

به نام خدا

آنی ها

دکتر افشین فتحی

فوق تخصص بیماریهای خون و سرطان کودکان

مرکز آموزشی و درمانی بوعلی- بخش خون و سرطان

# Definition of anaemia

- Anaemia is defined as a reduction in the **haemoglobin concentration** of the blood
- This results in a **decreased oxygen** carrying capacity

# Anemia (↓Hb and Hct)

MCV, RDW, Retic

MCV ↓

MCV (N)

MCV ↑

Retic ↓ or (N)  
RDW (N)

Retic, RDW ↑

Retic ↓ or (N),  
RDW (N)

Retic, RDW ↑

Retic ↓ or (N),  
RDW (N)

Retic, RDW ↑

- Iron deficiency anemia (↑RDW)
- Thalassemia trait
- Lead poisoning
- Chronic disease
- Sideroblastic anemia

- Thalassemia syndromes (SB thalassemia, Hb H disease)
- Hb C disorders
- Hb E disorders

- Chronic disease
- Transient erythroblastopenia of childhood
- Acute inflammation
- Acute hemorrhage
- Malignancy

- Immune hemolysis
- RBC membrane disorder (HS, He)
- RBC enzyme defects (G6PD, PK deficiency)
- Microangiopathic hemolysis (HUS, TTP, DIC)
- Sickle cell anemia

- Folate deficiency
- B12 deficiency
- Bone marrow failure (aplastic anemia, Fanconi anemia, DBA)
- Myelodysplastic syndrome
- Hypothyroidism
- Drug-induced (anti-convulsants)

- Active hemolysis with brisk reticulocytosis

Review of smear

Further diagnostic test

- Iron studies
- Hb electrophoresis
- Lead level

Review of smear

Further diagnostic test

- Other diseases (infection, renal, liver, metabolic)
- Coombs test
- Osmotic fragility
- Enzyme assays (G6PD, PK)
- Hb electrophoresis

Review of smear

Further diagnostic test

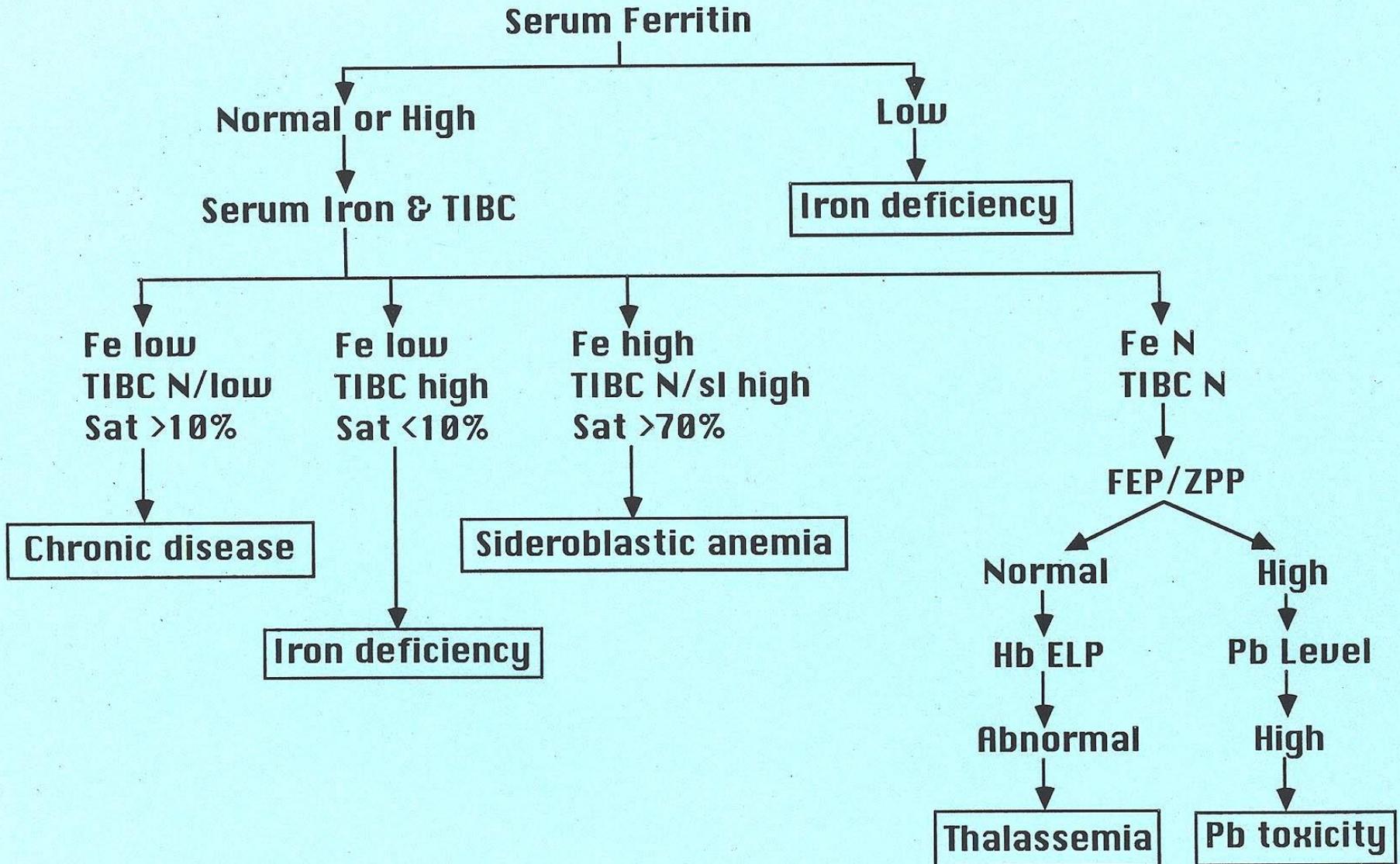
- Folate, B-12 level
- Thyroid function test
- Bone marrow aspirate and biopsy
- Evaluate hemolysis

# Diff. Diagnostic Tests

	Iron deficiency	Chronic disease	Thalasse-mia.	Siderobl.ane mia	Lead poisoning
S.Ferritin	↓	N ↑	N ↑	↑	N
TIBC	↑	↓	N	↓ N	N
S.Iron	↓	↓	N ↑	↑	Variable.
T.Satur.	↓	↓	N ↑	↑ N	↑
FEP	↑	↑	N	↑	↑
Marrow iron	-	+	+	+	+
Special tests	HbA <sub>2</sub> ↓	RF etc.	HbA <sub>2</sub> ↓ HbF ↑	Ring Siderobl	ALA↑, Pb↑

aminolaevulinic acid  
porphobilinogen

# MICROCYTIC HYPOCHROMIC ANEMIA



# Normal Levels

<b>Hb</b>	<b>13.5 – 14 gm %</b>
<b>R.B.C.</b>	<b>4.5 – 4.7 million/cu mm</b>
<b>Serum Iron</b>	<b>50 – 150 µg / dL</b>
<b>TIBC</b>	<b>300 – 360 µg / dL</b>
<b>Transferrin saturation</b>	<b>25 – 50 %</b>
<b>S. Ferritin level</b>	<b>30 µg / Lit</b>
<b>Red Cell protoporphyrin</b>	<b>30 µg / dL</b>
<b>Erythropoietin</b>	<b>15.20 U / Lit</b>
<b>MCV</b>	<b>76 – 100 fL</b>
<b>MCH</b>	<b>27 – 33 pg</b>
<b>MCHC</b>	<b>33.37 gm / dL</b>
<b>PCV</b>	<b>32 – 40 %</b>

**TABLE 149-2 Hematologic Values During Infancy and Childhood**

Age	Hemoglobin (g/dL)		Hematocrit (%)		Reticulocytes (%)	Leukocytes (per mm <sup>3</sup> )		Differential Counts					Nucleated Red Cells/100 WBCS
	Mean	Range	Mean	Range		Mean	Range	Neutrophils (%)		Lymphocytes (%)	Eosinophils (%)	Monocytes (%)	
								Mean	Range				
Cord blood	16.8	13.7-20.1	55	45-65	5	18,000	9000-30,000	61	40-80	31	2	6	7
2 wk	16.5	13-20	50	42-66	1	12,000	5000-21,000	40		48	3	9	3-10
3 mo	12.0	9.5-14.5	36	31-41	1	12,000	6000-18,000	30		63	2	5	0
6 mo-6 yr	12.0	10.5-14	37	33-42	1	10,000	6000-15,000	45		48	2	5	0
7-12 yr	13.0	11-16	38	34-40	1	8000	4500-13,500	55		38	2	5	0
Adult													
Female	14.0	12-16	42	37-47	1.6	7500	5000-10,000	55	35-70	35	3	7	0
Male	16.0	14-18	47	42-52									

WBCs, white blood cells.

From Behrman RE (ed): Nelson Textbook of Pediatrics, 14th ed. Philadelphia, WB Saunders, 1992.

# The reticulocyte count

- To be useful the reticulocyte count must be adjusted for the patient's hematocrit. Also when the hematocrit is lower reticulocytes are released earlier from the marrow so one can adjust for this phenomenon.

Thus:

- **Corrected retic.** = Patients retic. x (Patients Hct/45)
- **Reticulocyte index (RPI)** = corrected retic. count/Maturation time  
(Maturation time = 1 for Hct=45%, 1.5 for 35%, 2 for 25%, and 2.5 for 15%.)
- **Absolute reticulocyte count** = retic x RBC number.

