THALASSEMIA

Pre -Lecture Feedback Questionnaire

Q 1. Have you ever heard about a disease called thalassemia?

a. I know it from TV

b. I heard on the radio

c. I read in the newspaper

d. I heard at school

e. I have a relative with this disease

f. I know someone with this disease

g. I have a relative who is a thalassemia carrier

h. I have never heard

i. I learned from another source

Q 2. If you have heard about thalassemia, write what you know in a few sentences.

Q 3. Is this disease is inherited?

Yes, inherited

No

No idea

Q 4. Do you know the importance of being a carrier of these diseases?

a. I don’t know

b. If you know, explain in few words

Q 5. Do you know if you are a carrier for Thalassemia?

a. I don’t know

b. Yes I am a carrier for Thalassemia

c. I am not a carrier for Thalassemia

Q 6. Is it possible to identify carriers?

The world's thalassaemia capital

- 35-40 million carriers in India
- 100,000 thalassaemia majors, of whom 50% will not survive beyond the age of 25
- 10,000 live births of thalassaemia major every year
- Each person with thalassaemia spends on an average more than 1 lakh per year on treatment
- India spends around ₹15,000 crore on thalassaemia treatment each year
- The country's blood transfusion burden is 2,00,000 units every month
- 95% of patients' expenses is out of pocket with no help from the government
- 4 of 10 thalassaemia patients will be unemployed or underemployed because of disability-adjusted life years

What is the position of the disease in India?

- India is the thalassemia capital of the world with 40 million carriers and over 1, 00,000 patients.
- There is no prevention and control programme at the national level.
- With preventive health checks not being the norm in India, people suffering from thalassemia are unknowingly passing on this genetic disorder to their children.
- Over 1, 00,000 patients across the country die before they turn 20 due to lack of access to treatment.

Ref: The Hindu report on Thalassemia in India

- Every year approximately 100,000 children with Thalassemia Major are born world over, of which 10,000 are born in India.
- It is estimated that there are about 65,000-67,000 β-thalassemia patients in our country with around 9,000-10,000 cases being added every year

Learning objectives

- What is thalassemia?
- Molecular Pathology of thalassemia
- Pathophysiology of Thalassemia
- Classification of Thalassemia
- Clinical Presentation of Thalassemia
- Peripheral smear findings in Thalassemia
- How to diagnose a suspected case of thalassemia

THALASSEMIA SYNDROME

Definition :Heterogenous group of inherited disorders caused by genetic lesions leading to decreased synthesis of either α or ß globin chain of Hb A

Deficient synthesis of ß chain- ß Thalassemia

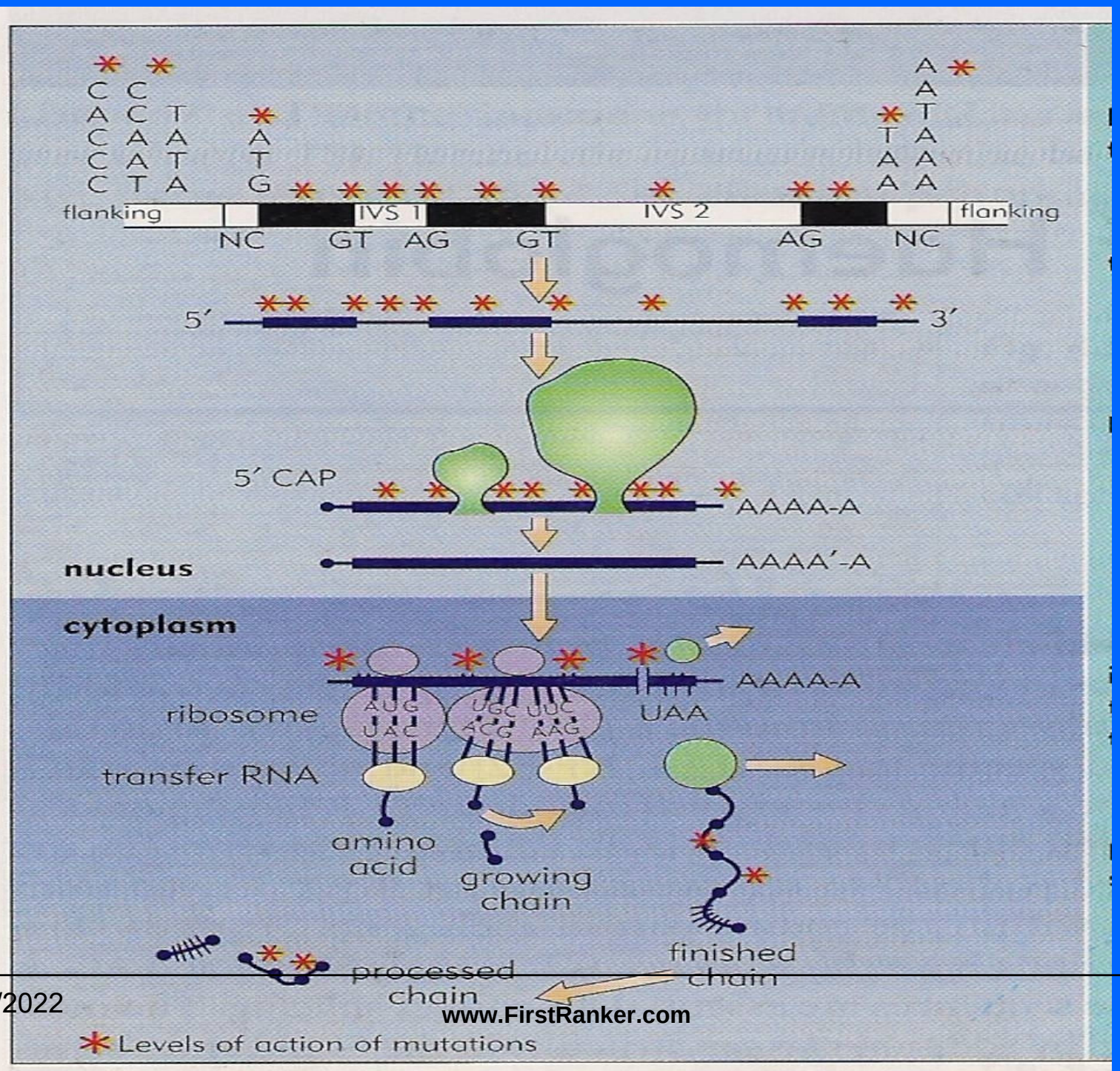
Deficient synthesis of α chain- α Thalassemia

GLOBIN SYNTHESIS:

Globin synthesis depends on two gene clusters situated on

Chromosome -11 for ß globin chain

Chromosome -16 for α globin chain



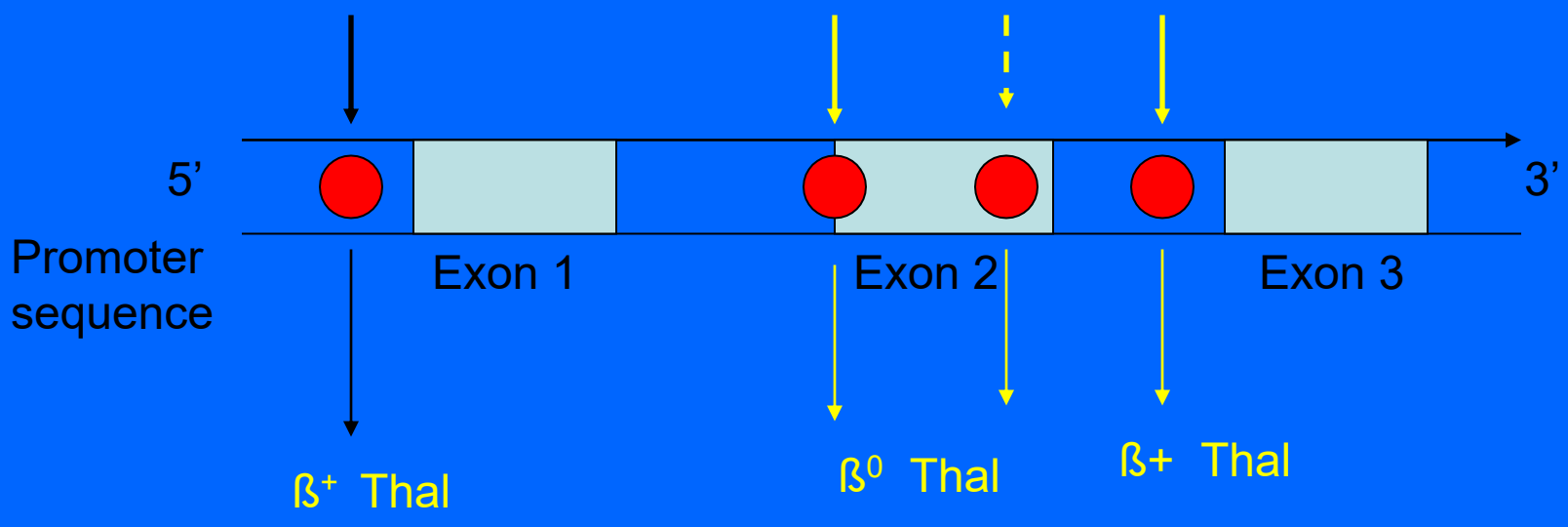
MOLECULAR PATHOGENESIS

- ß Thassemia
- 1) $ß^0$ –Thalassemia, Total absence of ß globin chain in homozygous state
- 2) $ß^+$- Thassemia, Reduced ß globin synthesis in homozygous state

Promoter region mutations

Chain Terminator Mutations

Splicing Mutations



PATHOPHYSIOLOGY OF THALASSEMIAS

- β- Thalassemia is due to an m-RNA abnormality this mutation reduces or inhibit the production of β- globin chains.

