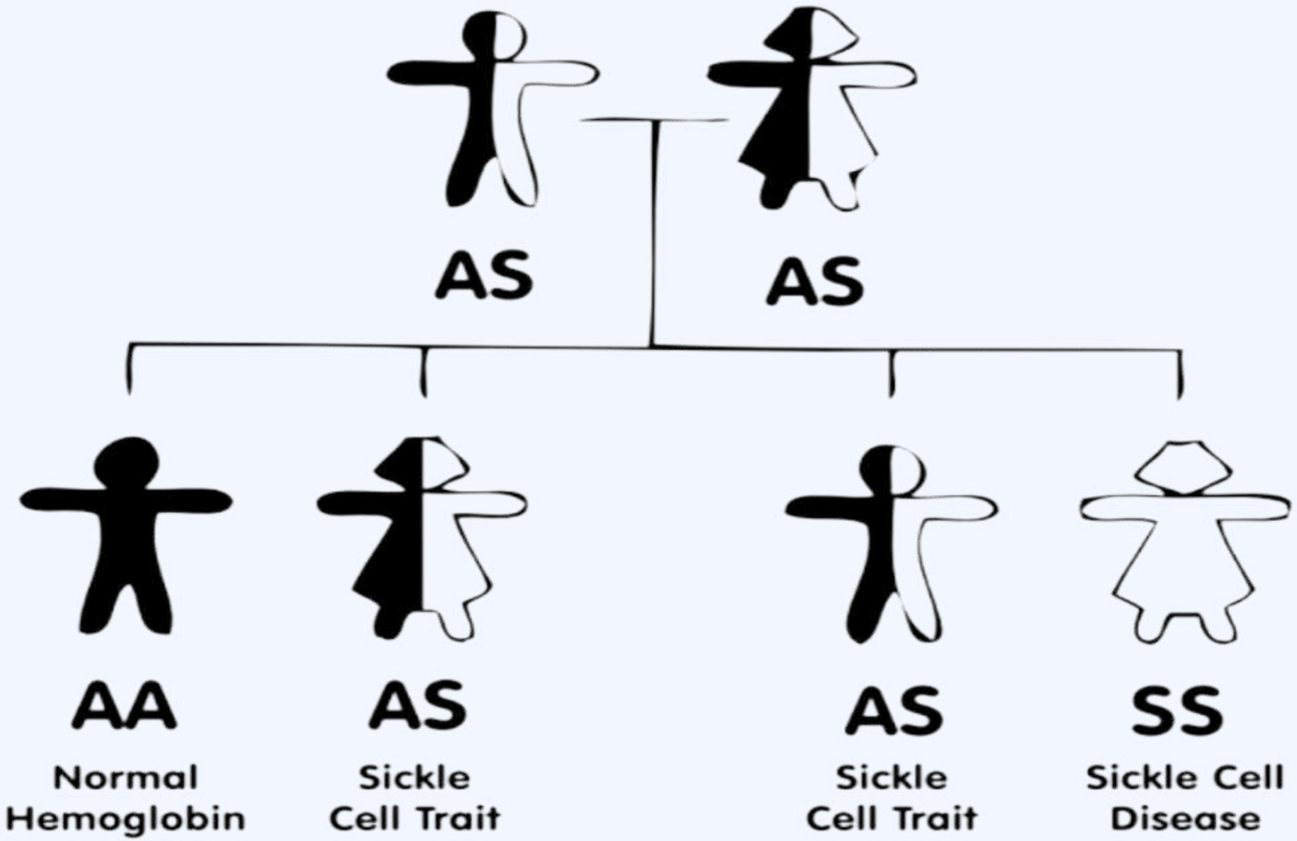
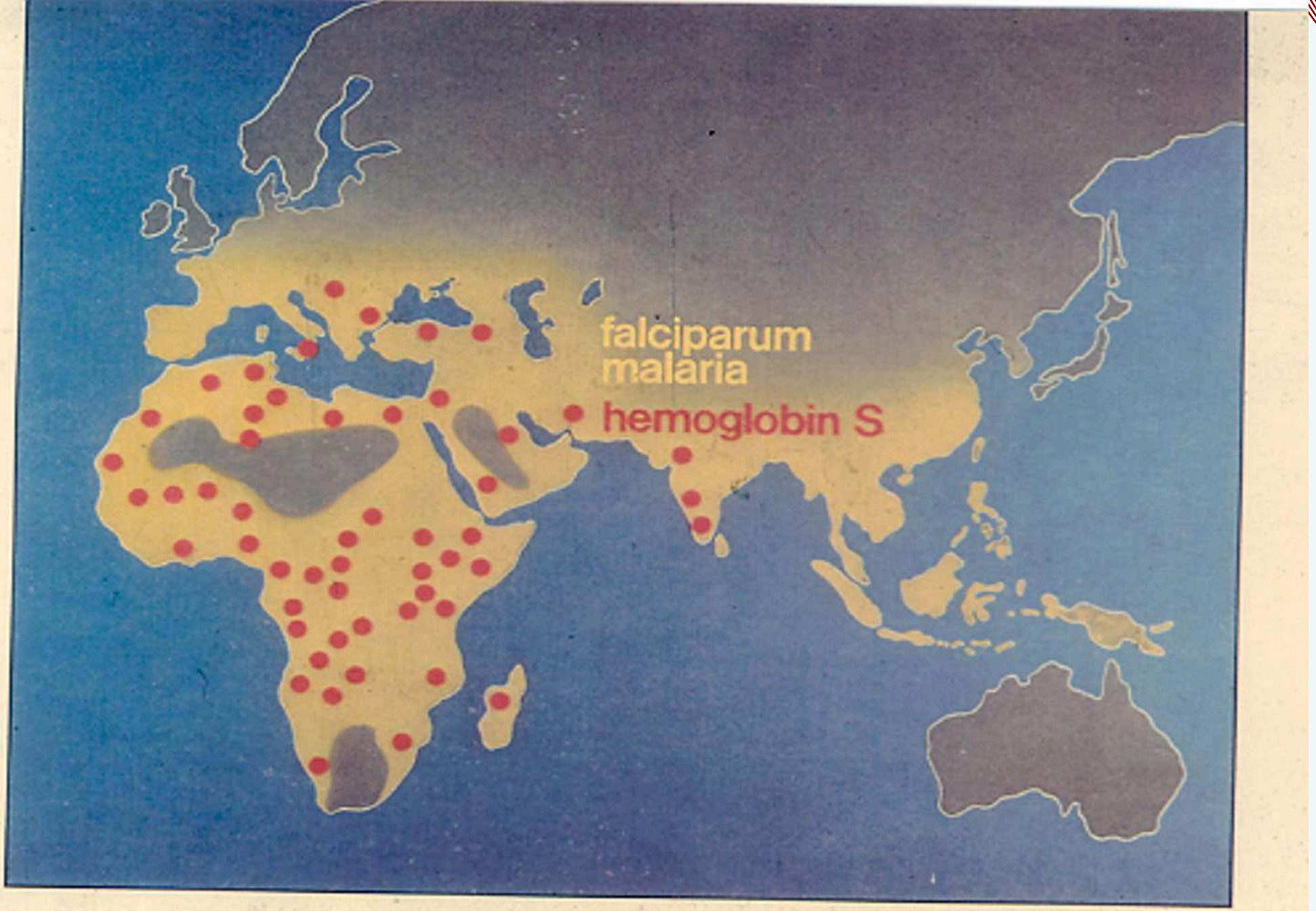
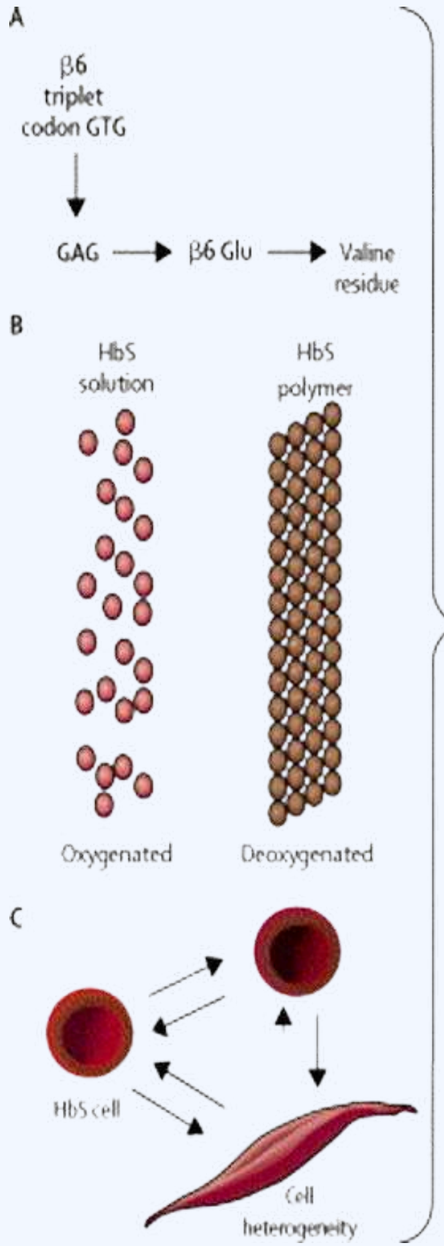