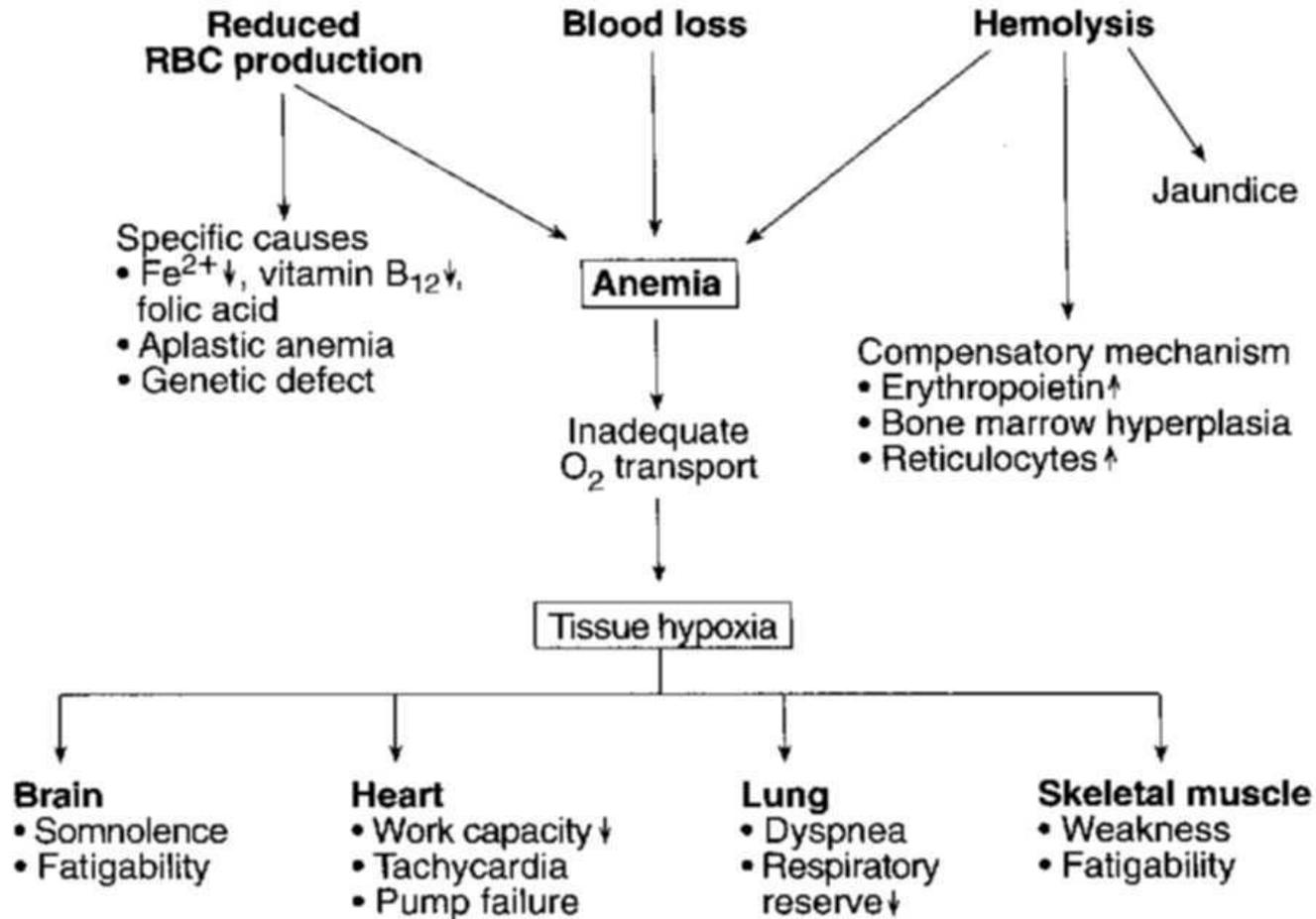
# The reticulocyte count (kinetic approach)

- Increased reticulocytes (greater than 2-3% or 100,000/mm<sup>3</sup> total) are seen in blood loss and hemolytic processes, **although up to 25%** of hemolytic anemias will present with a normal reticulocyte count due to **immune destruction** of red cell precursors.
- Retic counts are most helpful if extremely low (**<0.1%**) or **greater than 3%** (100,000/mm<sup>3</sup> total).

# WHO Classification of Anaemia

Degree	Hb%	Haematocrit (%)
Moderate	7-10.9	24-37%
Severe	4-6.9	13-23%
Very Severe	<4	<13%

# SYMPTOMS, AND SIGNS OF ANEMIA



# Classification of Anaemia: Microcytic Hypochromic

- $MCV < 80 \text{ fl}$
- $MCH < 27 \text{ pg}$

# Classification of Anaemia: Normocytic Normochromic

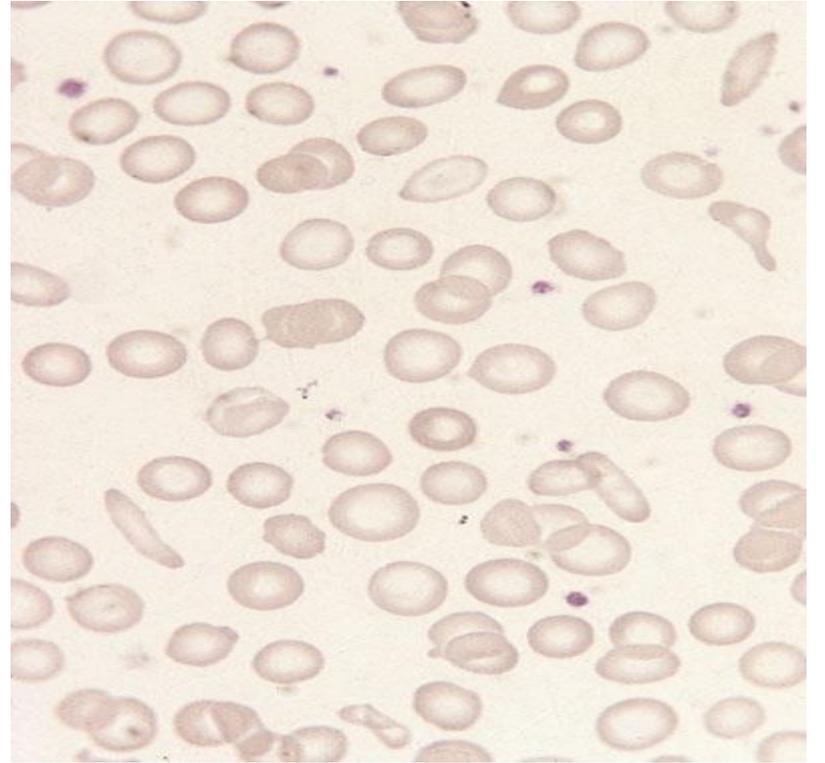
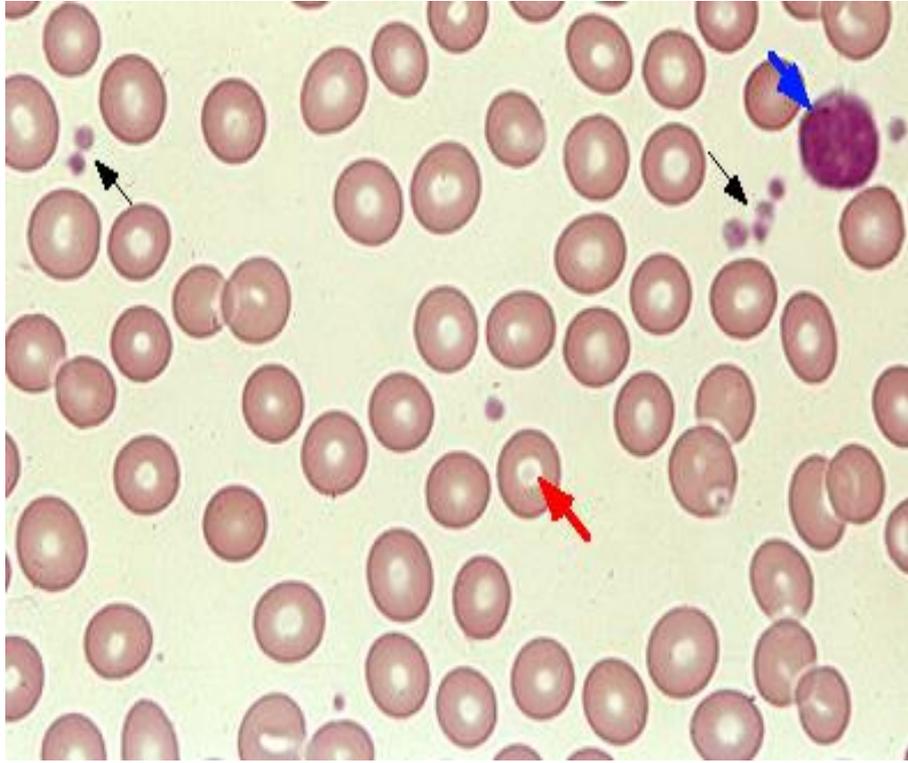
- MCV 80-100fl
- MCH >26pg

# Classification of Anaemia: Macrocytic

- $MCV > 100 \text{ fl}$
- **Megaloblastic**: vitamin B<sub>12</sub> or folate deficiency
- **Non-megaloblastic**: alcohol, liver disease, myelodysplasia, aplastic anaemia

# Iron deficiency anaemia

- **Assess for**
- **Dietary** Iron deficiency
- **Malabsorption**- coeliac
- **Chronic blood loss**
- Gastrointestinal
- Menorrhagia