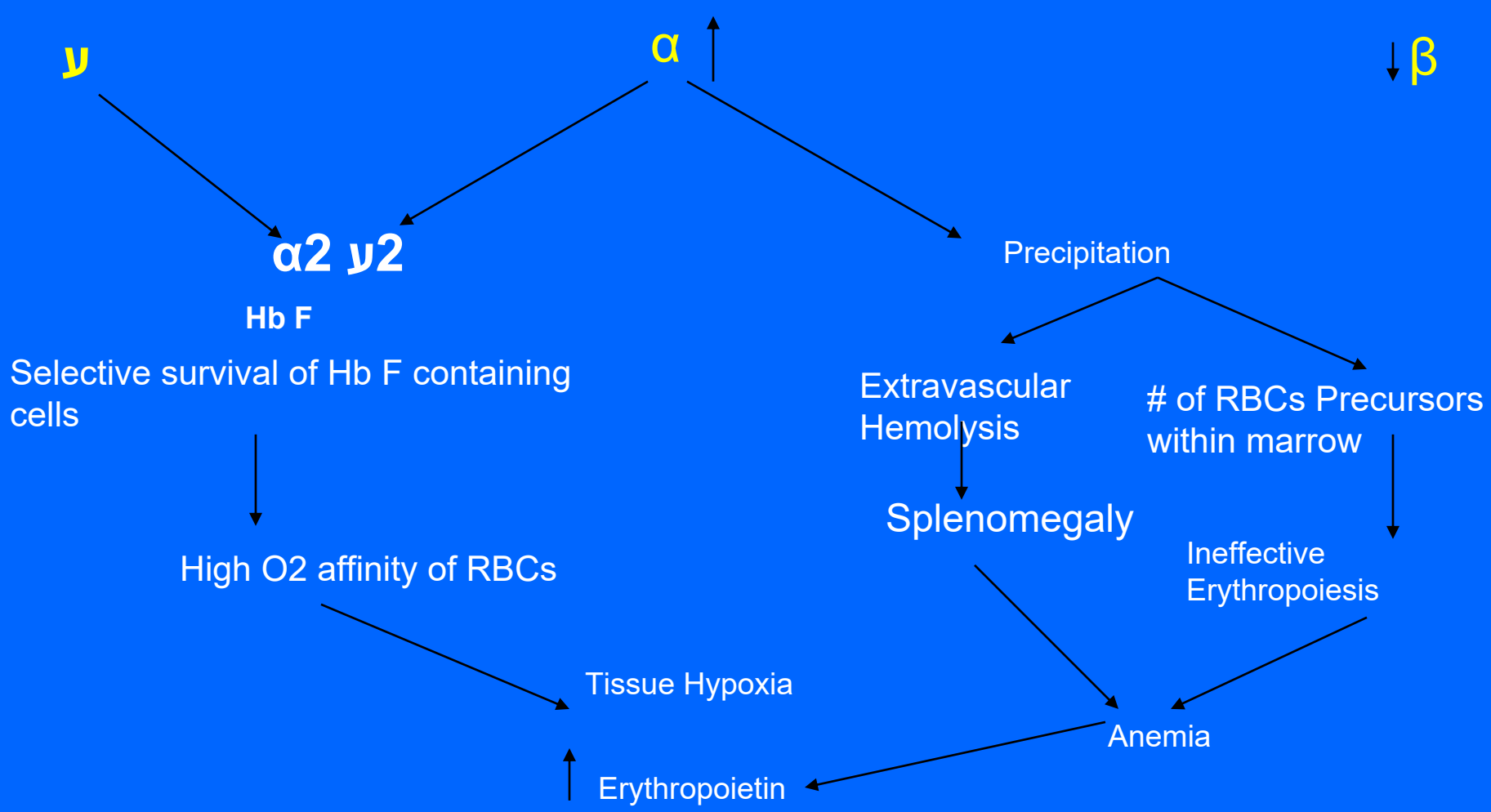
- Point mutation in or near the β- globin gene (Most Common) –

i) Defective splicing (splice do not occur or occur at wrong site)

ii) Stop codon – non sense lesions (chain terminate prematurely)

- Frame shift mutation (insertion or deletion of a single nucleotide, resulting in lengthening or shortening of DNA molecules)