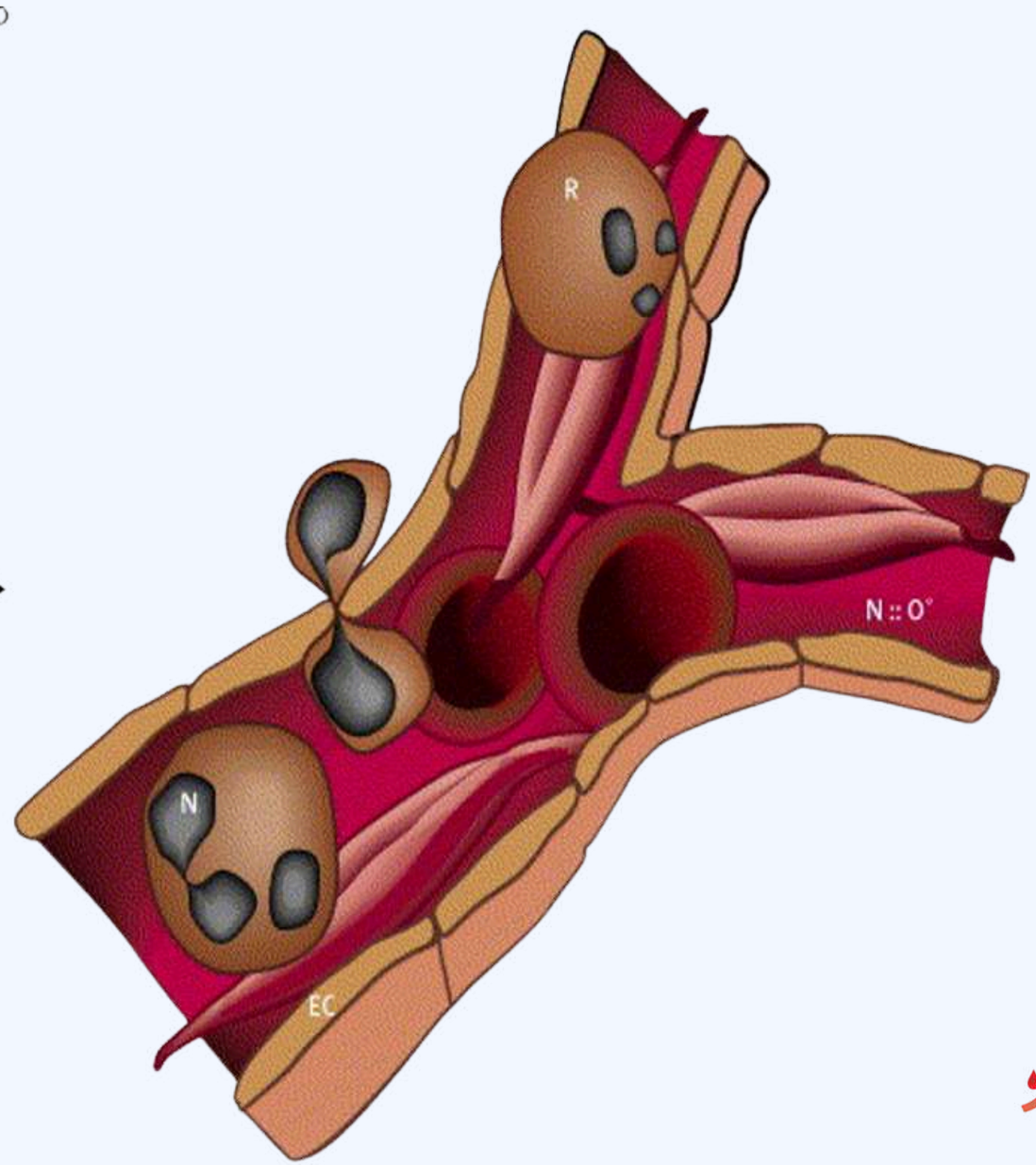
AS - Trait (Carrier)
AA - Usual (no sickle cell)
SS - Unusual (Sickle cell)