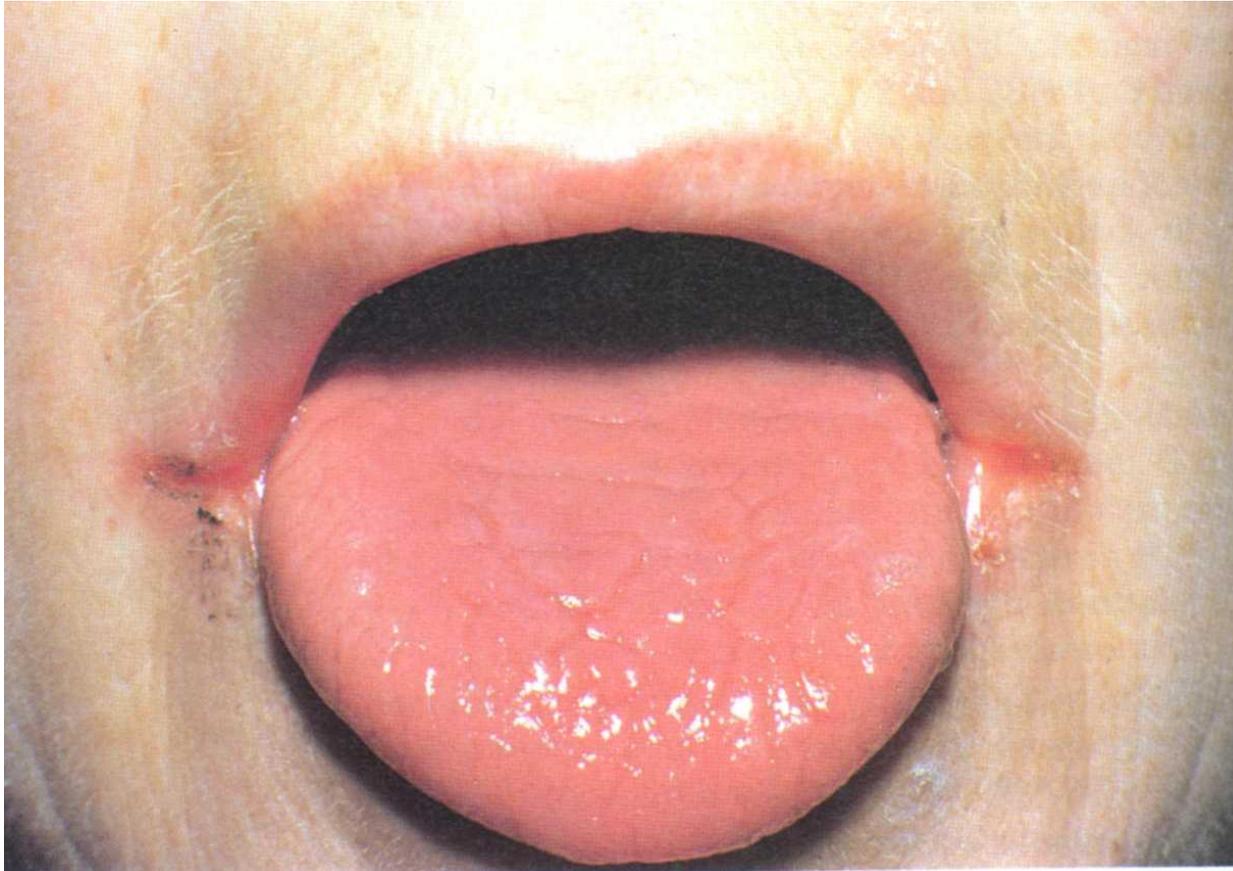


# Mentzer (MCV/RBC)

**13↑**      **Iron deficiency**

**10↓**      **thalassemia**

# ANGULAR CHEILITIS AND SMOOTH TONGUE IN IRON DEFICIENCY





# IRON DEFICIENCY ANEMIA CURE

- ORAL
  - 200 mg of iron daily 1 hour before meal (e.g. 100 mg twice daily)
  - How long?
    - 14 days + (Hg required level – Hg current level) x 4
  - half of the dose - 6 – 9 months to restore iron reserve
  - Absorption
    - is enhanced: vit C, meat, orange juice, fish
    - is inhibited: cereals, tea, milk

# درمان خوراکی فقر آهن

- 3 میلی گرم برای هر کیلو در روز
- شب با شکم خالی تک دوز
- شربت آهن هر 5 سی سی 40 میلی گرم آهن المانته دارد
- هر قرص 50 میلیگرم آهن المانته دارد
- ویتامین ث جذب آهن را افزایش میدهد

# Failure of Response to Oral Iron

- Continuing blood loss
- Failure to take tablets
- Wrong diagnosis-thalassaemia trait, sideroblastic anaemia
- Mixed deficiency-associated vitamin B<sub>12</sub> or folate deficiency
- Another cause for the anaemia, e.g. malignancy, inflammation
- **Malabsorption**
- Use of a slow release preparation

# درمان تزریقی فقر آهن

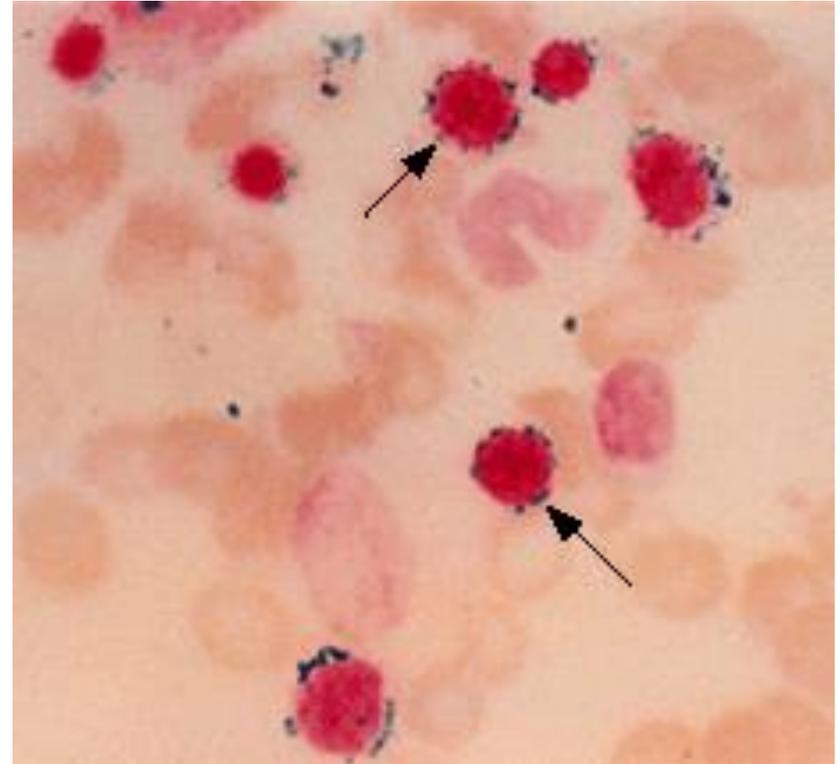
- تزریق آهن دکستران بصورت عضلانی Z
- تزریق آهن دکستران بصورت وریدی با دوز :

$$0.0442 \times (\text{HB} - \text{HB p}) \times W + (0.26 \times W)$$

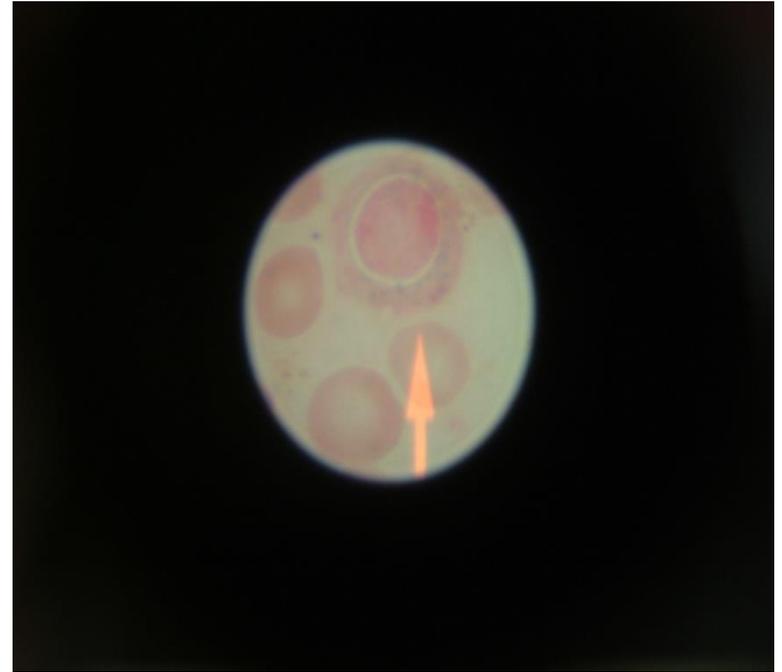
- 2 تا 3 بار در سال

# Sideroblastic anemia

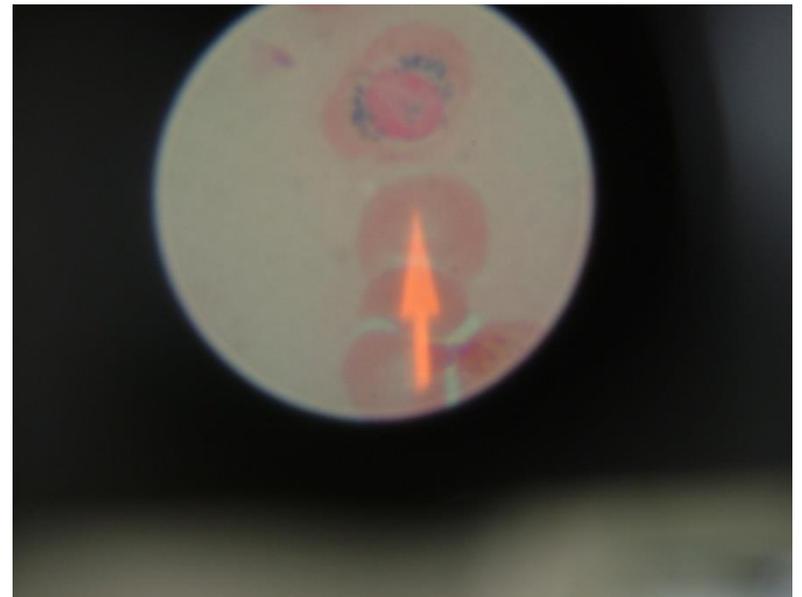
- Normocytic, normochromic or **Microcytic and Hypochromic**  
Except In Pearson Syndrome
- Reticulocytopenia
- Thrombocytopenia and Neutropenia
- **Ineffective Erythropoiesis**
- Ring Sideroblast (Greater Than 10% of Erythroid Precursor) in prussian blue-stained
- Mild to Moderate **Hemolysis**



- Acquired → Rings occur in **early cells**



- Conjenital → Rings Prodominante in **late** normoblasts



# Vitamin B<sub>12</sub>

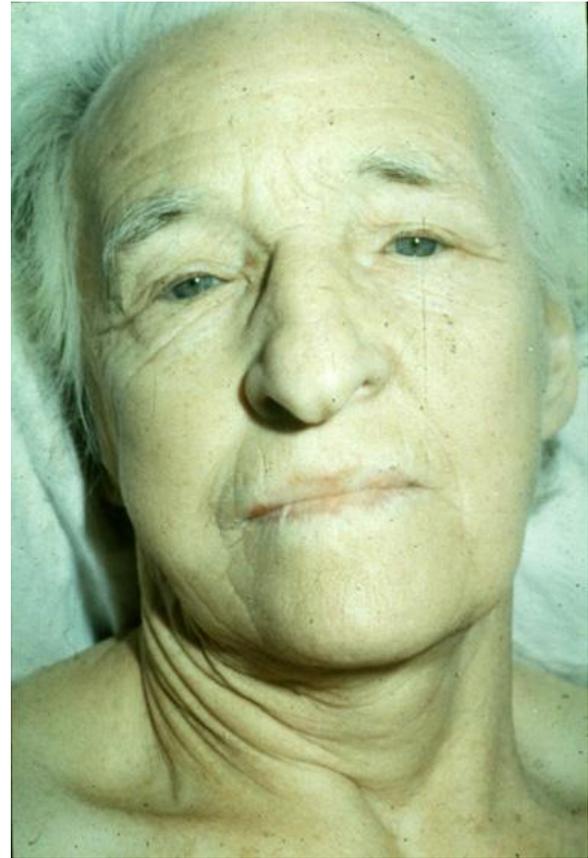
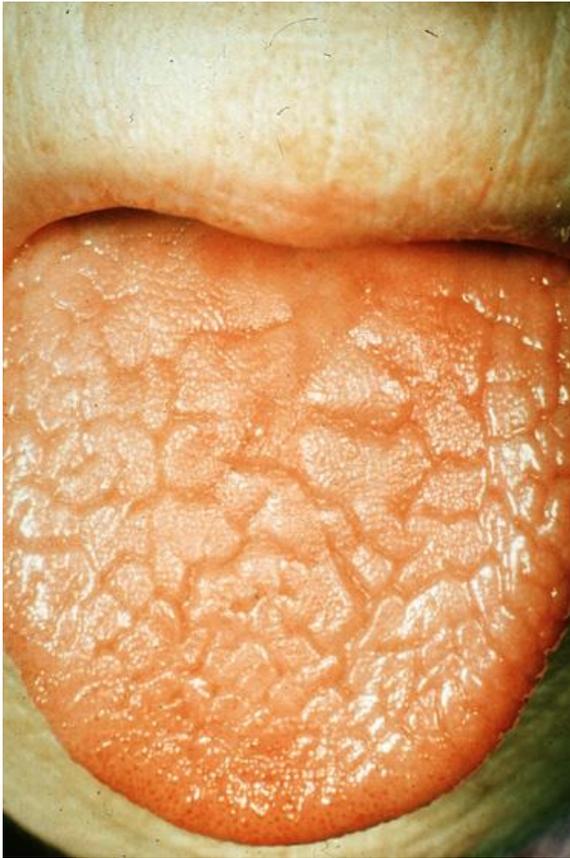
- Normal daily intake
- Main foods
- Cooking
- Minimal daily requirement
- Body stores
- Absorption
- site
- mechanism
- limit
- Usual therapeutic form
- 7-30 $\mu$ g
- Animal produce only
- Little effect
- 1-2 $\mu$ g
- 2-3mg (enough for 2-4yrs)
- Ileum
- Intrinsic factor
- 2-3 $\mu$ g
- Hydroxocobalamin