Patho - Physiology of Thalassemia



Anemia

↑ Tissue Hypoxia
erythropoietin

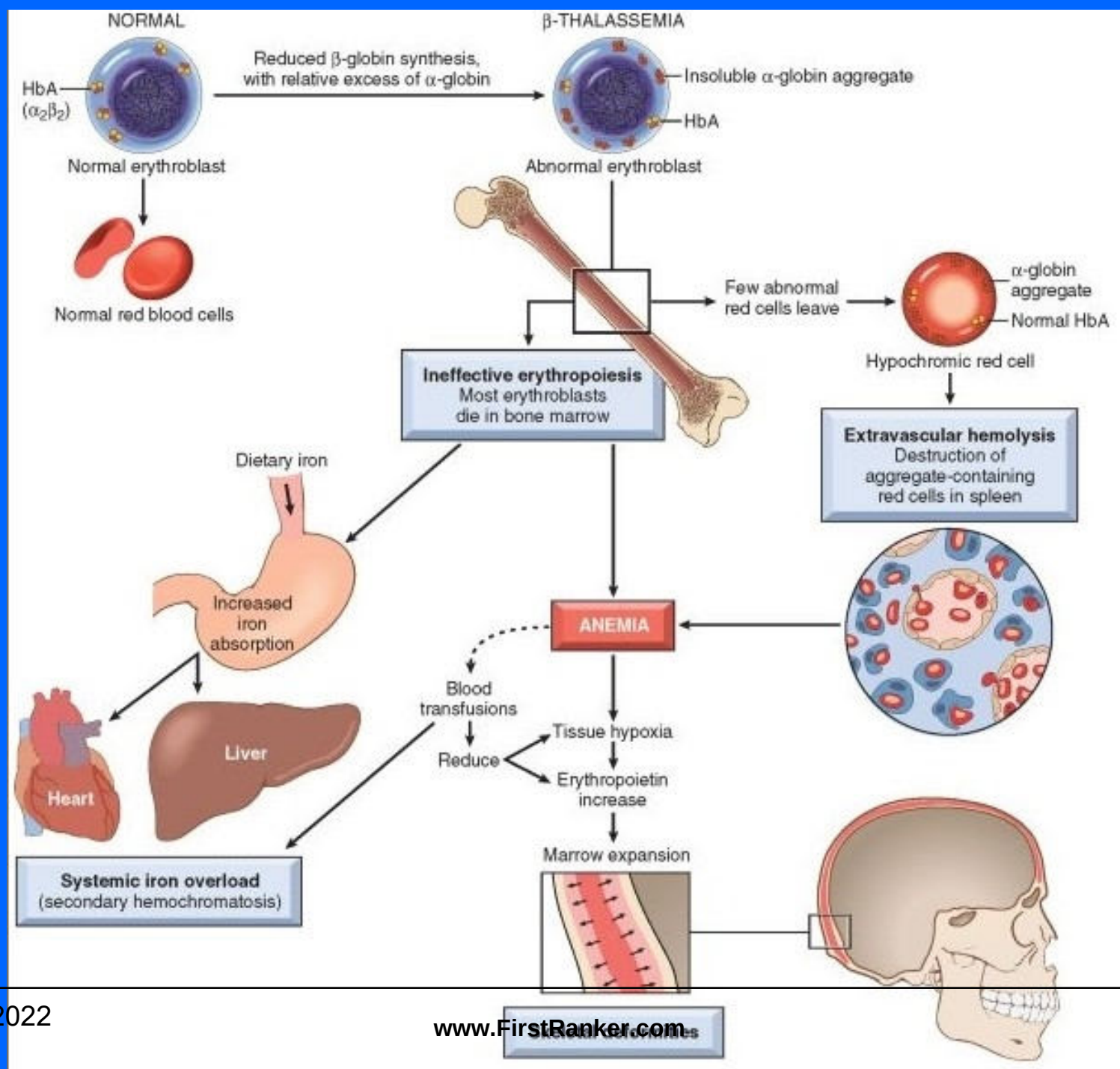
Blood Transfusion

Marrow Expansion

↑ Iron absorption
Iron Loading

↑
Bone Deformity
Metabolic Rate
Gout
Folate Deficiency

Endocrine Deficiencies
Cirrhosis
Cardiac Failure
Death



Clinical & Genetics Classification of Thalassemias

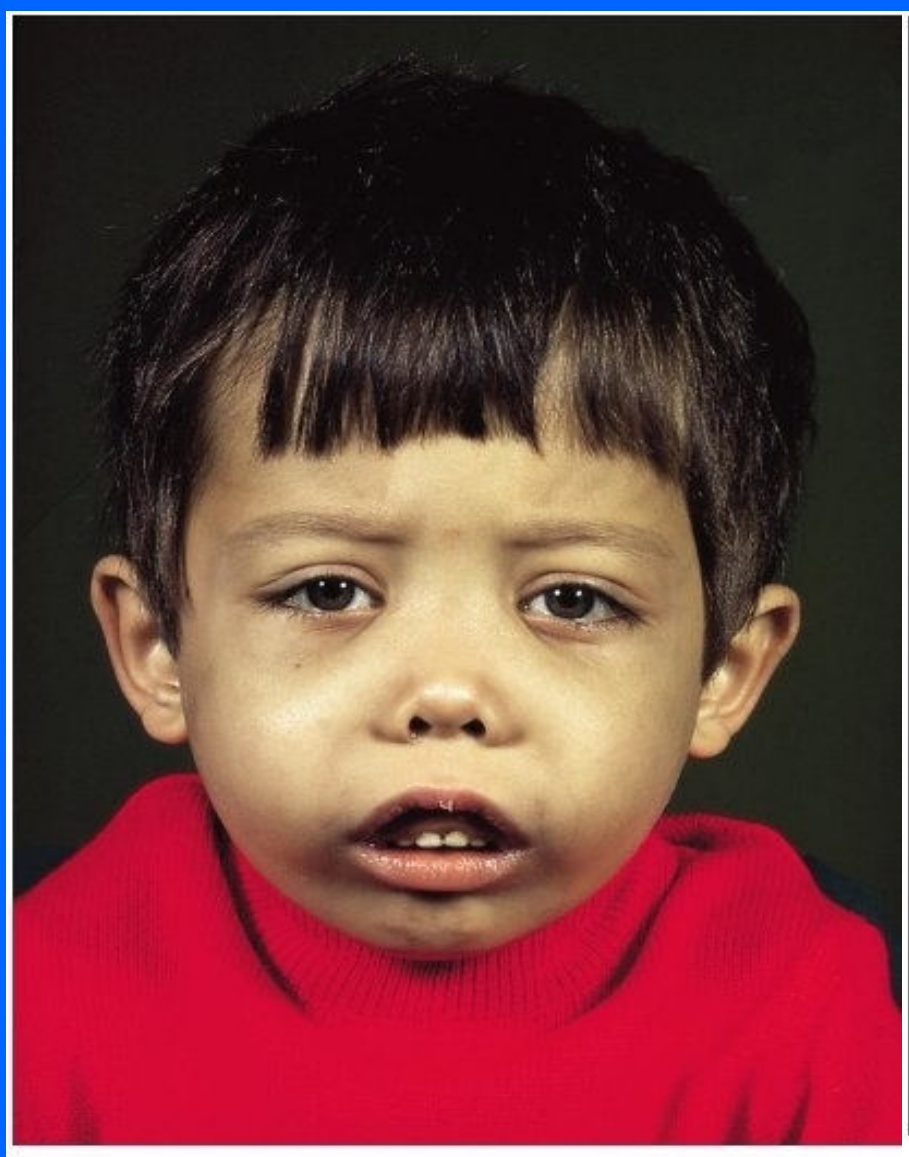
Clinical	Genotype Nomenclature	Disease
β Thalassemia Major	Homozygous β thal (β^0/β^0) β^+/β^+	Severe
β Thalassemia Intermedia	β^+/β^+ β^+/β^0 β^0/β β^+/β	Severe but doesn't require regular BT
β Thal minor	β^0/β, β^+/β	Asymptomatic

Alpha Thalassemia

Clinical	Genotype Nomenclature	Disease
a) Silent Carrier	- α/ α α	Asymptomatic
b) α – Thal trait	--/ α α	Asymptomatic (like β Thal minor)
c) Hb. H disease	--/- α	Severe
d) Hydrops fetalis	--/--	Lethal in uterus

Clinical Presentation

- Children with thalassemia remains asymptomatic till the age of 6 months.
- Mostly having symptoms related to anaemia like Jaundice
  Fatigue
  Pallor
  Shortness of breath
  Delayed growth/puberty
  Skeletal deformities



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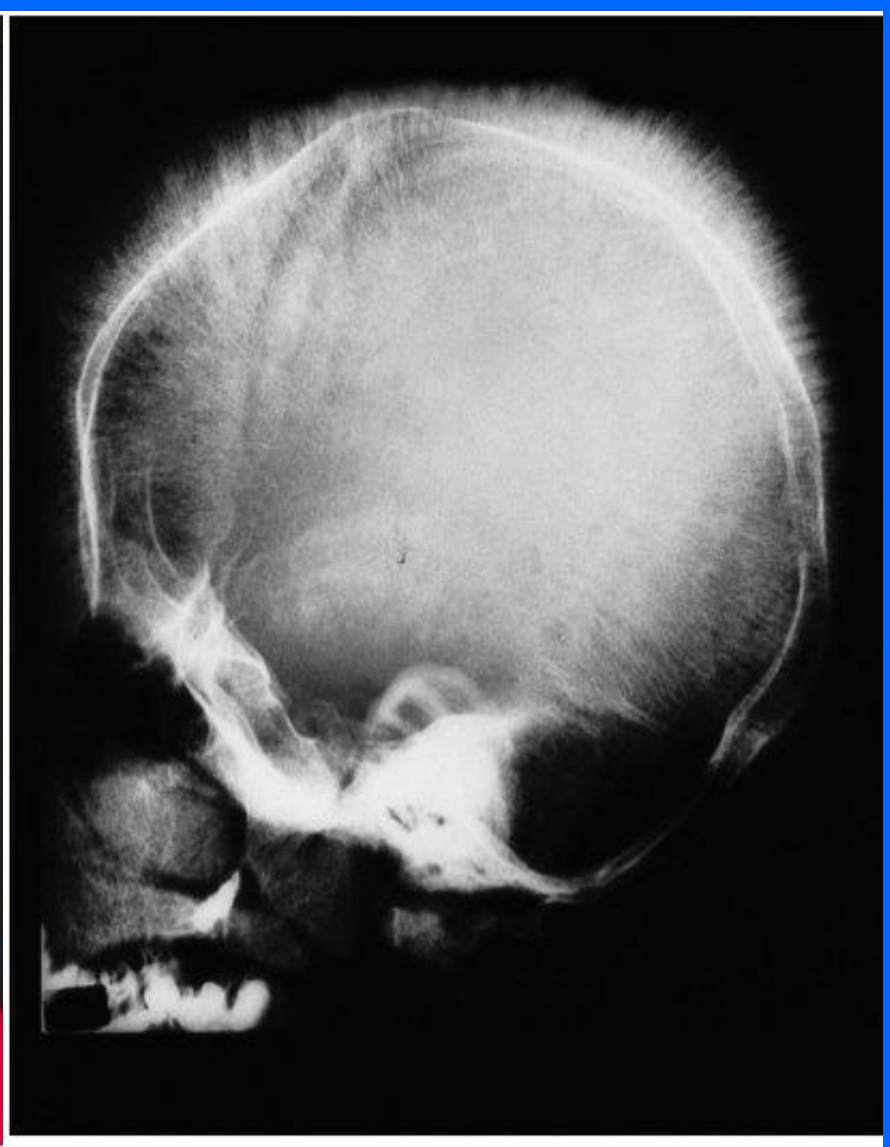