Transparency 18. Geographic Distribution of Hemoglobin S and *Falciparum Malaria*

PATHOPHYSIOLOGY OF SICKLE CELL DISEASE





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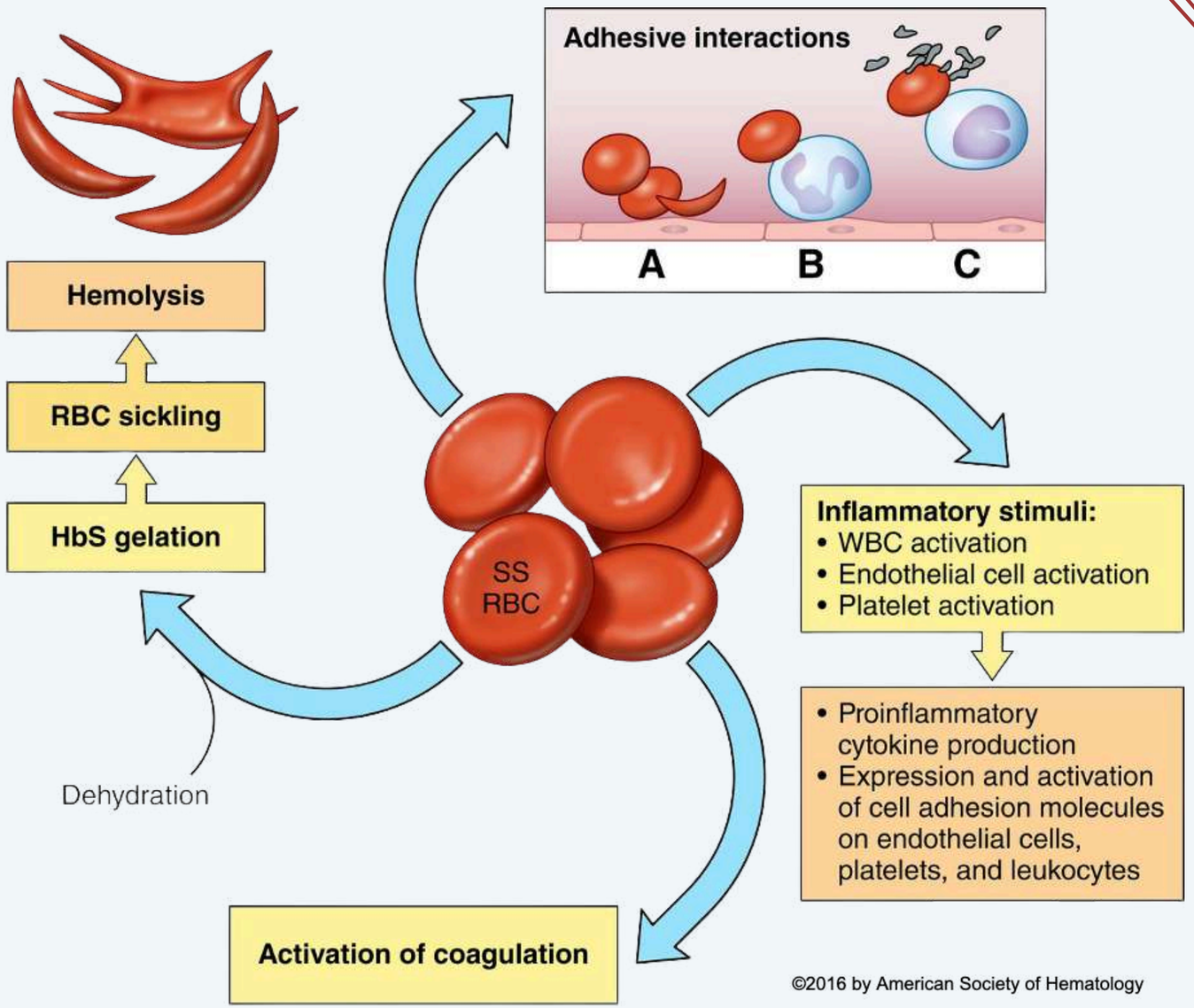
THE SICKLE RED BLOOD CELL (SS RBC) AS SOURCE OF MULTIPLE PATHOPHYSIOLOGIC PATHWAYS.