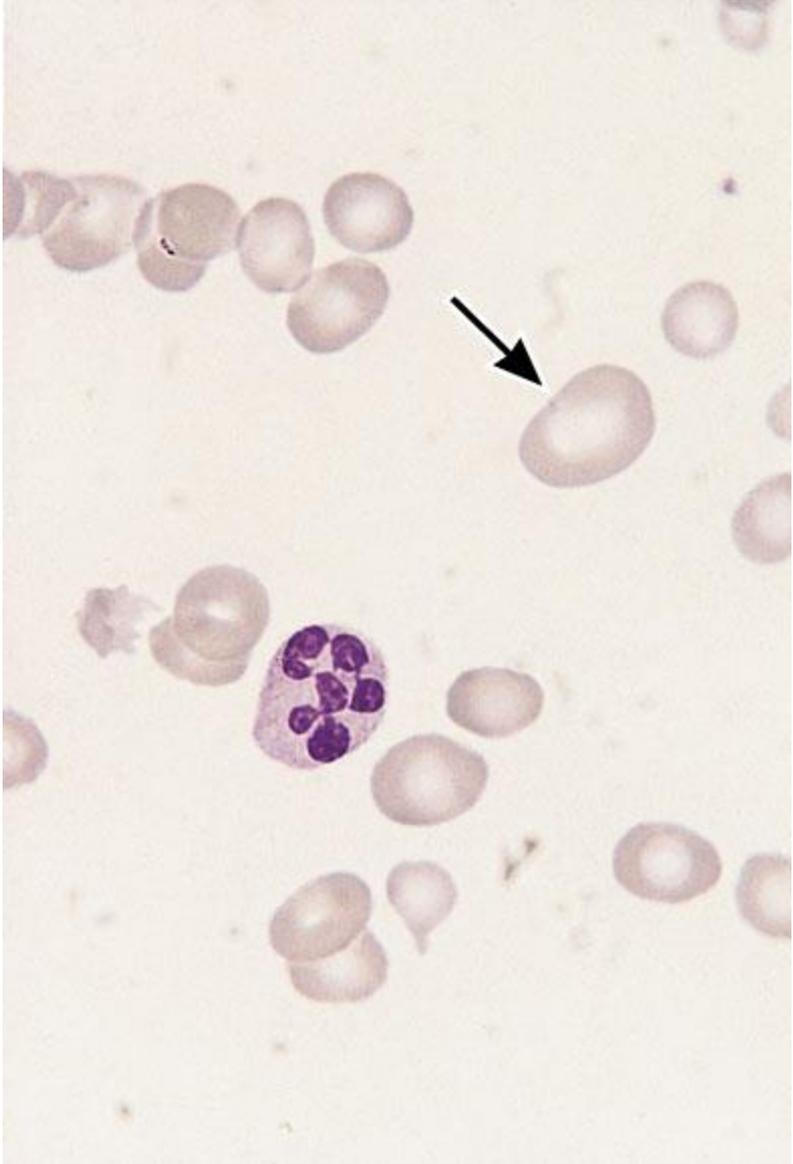
# Pernicious Anaemia

- **Autoimmune** attack on the **gastric mucosa** leading to atrophy of the stomach
- Females > males
- Associated **autoimmune diseases**
- Tends to occur in families

# Megaloblastic Anaemia: Clinical

- **Insidious onset** of symptoms and signs of anaemia
- **Lemon yellow jaundice**
- Glossitis, angular stomatitis
- Purpura
- Neuropathy-subacute combined **degeneration** of the cord (neuropathy affecting the peripheral sensory nerves and posterior and lateral columns)





## درمان کمبود B 12

- 1000 میکرو روزانه برای یک هفته بعد 100 میکرو هر هفته برای یک ماه بعد هر ماه 100 میکرو
- در آنمی پرنسیوز 1000 میکرو هر 3 ماه
- در اختلال متابولیسم 1000 میکرو 2 تا 3 بار در هفته
- در موارد شدید دوز شروع کننده **0.2 میکرو** برای هر کیلو بصورت زیر جلدی برای پیشگیری از افت کشنده پتاسیم

# Folic Acid

- Normal daily intake
- Main foods
- Cooking
- Minimal daily requirement
- Body stores
- Absorption
- site
- mechanism
- limit
- Usual therapeutic form
- 200-250 $\mu$ g
- Most liver, greens, yeast
- Easily destroyed
- 100-150 $\mu$ g
- 10-12mg (4mths supply)
- Duodenum and jejunum
- Converted to methylTHF
- 50-80% of dietary intake
- Folic acid

# Causes of Folic Acid Deficiency

- **Nutritional** -old age, poverty, diet etc
- **Malabsorption**- tropical sprue, coeliac disease, Crohn's disease
- **Excess utilization**
- Physiological-pregnancy, lactation, prematurity
- Pathological-haemolytic anaemia, myelofibrosis, malignant disease, inflammatory disease
- **Drugs**-anticonvulsants
- **Mixed**-liver disease, alcoholism, intensive care

## درمان کمبود اسید فولیک

- 5 میلی گرم روزانه (100 میکرو برای هر کیلو ) به مدت یک ماه
- در موارد سوء جذب 5-15 میلیگرم برای هر کیلو در روز