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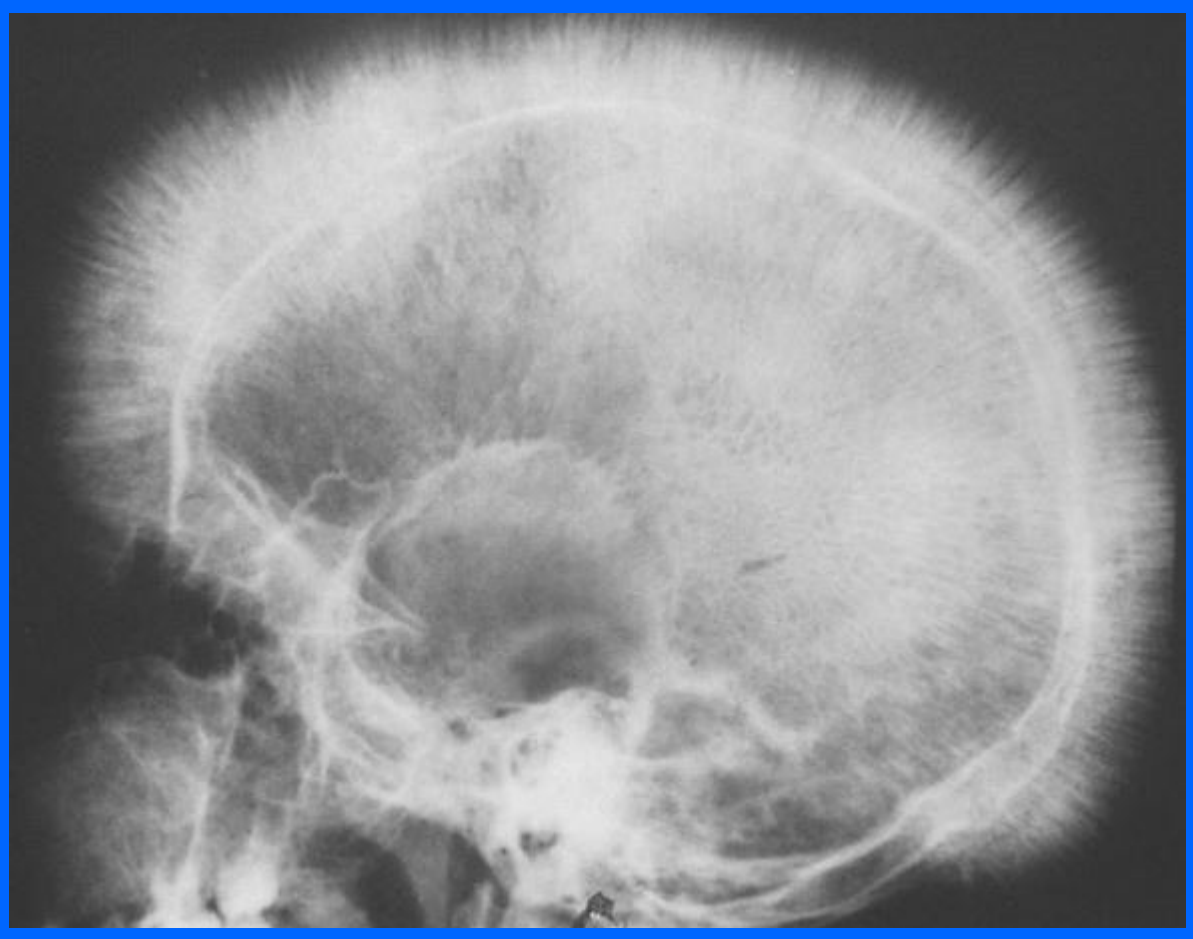
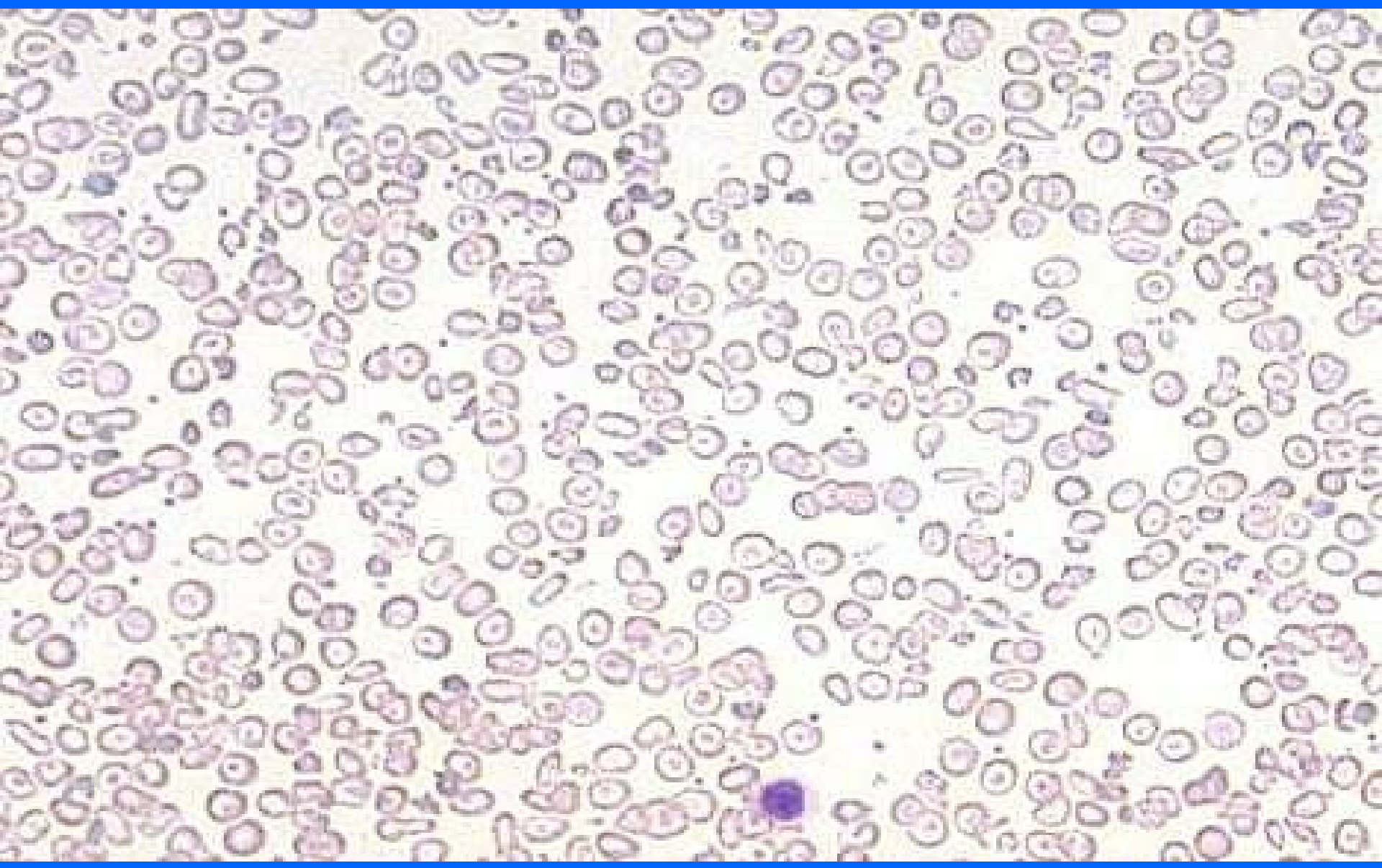


Clinical Presentation contd..