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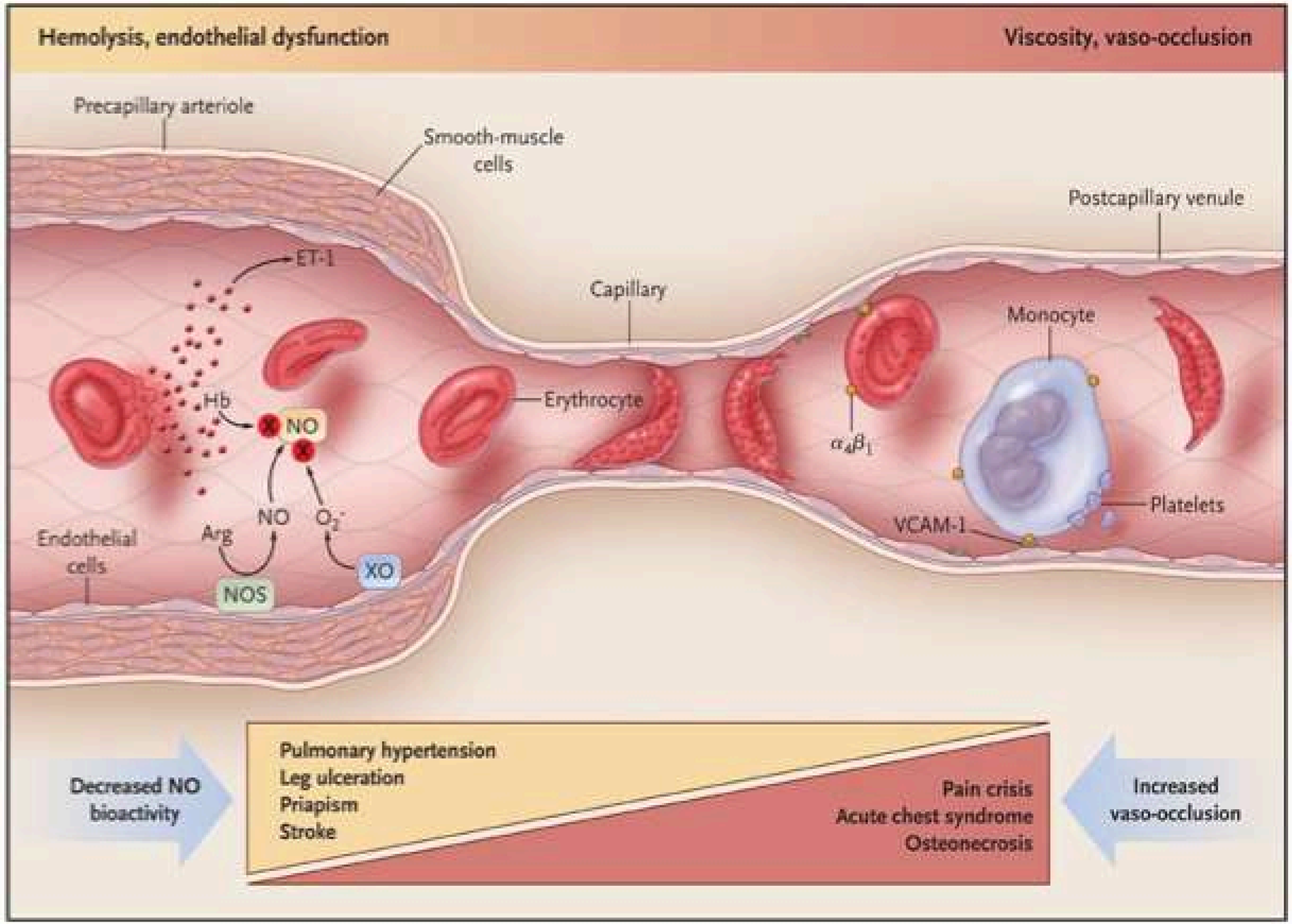
blood