# مسیر جنگلی همیشه سوئی

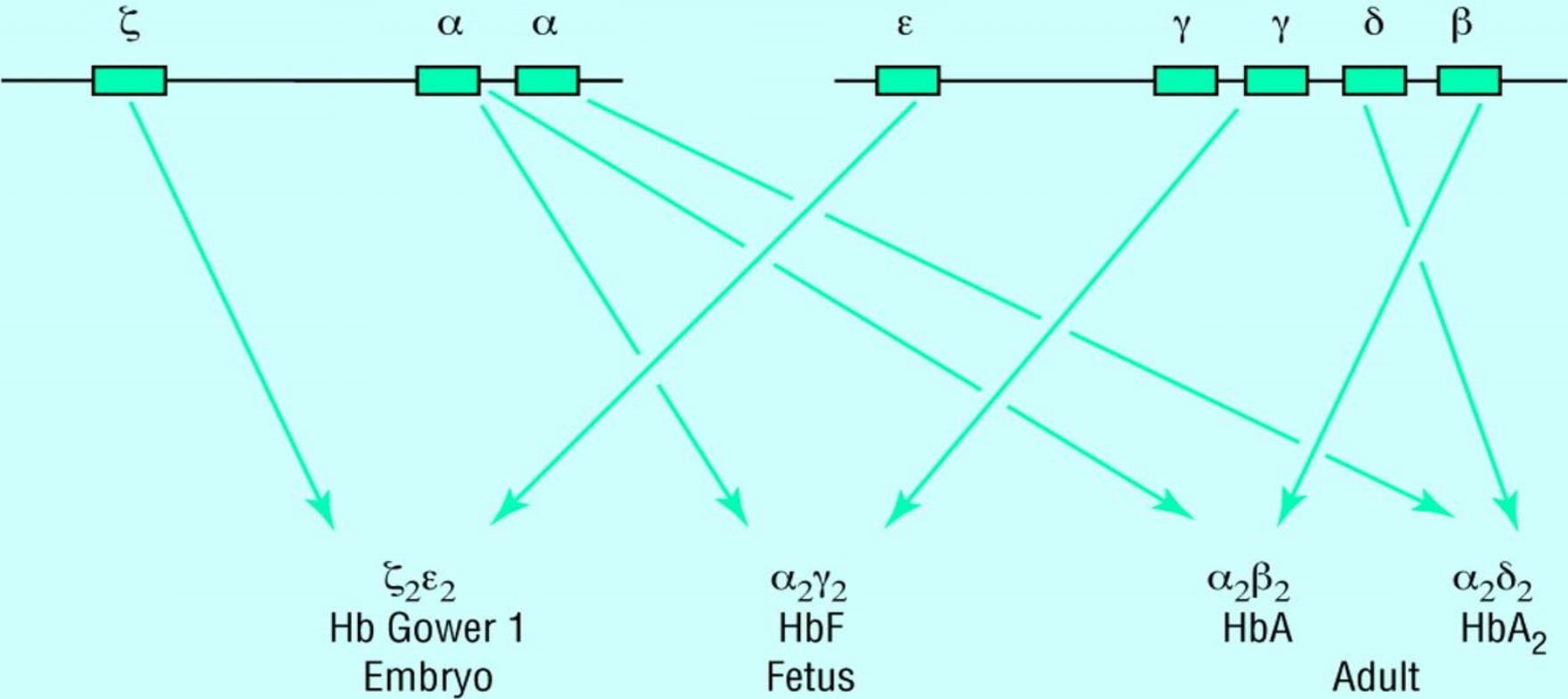




**Old World Thalassemia Distribution**

Chromosome 16

Chromosome 11

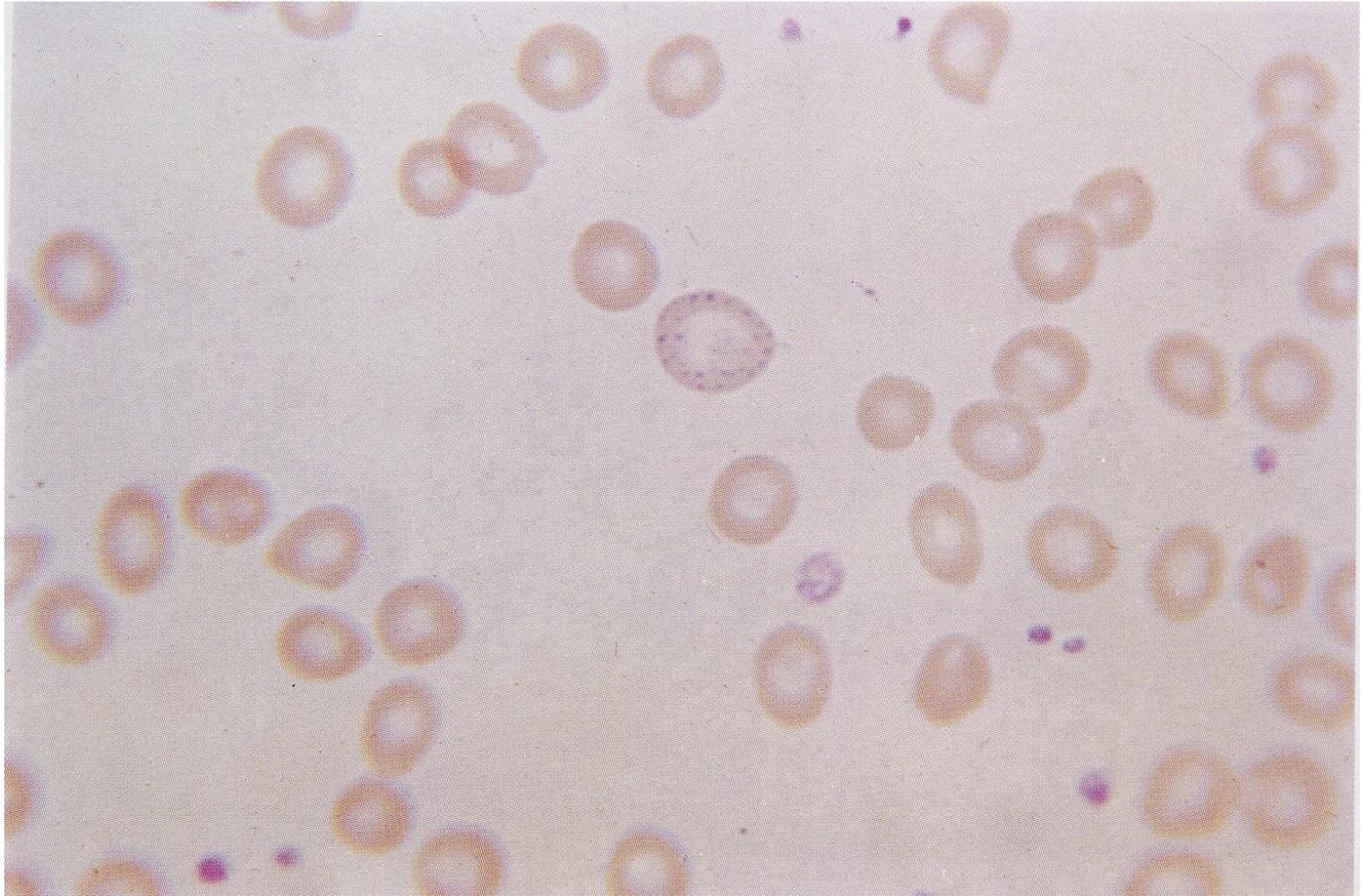


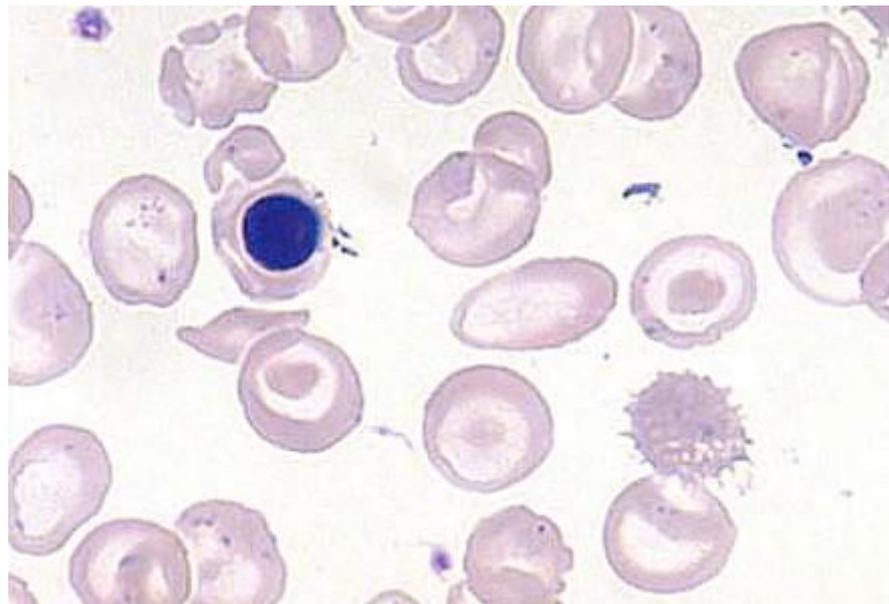
# Classification & Terminology

## Beta Thalassemia

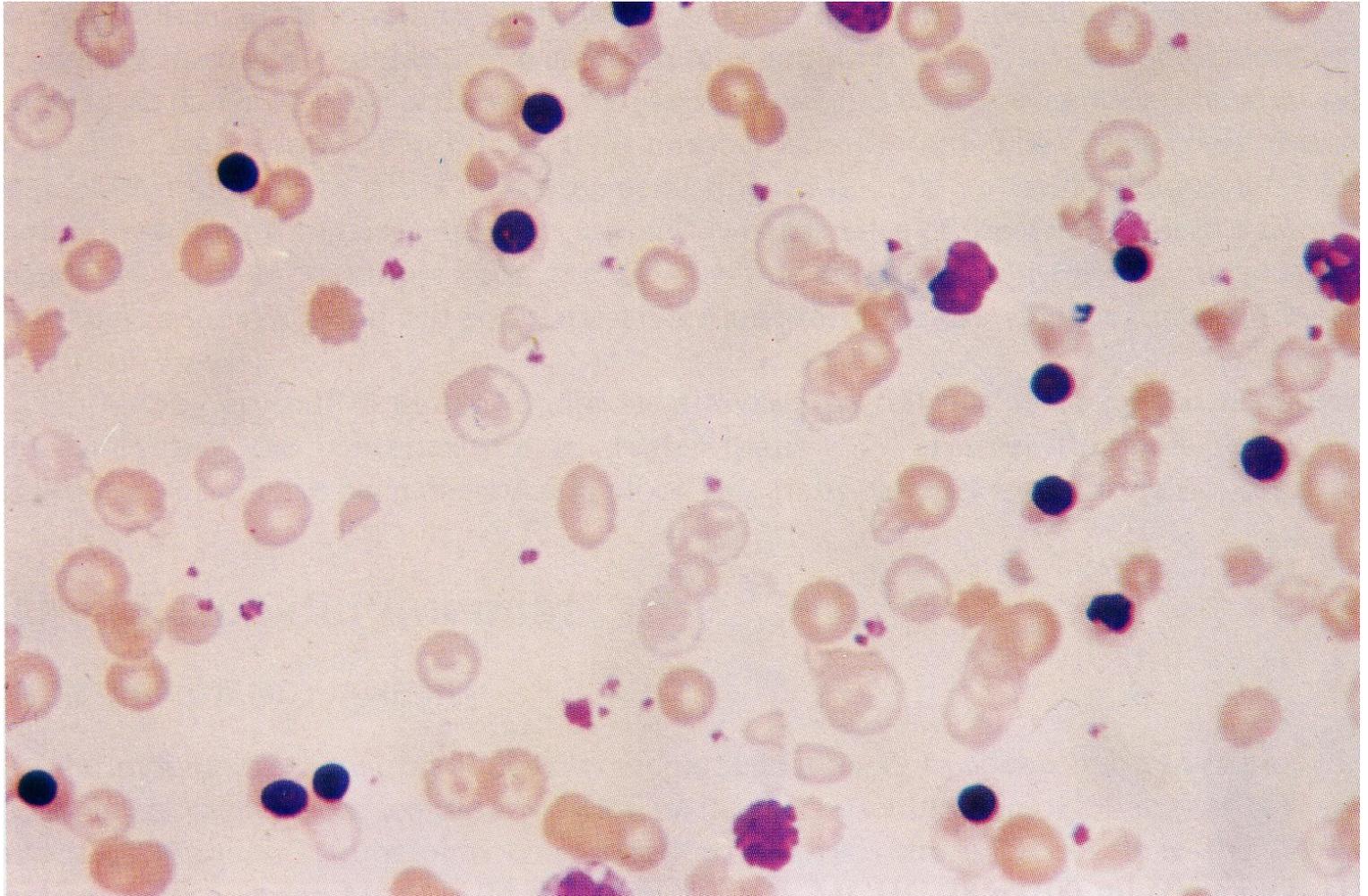
- Normal  $\beta/\beta$
- Minor  $\beta/\beta^0$   
 $\beta/\beta^+$
- Intermedia  $\beta^0/\beta^+$
- Major  $\beta^0/\beta^0$   
 $\beta^+/\beta^+$