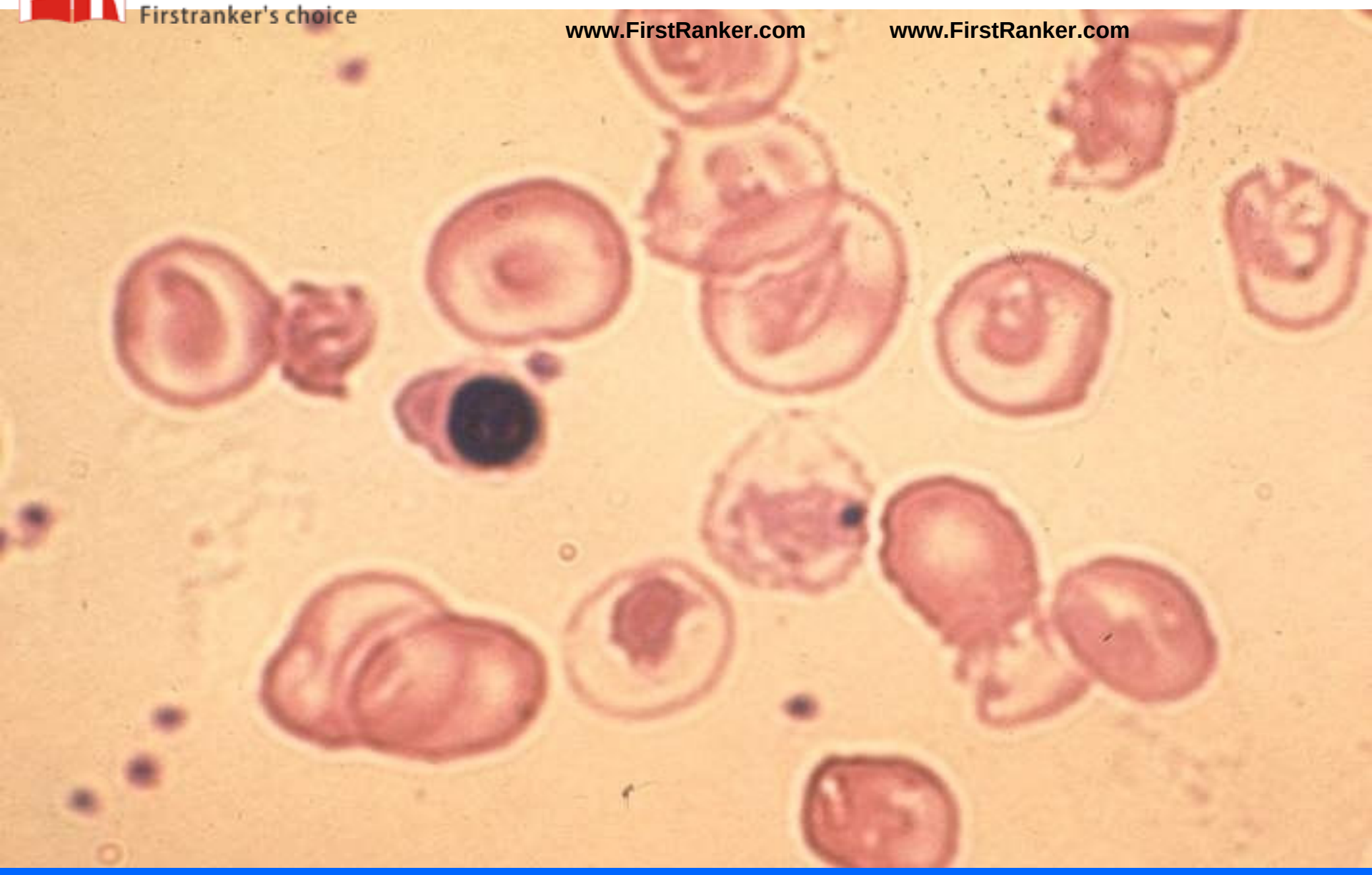
- Organomegaly – Hepatomegaly
  Splenomegaly
  Lymphodenopathy

Skull X-Ray: New bone formation on the outer table producing perpendicular radiations resembling a crew-cut appearance.

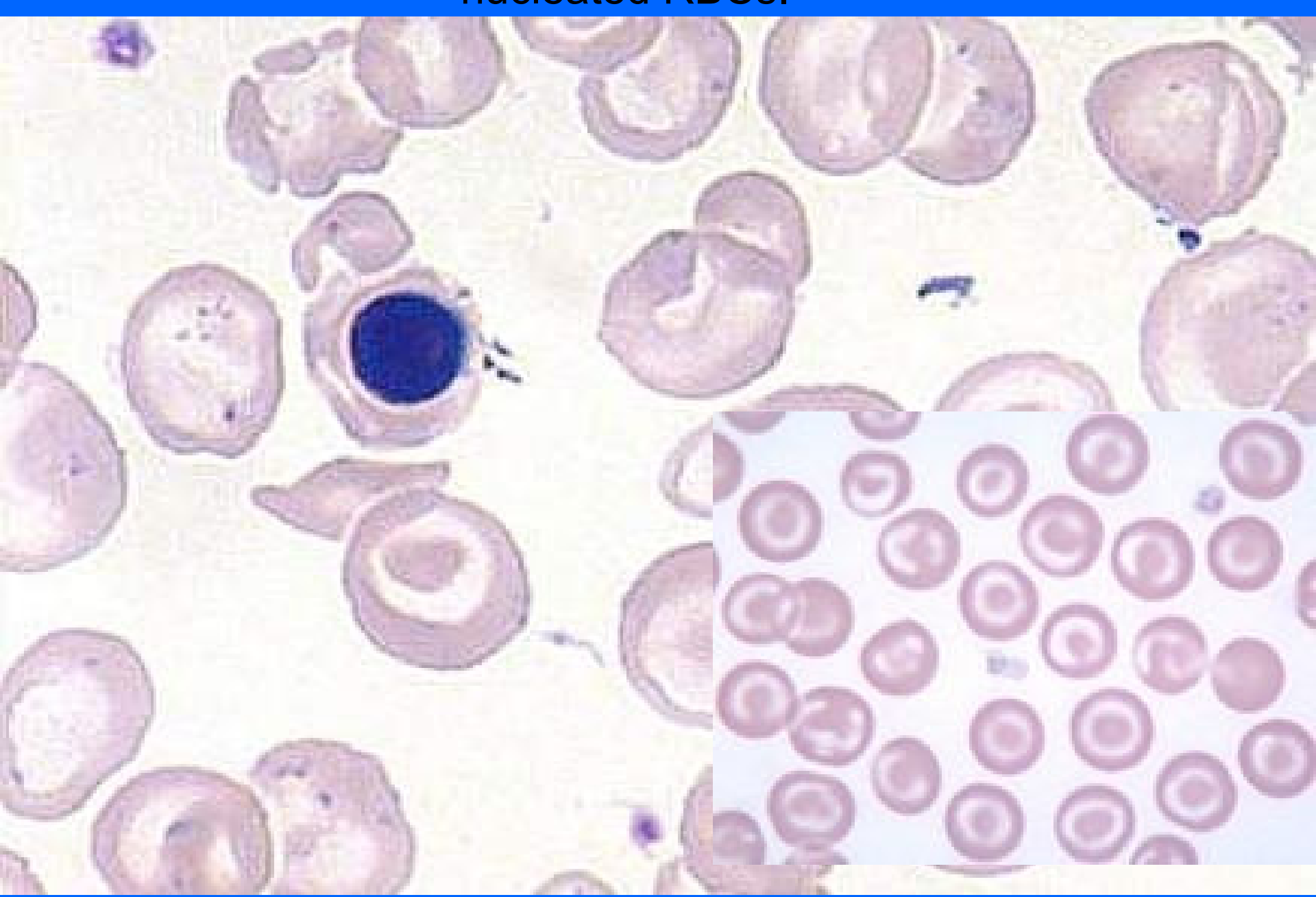
Peripheral smear findings



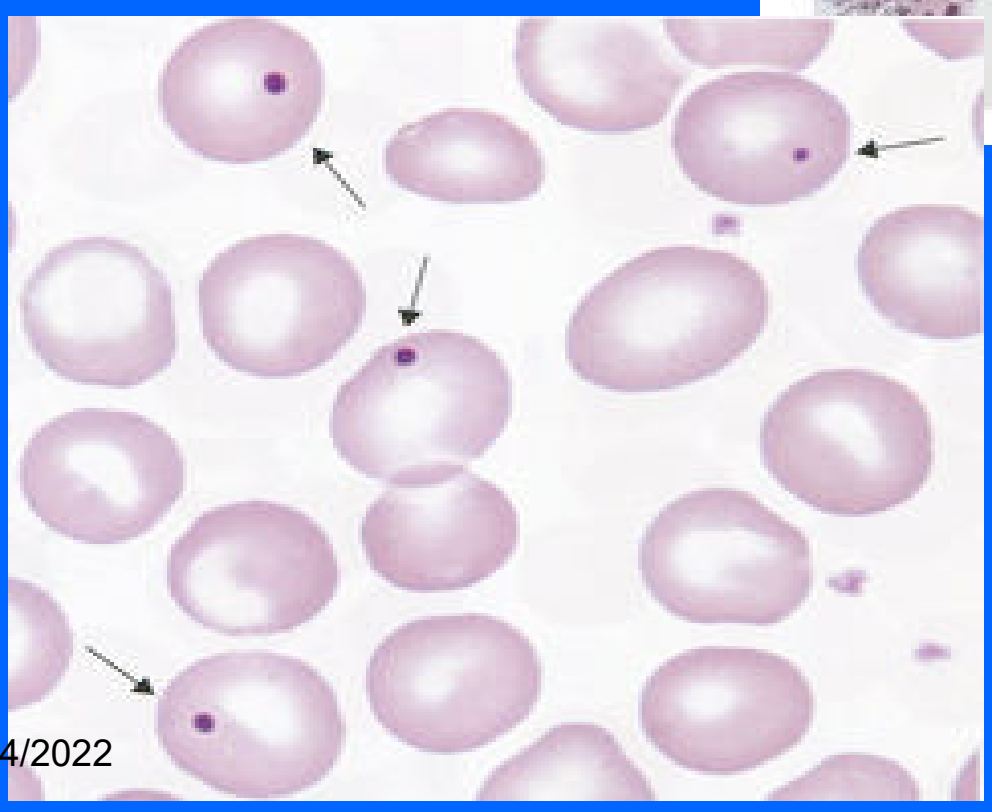
marked poikilocytosis, anisocytosis, and polychromatophilia