HYPOTHETICAL MECHANISMS OF SCD CLINICAL SUBPHENOTYPES



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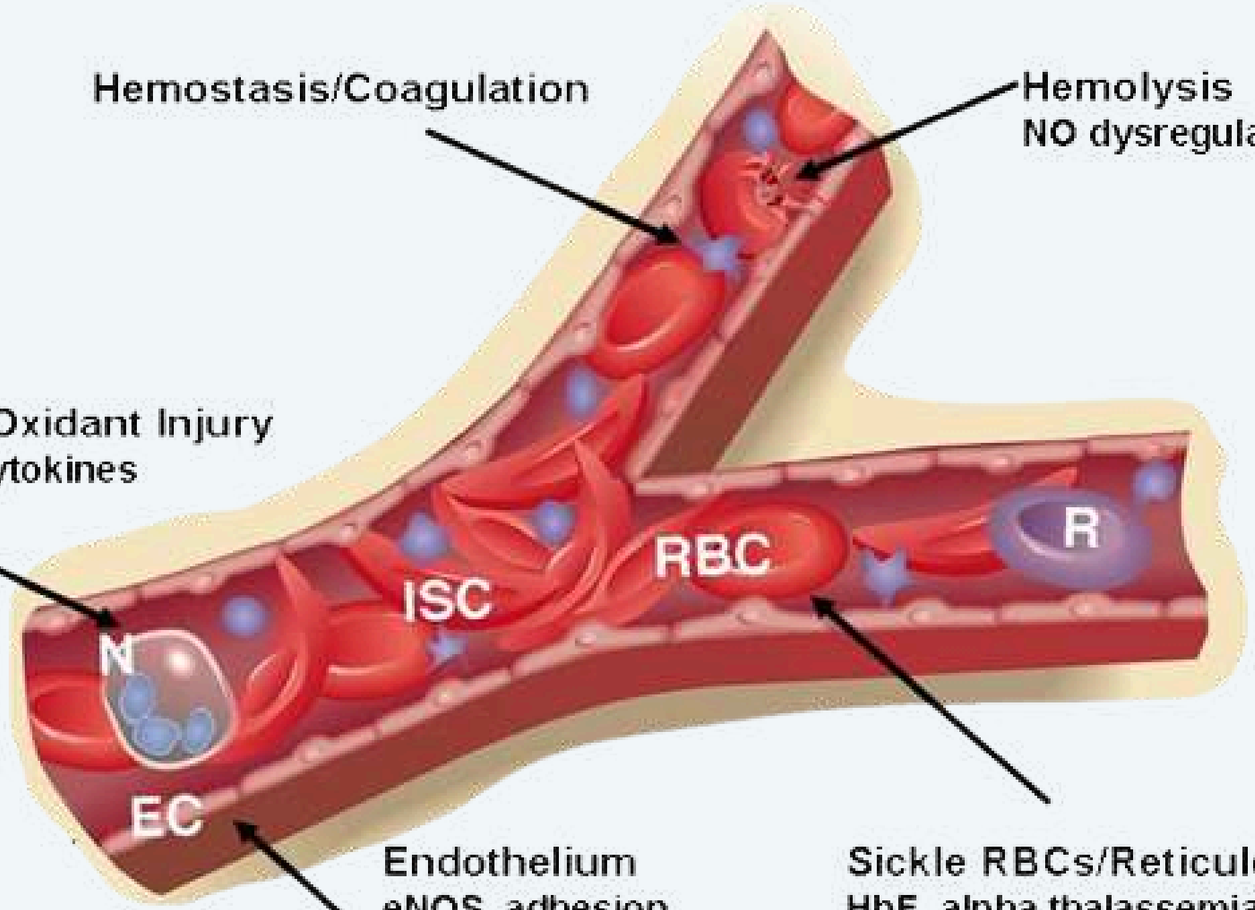
Genetic Modulation of Sickle Cell Disease



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GENOTYPE/PHENOTYPE CORRELATION IN SCD

- Phenotype of SCD is variable
- The most important of the factor is the beta S globin gene haplotype
- Haplotype is a combination of alleles at multiple linked loci that are transmitted together
- In the beta S gene, this is determined by RFLPs in the flanking regions of the gene cluster
  -