# Thalassemia minor

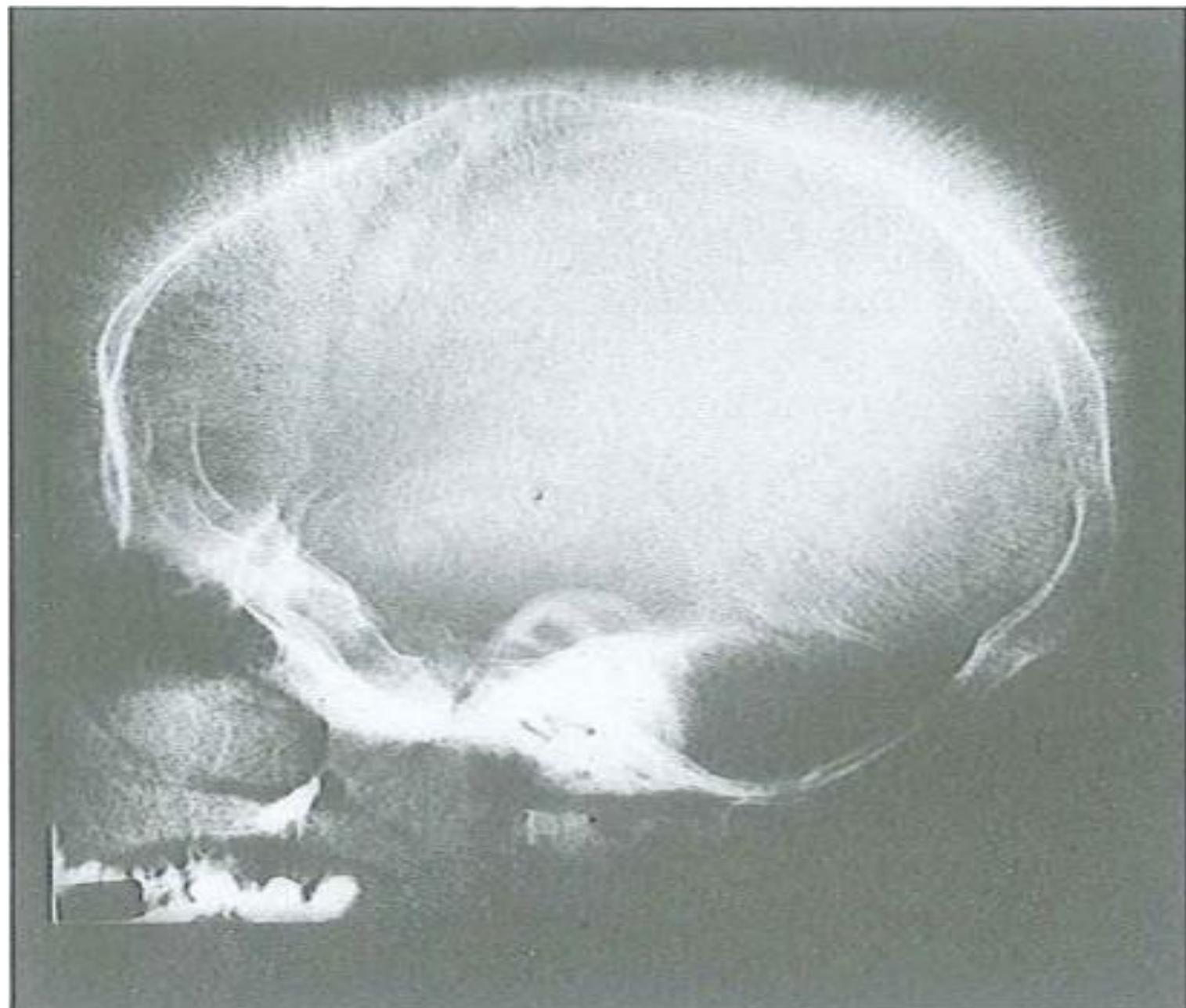




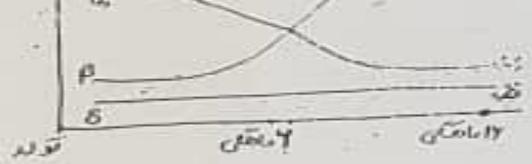
# Thalassemia major







Hb F =  $\alpha_2 \beta_2$   
 Hb A<sub>2</sub> =  $\alpha_2 \delta_2$   
 Hb barts =  $\gamma_4$   
 Hb H =  $\beta_4$



$F = V_0 / A = 75\%$   
 $A = 9V / F = 1 / A_2 = 1.35\%$   
 $A = 90 / F = 1 - 10 / A_2 = 3.0 - 1.1$

$A = 90 / F = 1 - 10 / A_2 = 3.0 - 1.1$   
 $F = A \Rightarrow 50\%$

Hb = 9.1  $\uparrow$  ← مقهور  
 RBC  $\uparrow$   
 MCV  $\downarrow$   
 Hb = 7.9 ← فقره  
 Hb = 7.7 ← فقره  
 Hb = 7.7 ← فقره

سبب تالیفی  
 $\beta^+ / \beta$   
 $\beta^+ / \beta^+$   
 $\beta^+ / \beta^+$   
 $\beta^0 / \beta$   
 $\beta^0 / \beta^+$   
 $\beta^0 / \beta^+$

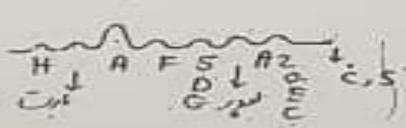
$F = 90 / \uparrow$      $A = 1 - 10 / \uparrow$      $A_2 = ? \uparrow$

Barts =  $\uparrow$   
 $(A - F) A_2 = \downarrow 2$   
 Hb H = F barts  $\uparrow$   
 وقت آنتی بادی سوراخ باستان  
 آنتی بادی سوراخ باستان  
 و H در آن سوراخ سوراخ باستان

Hb H =  $\downarrow 5 /$  ← در زمان - وقت آنتی بادی  
 Hb H =  $5 - 10 /$  ← در زمان - وقت آنتی بادی  
 Hb H =  $10 - 15 /$  ← در زمان - وقت آنتی بادی  
 barts =  $100 /$  ← آنتی بادی سوراخ باستان

سبب تالیفی  
 $\alpha \alpha / \alpha \alpha$   
 $\alpha - \alpha / \alpha \alpha$

آهنی هایدروکسیل / سوراخ باستان (RBC  $\uparrow$ )    آنتی بادی سوراخ باستان (A<sub>2</sub> سوراخ باستان)



(HPFH  $\rightarrow F \uparrow 90\%$ )  
 در زمان آهنی

سبب تالیفی  $\beta \beta$  (سوراخ باستان)  
 سوراخ باستان  $\alpha \alpha$  / سوراخ باستان  
 سوراخ باستان  $\alpha \alpha$  / سوراخ باستان

$S \downarrow < 50\%$      $A > 50\%$   
 $A =$  سوراخ باستان     $\beta^+ / S$   
 $A =$  سوراخ باستان     $\beta / S$   
 $S \uparrow 50\%$      $A < 50\%$

سبب تالیفی  $\beta^+ / S$   
 سبب تالیفی  $\beta / S$   
 سبب تالیفی  $S / S$   
 سبب تالیفی  $C / S$   
 سبب تالیفی  $S / S$   
 سبب تالیفی  $C / S$

در وقت سوراخ باستان  
 در وقت سوراخ باستان  
 در وقت سوراخ باستان

# Hb patterns in haemoglobin disorders

% Haemoglobin	A	F	A <sub>2</sub>	S	Other
Normal	97	<1	2–3		
β thalassaemia trait	80–95	1–5	3–7		
β thalassaemia intermedia	30–50	50–70	0–5		
β thalassaemia major	0–20	80–100	0–13		
HPFH (Black heterozygote)	60–85	15–35	1–3		
HPFH (Black homozygote)		100			
α thalassaemia trait	85–95				Bart's 0–10% at birth
HbH disease	60–95				H 5–30% Bart's 20–30% at birth
HbBart's hydrops					Bart's 80–90%

# Clinical Outcomes of Beta Thalassemia

## ○ Beta Thalassemia minor (trait)

- asymptomatic
- microcytosis
- minor anemia

## ○ Beta Thalassemia intermedia

- symptoms similar to **Cooley Anemia but less severe**

## ○ Beta Thalassemia major (Cooley Anemia)

- most severe form
- moderate to severe anemia
- intramedullary hemolysis (RBC die before full development)
- peripheral hemolysis & splenomegaly
- skeletal abnormalities (overcompensation by bone marrow)
- **increased risk of thromboses**
- pulmonary hypertension & congestive heart failure

# Classification & Terminology

## Alpha Thalassemia

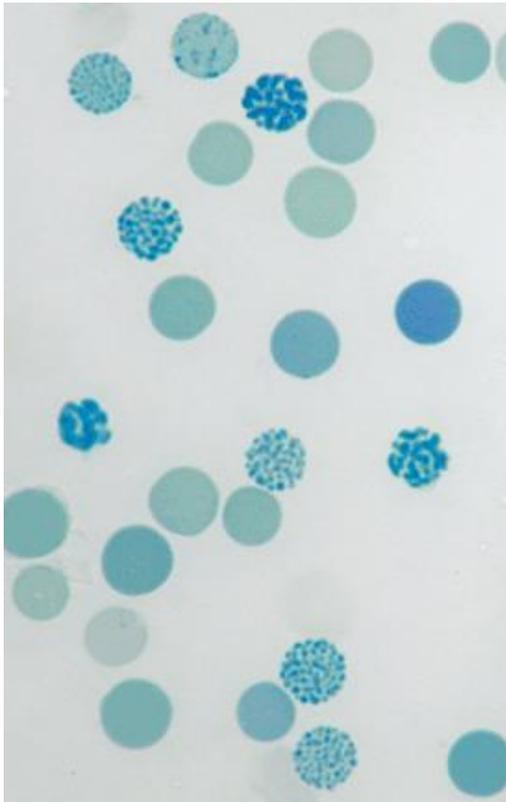
- Normal  $\alpha\alpha/\alpha\alpha$
- Silent carrier  $-\alpha/\alpha\alpha$
- Minor  $-\alpha/-\alpha$   
 $--/\alpha\alpha$
- Hb H disease  $--/-\alpha$
- Barts hydrops fetalis  $--/--$

# Clinical Outcomes of Alpha Thalassemia

- Silent carriers
  - asymptomatic
  - “normal”
- Alpha Thalassemia minor (trait)
  - no anemia
  - microcytosis
    - unusually small red blood cells due to fewer Hb in RBC
  - “normal”
- Alpha Thalassemia intermedia (“Hemoglobin H”)
  - microcytosis & hemolysis (breakdown of RBC)
    - results in severe anemia
  - bone deformities
  - splenomegaly (enlargement of spleen)
  - “severe and life threatening”

# HB H ( $\beta$ 4)

**Stained Supravivally**



**Golf Ball**



# Treatment of Thalassaemia Trait

- Reassurance
- Evaluation of iron status
- Antenatal/ genetic counselling

# Treatment for Beta Thalassemia

- Trait – **no** treatment required
- Intermedia
- Major (Cooley anemia)
  - **Regular folate** supplementation
  - **RBC transfusion** (**Splenectomy** may decrease need for transfusions)
    - to maintain [Hgb] ~**9-10g/dL**
    - Blood transfusions → iron accumulation → iron overload
    - Iron chelators (**diferroxamin**)

# Treatments for Alpha Thalassemia

- Silent Carrier – **no** treatment required
- Trait (Minor) – **no** treatment required
- Hemoglobin H Disease – **Folate**
  - avoid iron supplements
- Major (Hemoglobin Bart's) – **RBC transfusion**  
while still in womb, else fetus is stillborn or  
dies shortly

# Iron overload and chelation

- Can occur in any patient requiring chronic transfusion therapy or in hemochromatosis.
- Liver biopsy is the most accurate test though MRI is being investigated.
- Ferritin is a good starting test.
- 120 cc of red cells/kg of body weight is an approximate point at which to think about iron overload