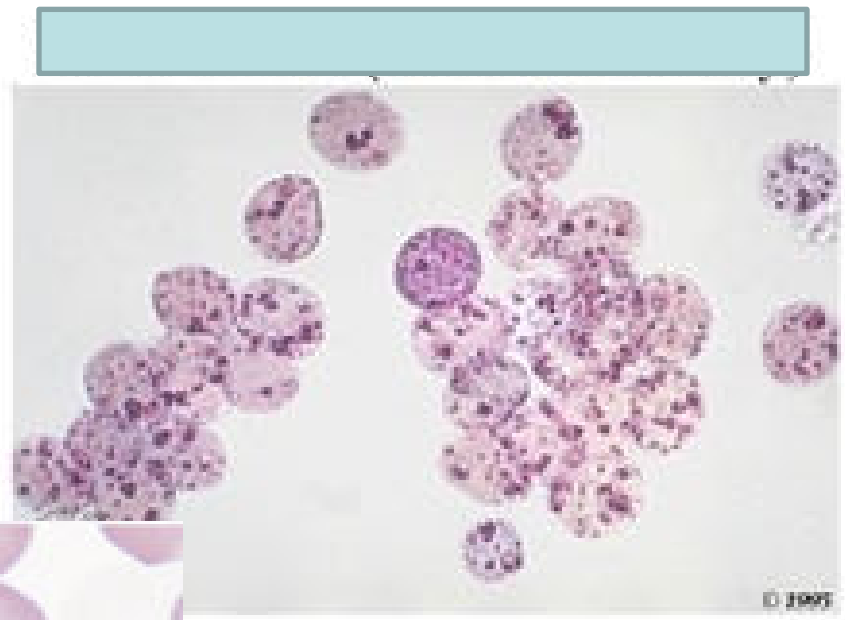


The signs of active normoblasts in erythropoiesis are in evidence: Howell-Jolly bodies, polychromatophilia, and nucleated RBCs.