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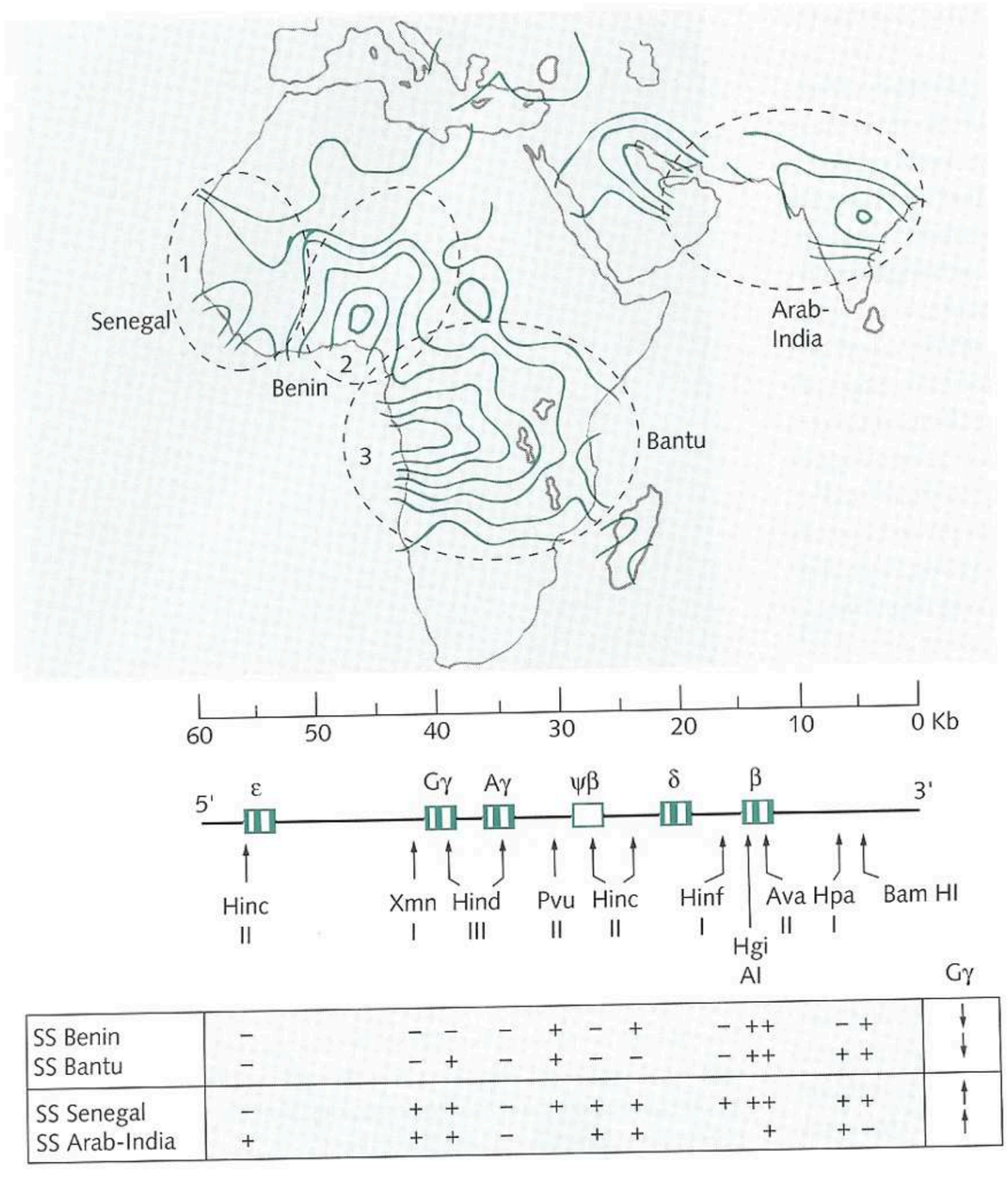


Fig. 14.4 β gene cluster haplotypes linked to β^s in Africa and the Middle East/Pakistan/India

At the top of the figure are shown the geographic distributions corresponding to the haplotypes described below. A haplotype is a particular array of polymorphic sites (that is, sites that vary among individuals), defined here by the capacity of endonuclease enzymes to recognize the short sequence and cut the DNA.