# Iron overload and chelation

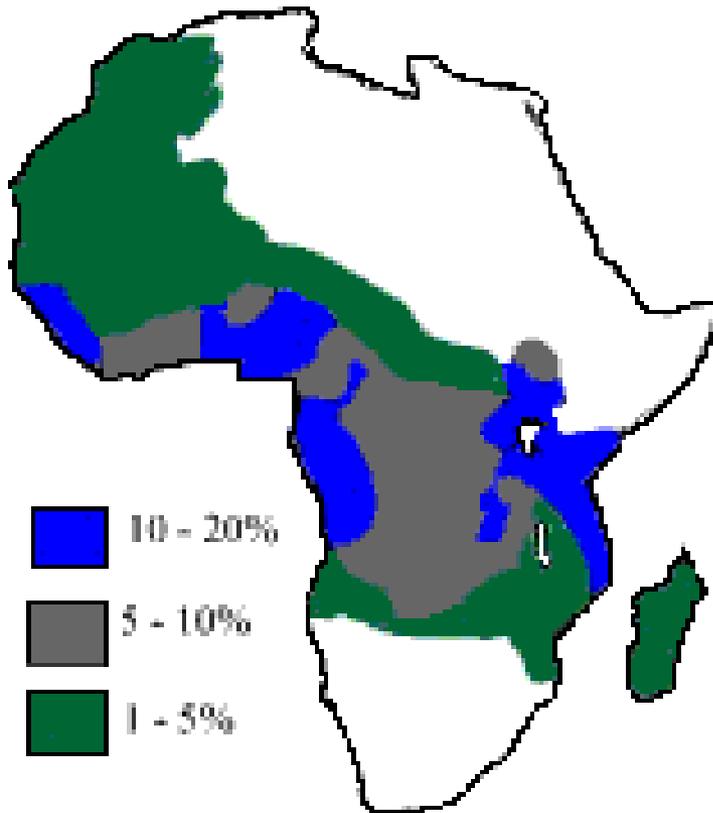
- Chelator, deferoxamine
  - 25 mg/kg sq per day over 8 hours.
  - Supplementation with vitamin C may aid excretion.
  - Oototoxicity, eye toxicity, allergic reactions.
  - Discontinue during an infection.
- Oral chelators are in development.

# آبشارهای شوشتر



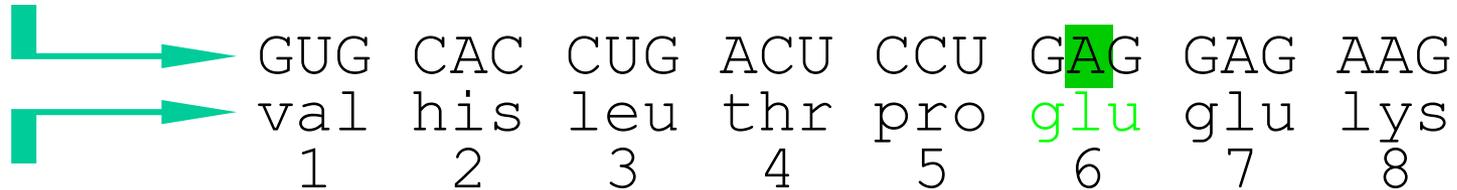
# Sickle Cell Gene

# Severe Malaria



# Sickle Cell Hemoglobin

Normal mRNA

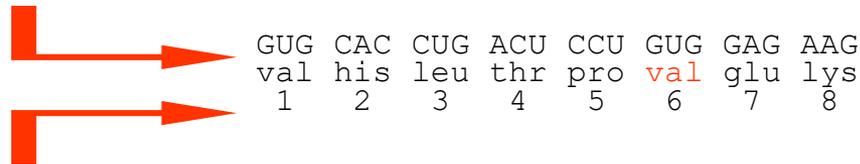


Normal protein

Mutation  
(in DNA)



Mutant mRNA

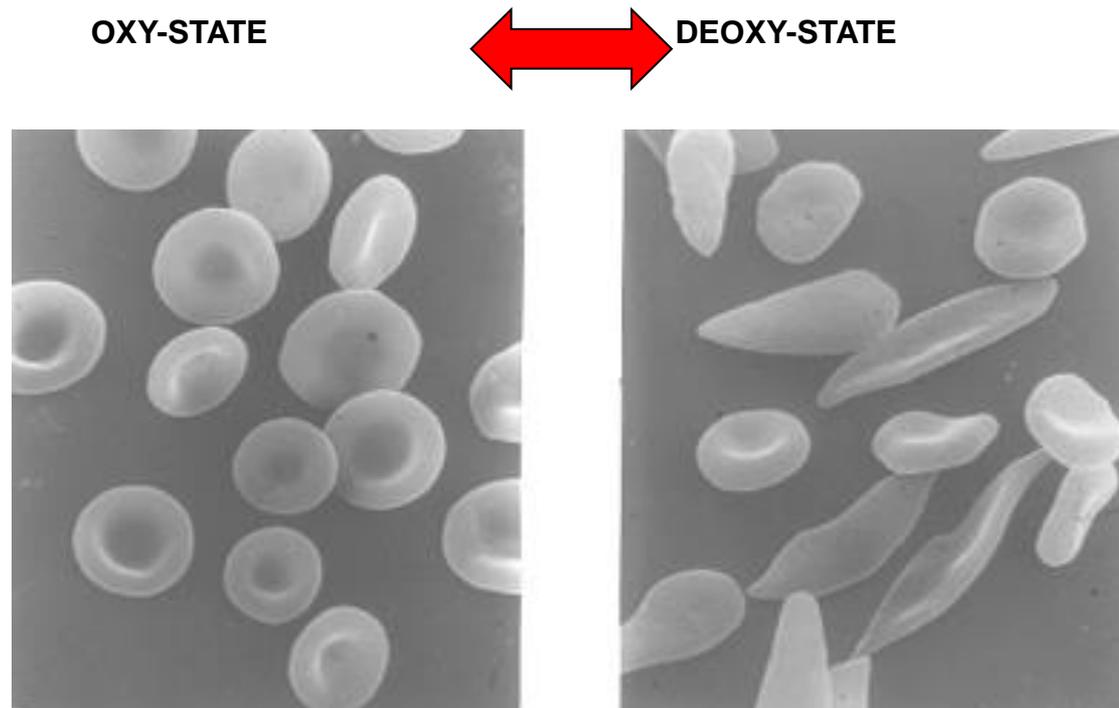


Mutant protein

Glutamate (glu), a negatively charged amino acid, is replaced by valine (val), which has no charge.

# Red Blood Cells from Sickle Cell Anemia

- **Deoxygenation of SS erythrocytes leads to intracellular hemoglobin polymerization, loss of deformability and changes in cell morphology.**

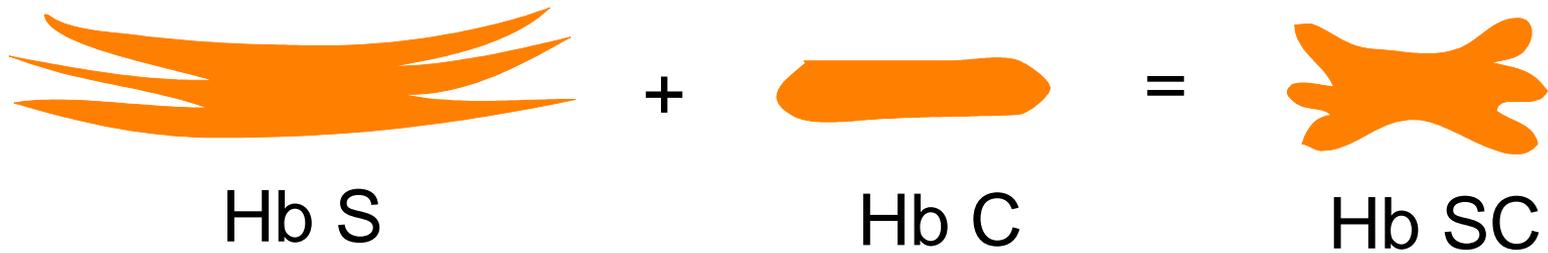


# Sickle Cell Trait

- Sickle haemoglobin (S) + Normal haemoglobin (A) in RBC
  - Adequate amount of normal Hb (A) in red blood cells
    - RBC remain flexible
    - Carrier
    - **Do Not have the symptoms** of the sickle cell disorders, with 2 exceptions
      1. Pain when Less **Oxygen than usual** (scuba diving, activities at high altitude (12,000ft), under general anaesthesia)
      2. Minute **kidney** problems