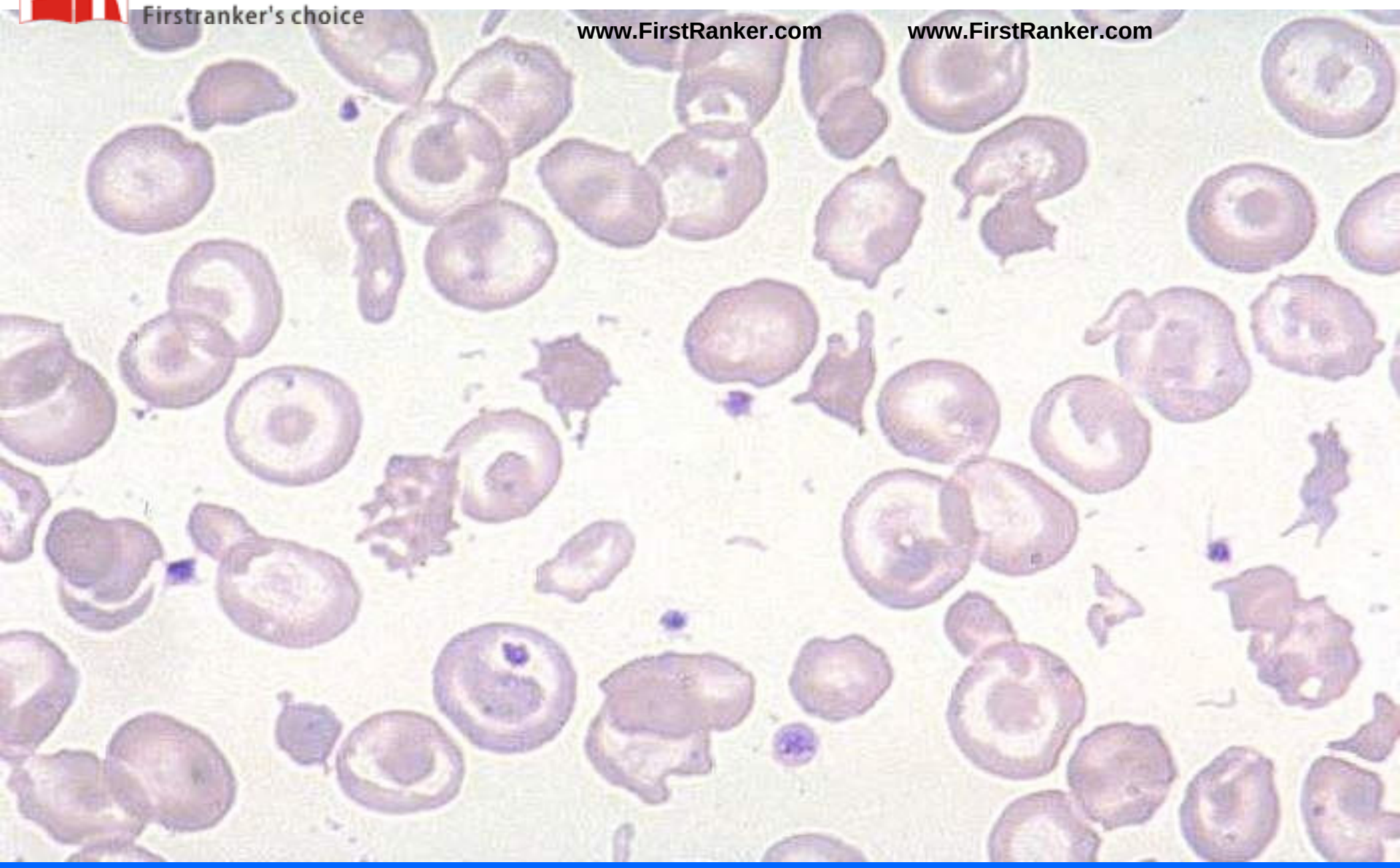


nucleated RBC & Target cells

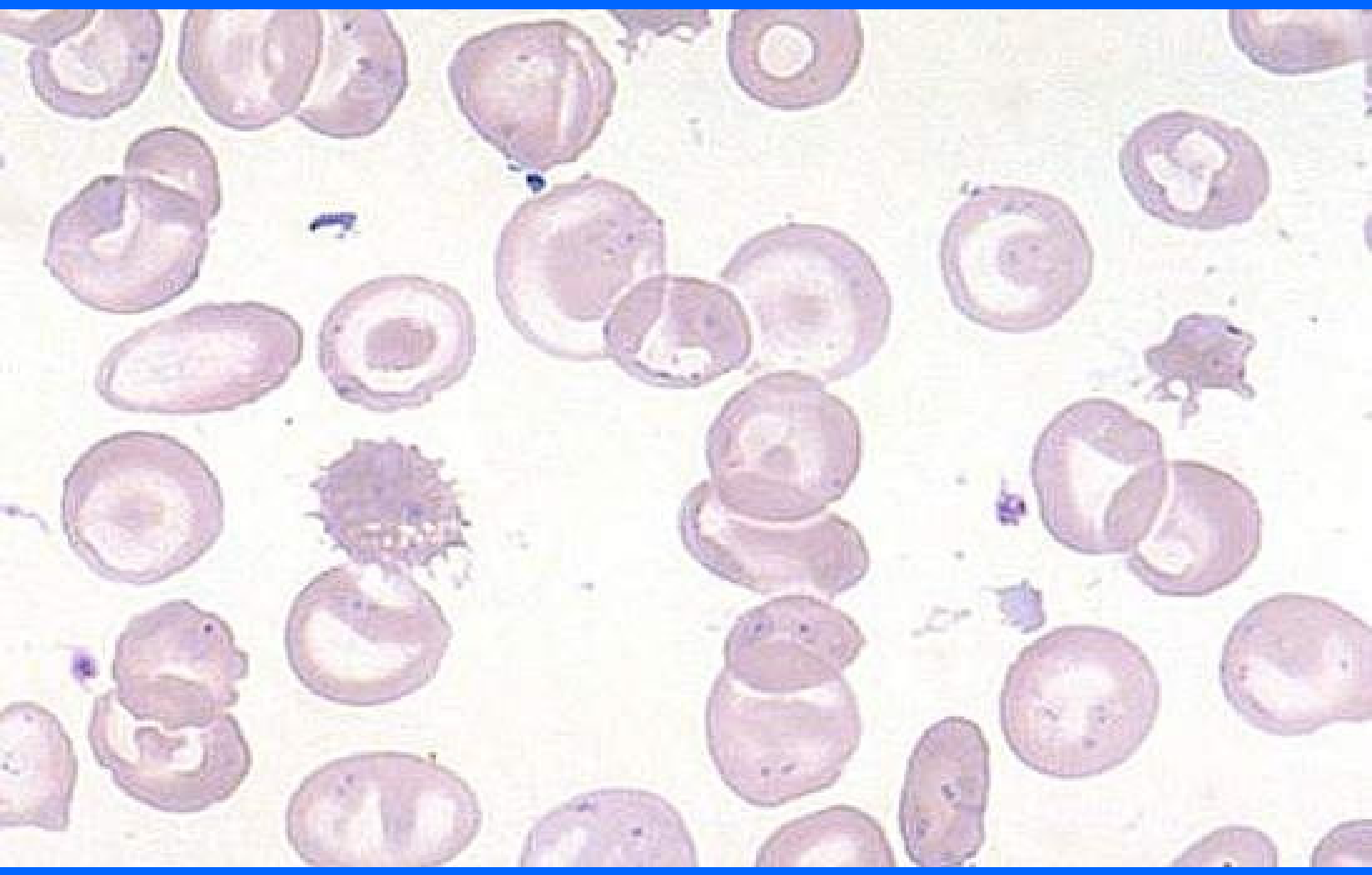




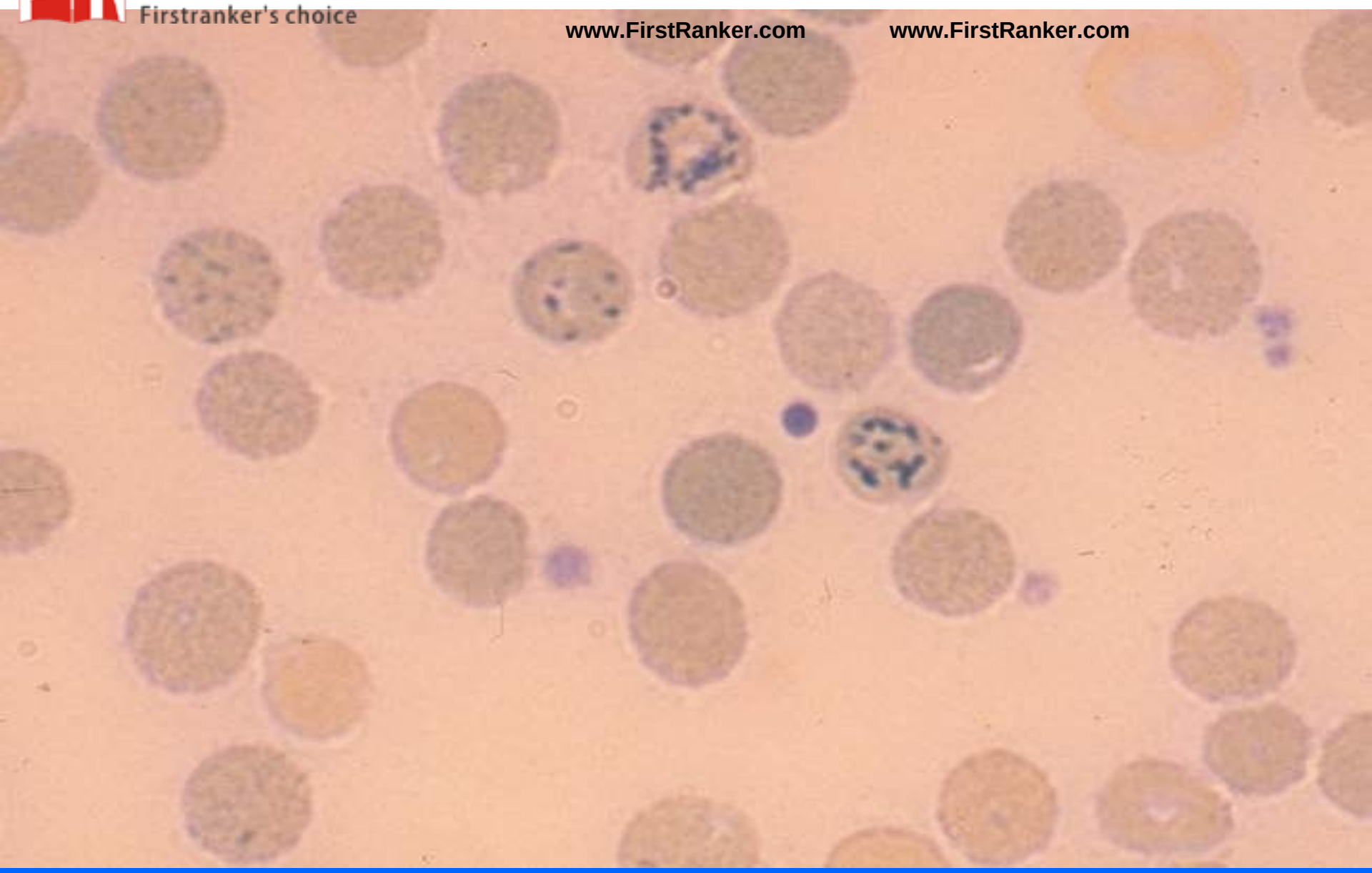
basophilic stripping.



acanthocytes, spherocytes, target cell,and schistocytes.



leptocyte and target cell.



Reticulocytosis - demonstrated by new methylene blue stain

- **RBCs:** marked poikilocytosis, anisocytosis, and polychromatophilia.
- The predominant poikilocyte is the target cell.
- The poikilocytes of hemolysis are also seen: acanthocytes,
  spherocytes,
  burr cells, and schistocytes.

- Moderate to marked basophilic stippling is seen in both the nucleated and non-nucleated forms of erythrocytes.

- **Nucleated RBCs** which are almost invariably present are often numerous and may outnumber the leukocytes.
- The **last two nucleated RBC stages,** the polychromic normoblast and orthochromic normoblasts, are the predominant forms seen.

- **Reticulocytosis** is usually present and may be quite high, e.g., 20% or greater.