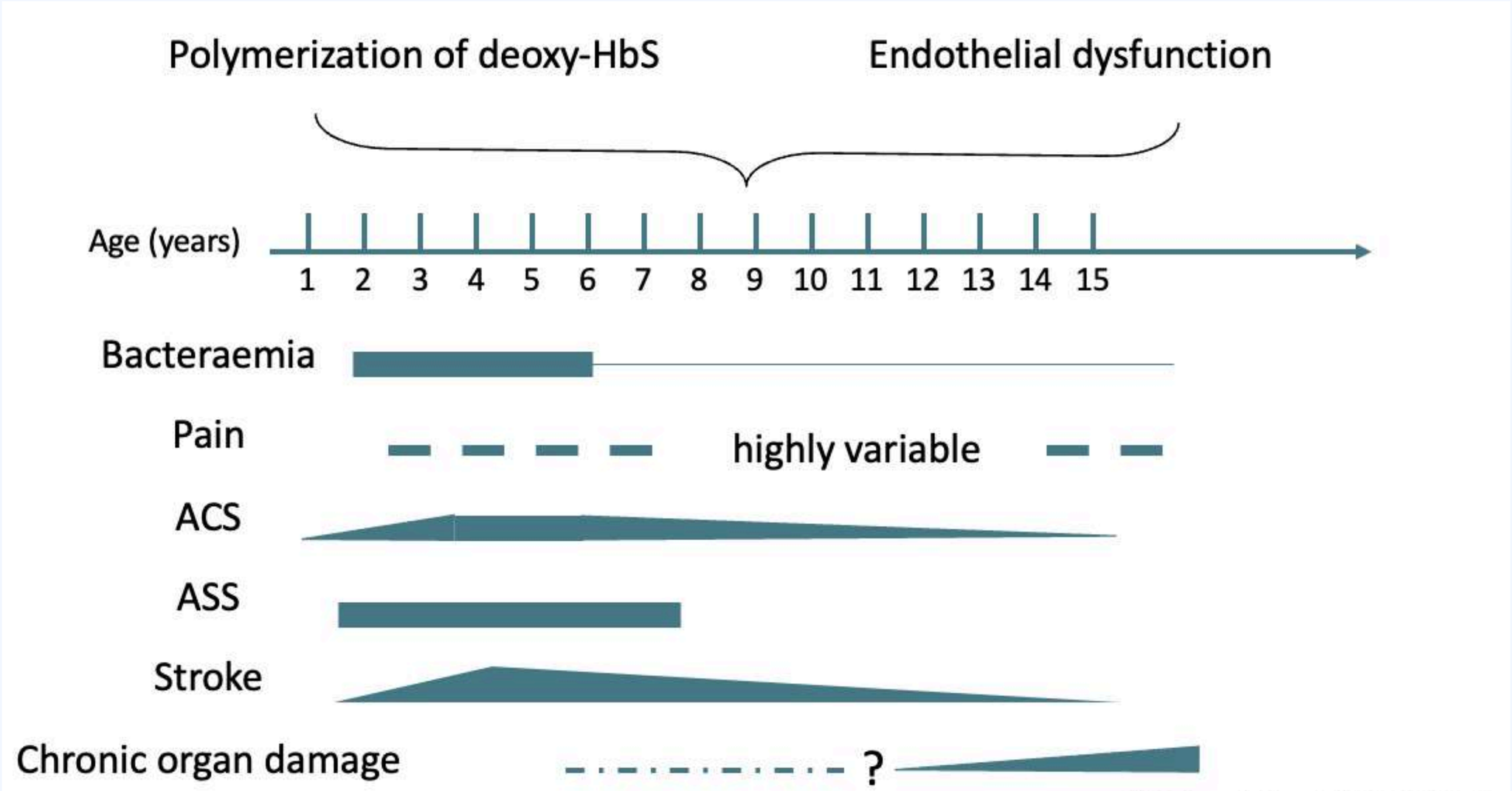
BETA S HAPLOTYPES AND CLINICAL SEVERITY

- Target organ dysfunction is directly related to haplotype background
- The mildest disease is associated with the Saudi Arabia/India (SAI) and the Senegal (SEN) haplotypes
- The most severe disease is associated with the Bantu (BAN) haplotype
- Benin (BEN) and Cameroon (CAM) are intermediate
  -

HB F LEVELS AND CLINICAL SEVERITY

- The heterodimer ($\alpha_2\beta^S\gamma$) is more soluble than the homotetramer ($\alpha_2\beta^S{}_2$)
- Hb F of ≥ 20% is associated with mild disease and decreased major organ complications
- Hb F ≥30% is asymptomatic