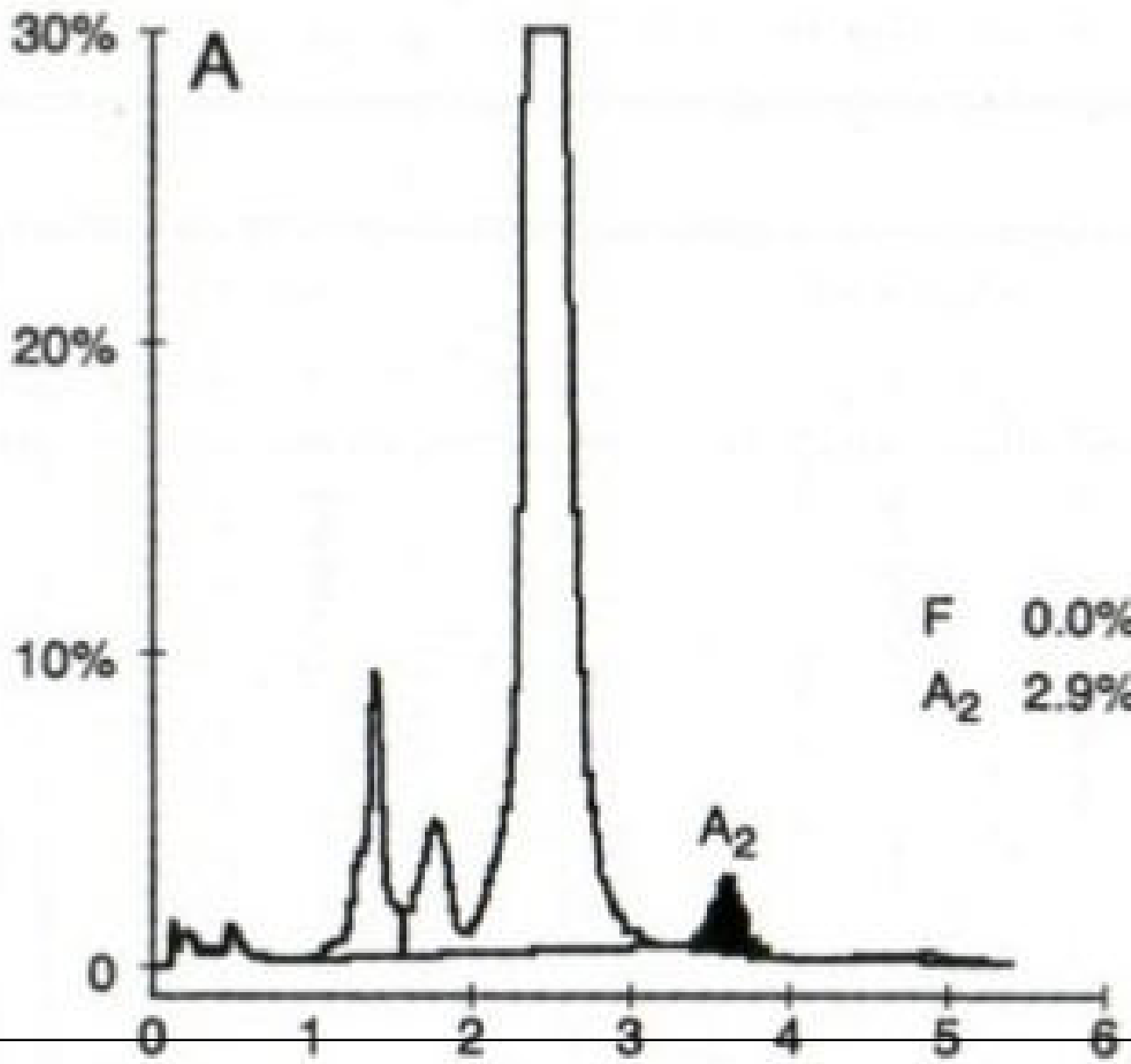
The signs of active erythopoiesis:

Howell-Jolly bodies,
polychromatophilia,
and nucleated RBCs.

- **Leukocyte:** Leukocyte counts range from 10,000-25,000/mm3, and occasionally present immature form.

METHODS FOR INVESTIGATION OF THALASSEMIA

- **Complete Blood Count (Rule of 3)**
- **HbA_2 and Hb F, measurement by HPLC**
- **Molecular methods e.g, PCR for mutational analysis.**



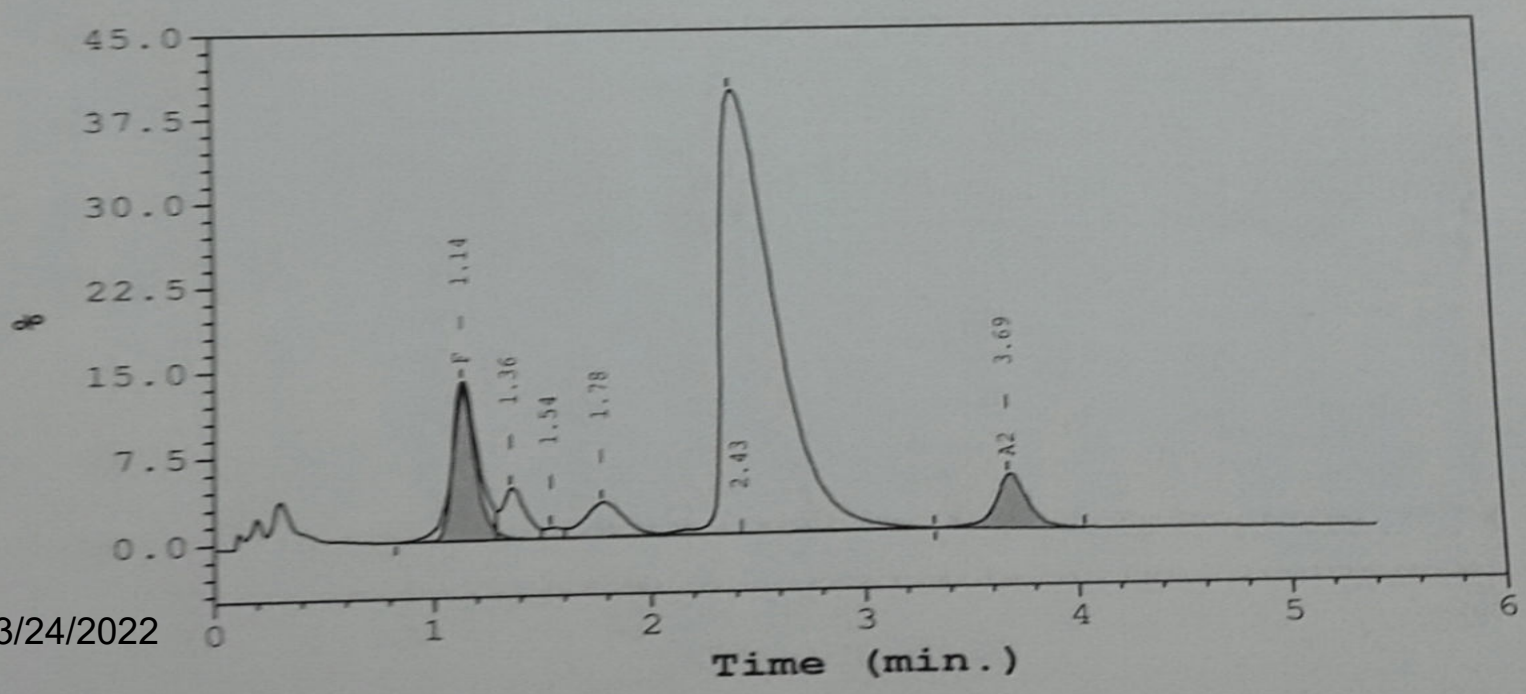
Peak Name	Calibration Area %	Area %	Retention Time (min)	Peak Area
F	10.9*	---	1.14	267693
P2	---	3.6	1.36	90614
Unknown	---	0.6	1.54	14332
P3	---	4.3	1.78	105841
Ao	---	75.3	2.43	1873525
A2	4.7*	---	3.69	135421

Total Area: 2,487,426

F Concentration = 10.9* %
A2 Concentration = 4.7* %

*Values outside of expected ranges

Analysis comments:



Management

- Haematopoietic stem cell transplantation
- Blood transfusion
- Chelation Therapy(Deforaxmine,Defriporone)
- Hydroxyurea

Post-Lecture Feedback Questionnaire

What are the main characteristics of thalassemia?

What are the complaints of the patients?

What is the treatment?

Q 2. Are the disease inherited?

a. Yes, inherited

b. No

c. I have no idea

Q3. What is the impact of consanguineous marriages on these diseases?

Q4. What is the impact of being a carrier of these diseases?

Q5. Do you want to have a blood test to learn if you are a hemoglobinopathy carrier?

a.Yes

b.No

Q6. What is your opinion about the study?

QN 1.Which ONE of the following is NOT a feature of thalassaemia intermedia?

A) It may be due to homozygous β^o thalassaemia

B) It may be associated with extramedullary haemopoiesis

C) It is usually associated with splenomegaly

D) It may cause iron overload

QN2. Which ONE of these statements is TRUE about β - thalassaemia major?

- A. The major cause of death is liver failure
- B. It requires iron chelation at diagnosis
- C. It is usually caused by deletion of β globin genes
- D. It may be diagnosed antenatally

QN3. Which ONE of the following statements is TRUE about β - thalassaemia trait?

A. It is associated with a raised haemoglobin A_2 level

B. It is associated with iron overload

C. It is associated with a reticulocytosis

D. It is associated with splenomegaly

Points to be remember

- Most common cause of β+ Thalassemia
- Most common cause of β0 Thalassemia
- β Thalassemia :MC type of mutation seen
- α Thalassemia : MC type of mutation seen
- Role of Hydroxy urea in Thalassemia
- D/D of MCHC anemia
- Lab diagnosis of thalassemia