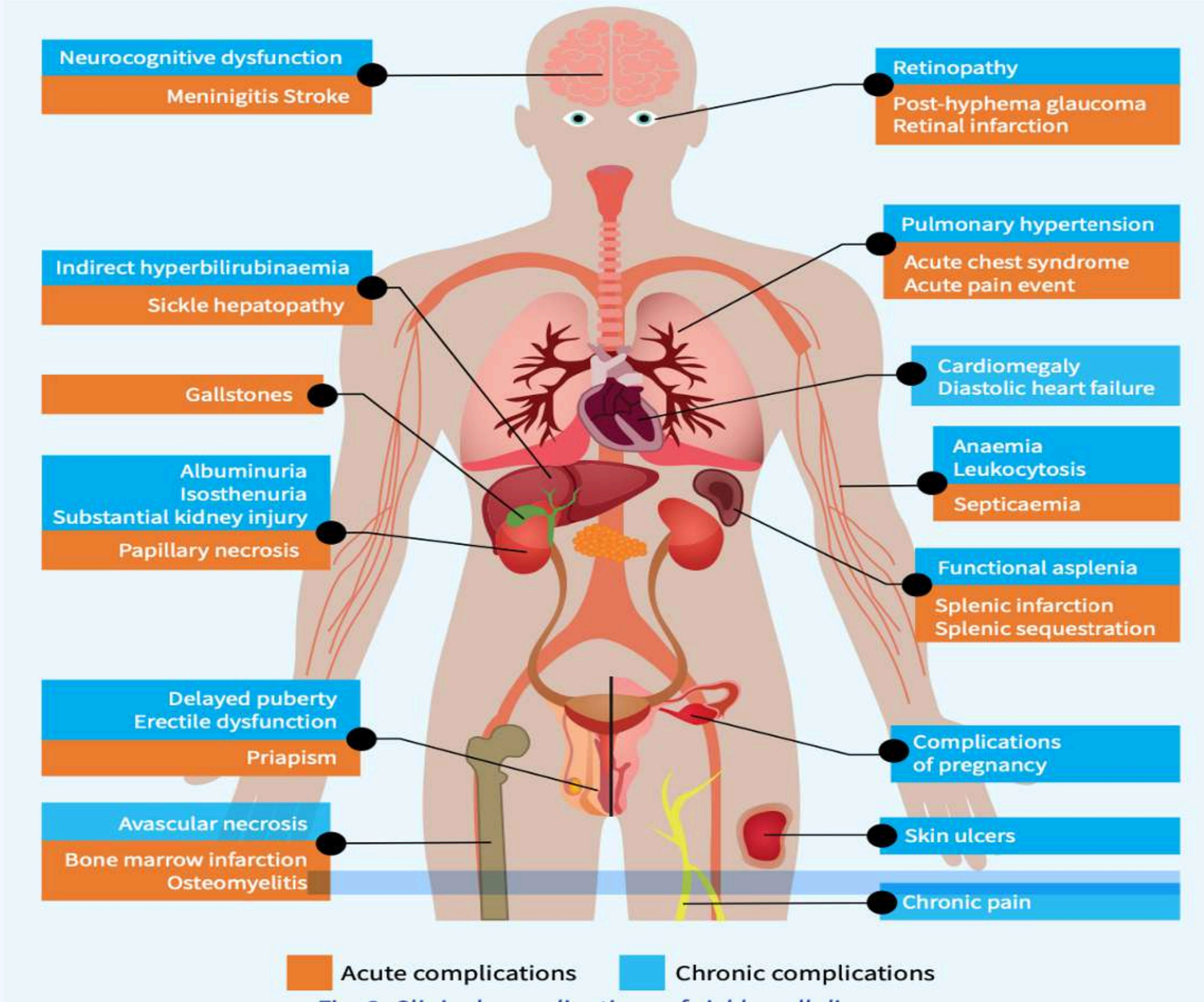
COMPLICATIONS OF SCD IN CHILDREN



ACS = acute chest syndrome;
ASS = acute splenic sequestration.

Gill FM, et al. Blood. 1995;86:776-83.
Ohene-Frempong K, et al. Blood. 1998;91:288-94.
Castro O, et al. Blood. 1994;84:643-9.

COMPLICATIONS OF SCD



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SICKLE CELL DISEASE PEDIATRICS: CLINICAL FEATURES

- **Vaso-occlusive Episodes (VOE)**
- **Infections/Sepsis -**
  - S. pneumoniae
  - N. meningitidis
  - H. influenzae
- **Acute Chest Syndrome**
- **Splenic Sequestration**
- **Aplastic Crisis**
- **Stroke**
- **Priapism (adolescents)**
  -

MODIFIERS OF DISEASE SEVERITY

- α- thalassemia
- High Hb F determinants
  - Linked (β-globin haplotypes)
    - a **haplotype** is a combination of alleles at multiple linked loci that are transmitted together
  - Unlinked (X-chromosome, others)
- Other genetic factors
  - Coagulation related polymorphisms
  - Endothelial cell function
  - Inflammatory mediators
  - RBC membrane function
  - Others

EFFECTS OF α-THALASSEMIA IN SICKLE CELL ANEMIA

CELLULAR:

- Decreased Mean Corpuscular Hemoglobin Concentration
- Decreased Hb S polymer
- Decreased RBC cation loss
- Decreased RBC density
- Increased RBC deformability

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FACTORS INFLUENCING HB F LEVELS IN SICKLE CELL ANEMIA

- Age
- Gender (F>M)
- β^s-globin gene cluster haplotype
- F-cell Production locus (FCP) (Xp22.2)
- Others (Oncogenes on chromosomes 2 & 6?)

DIAGNOSIS

- **Screening with solubility and sickling tests**
- **Hb electrophoresis**
- **Cellulose acetate**
  - Citric agar
  - Isoelectric focusing (IEF)

- **High-performance liquid chromatography (HPLC)**
- **Point-of-care testing kits**
- **Molecular studies**

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MANAGEMENT

- **NEWBORN SCREENING**
- **GENETIC COUNSELLING**
- **COMPREHENSIVE CARE**
  - **Penicillin prophylaxis**
  - **Health surveillance**
    - TCD, abdominal ultrasound, hip X-ray/MRI etc
  - **Immunization (pneumococcal)**
  - **Malaria chemoprophylaxis**
  - **Disease-modifying drugs**
    - Hydroxyurea
- **CURATIVE THERAPY**
  - **Stem-cell transplant**
  - **Gene therapy**

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PUBLIC HEALTH IMPLICATIONS

- **HIGH PREVALENCE IN SSA**
- **WHO GUIDANCE FRAMEWORK CALLS**
  - **National policy**
  - **Early infant diagnosis**
  - **Supply of essential drugs and devices**
    - Hydroxyurea and POCT diagnosis
  - **Capacity building**
  - **Integration into NCD programs**
    - PEN, PEN-Plus
    - Immunization
    - Child/maternal services
- **ADVOCACY**
    - Most important

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THANK YOU!

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