# Morphologic Findings

## Hb SS vs. Hb SC vs. Hb CC



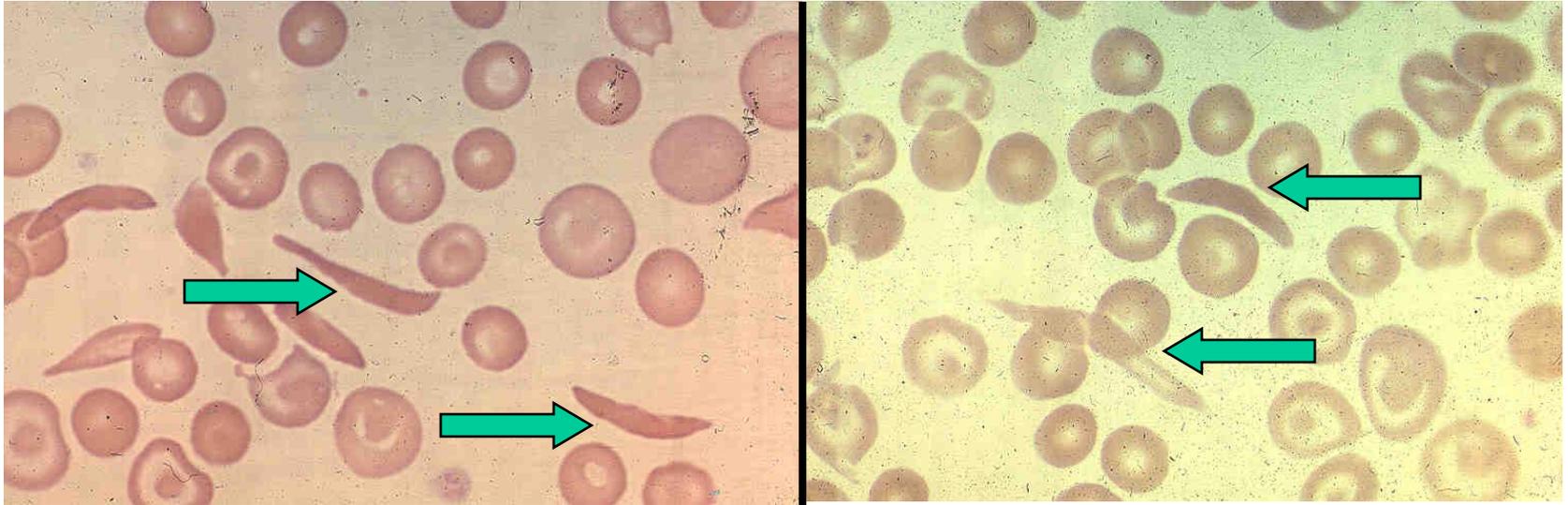
+



=



# Sickle Cells

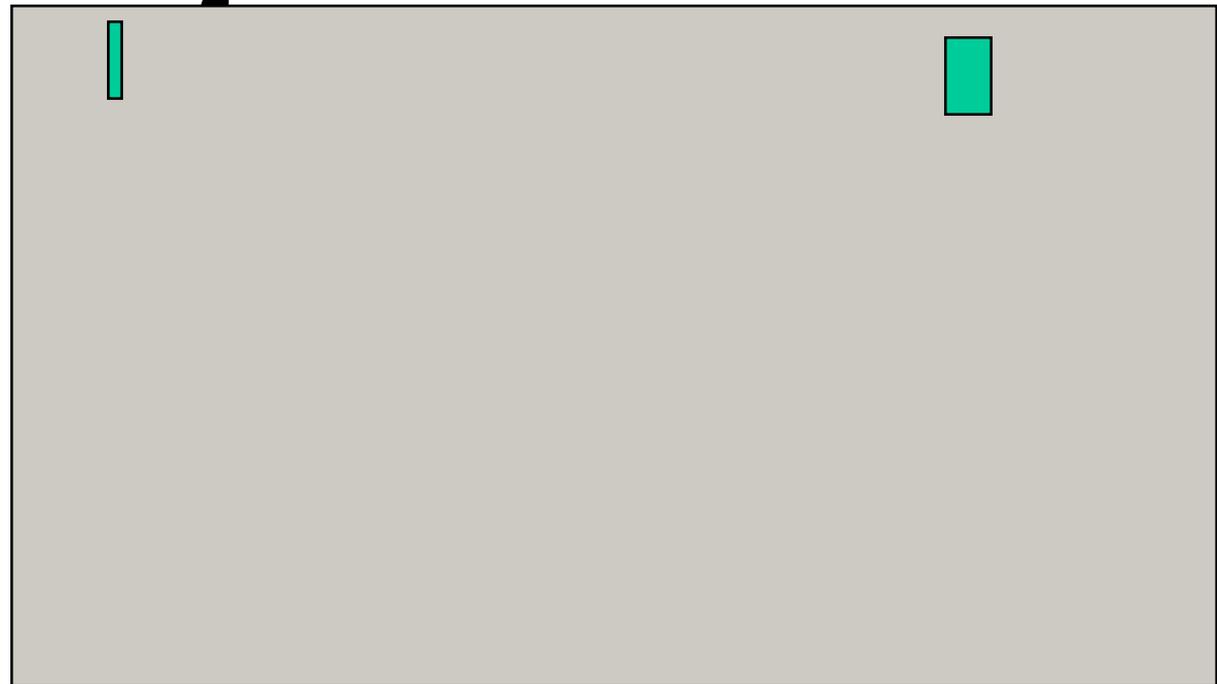


# Secondary Laboratory Investigation

## Cellulose Acetate Hb Electrophoresis

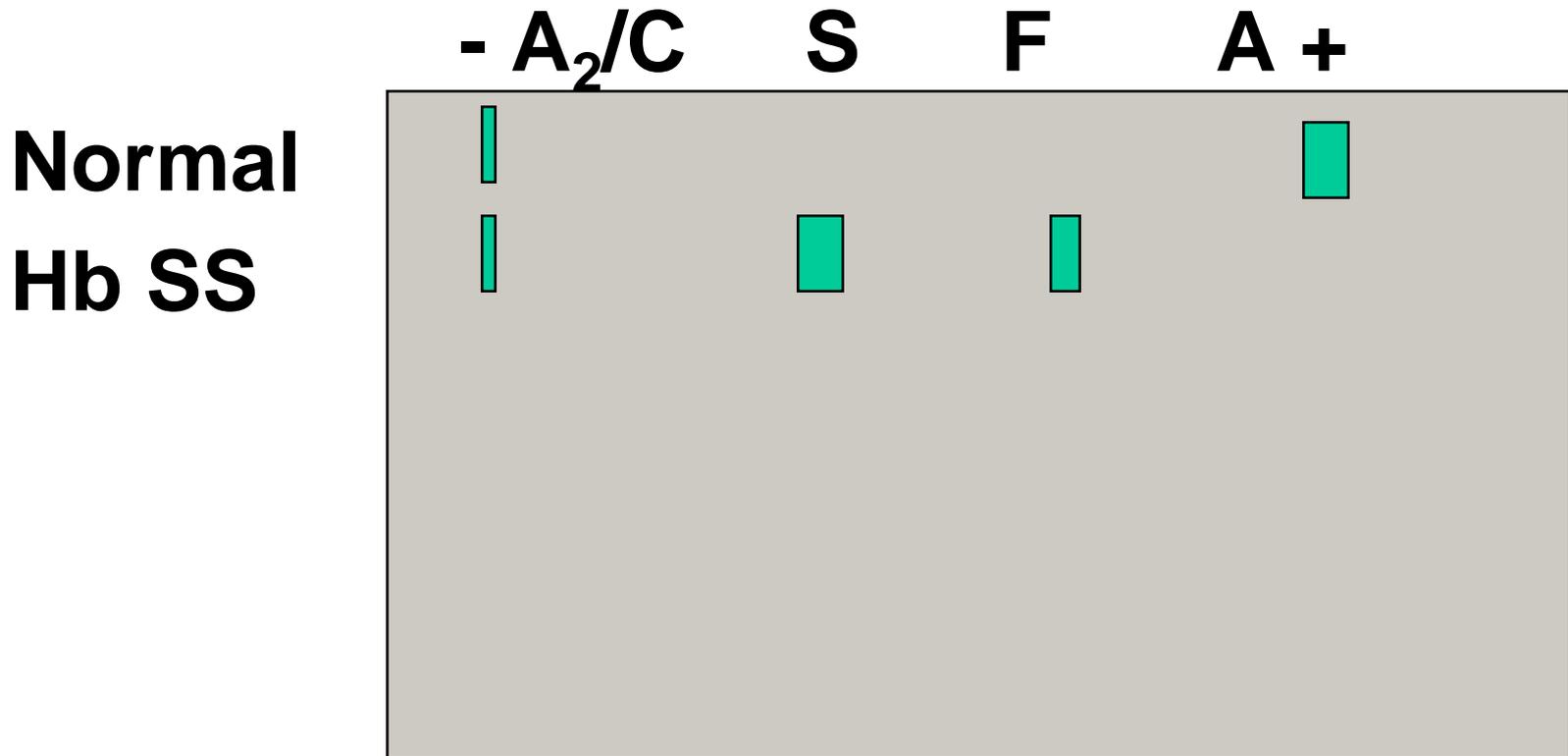
- A<sub>2</sub>/C      S      F      A +

Normal



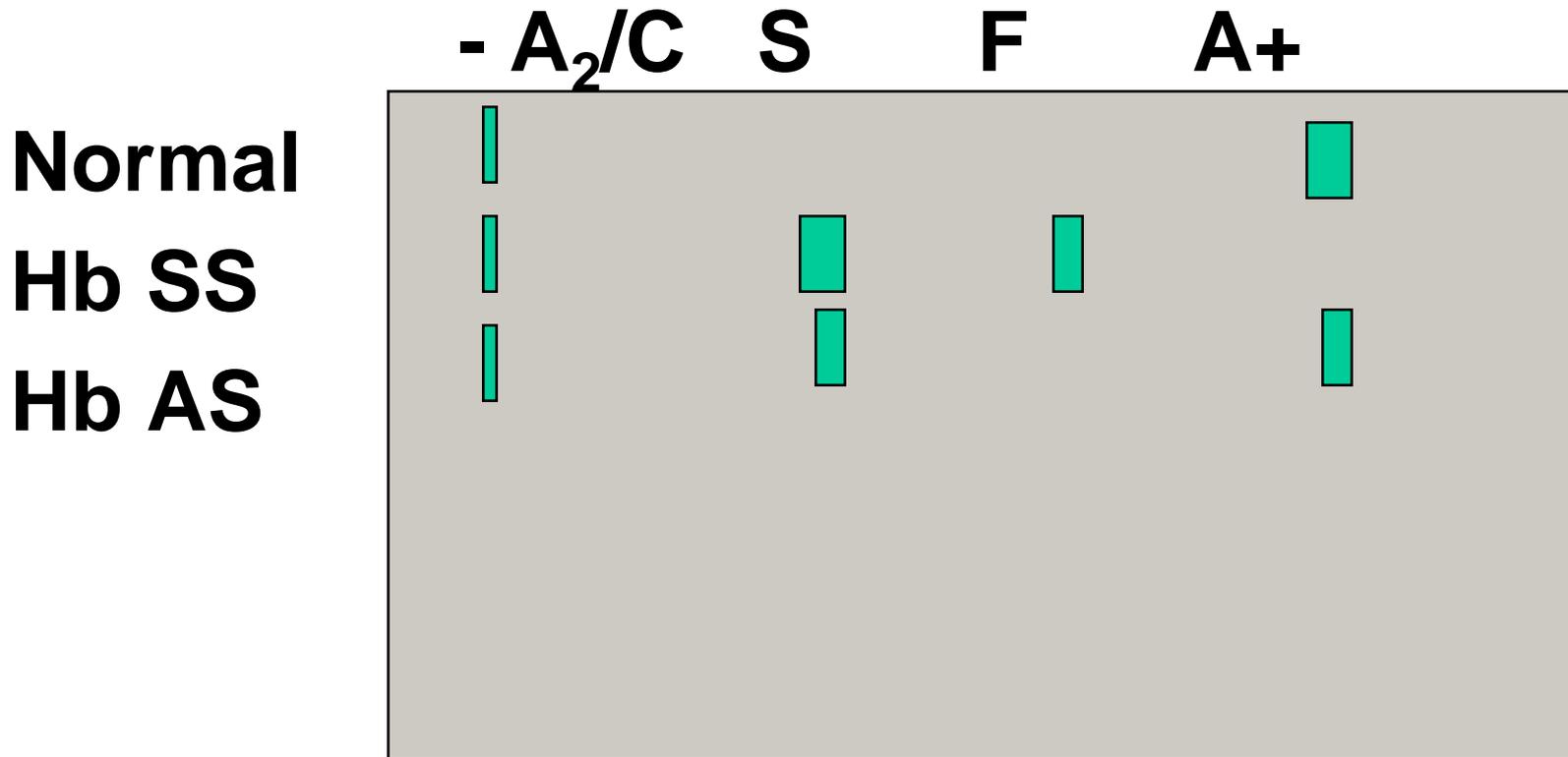
# Secondary Laboratory Investigation

## Cellulose Acetate Hb Electrophoresis



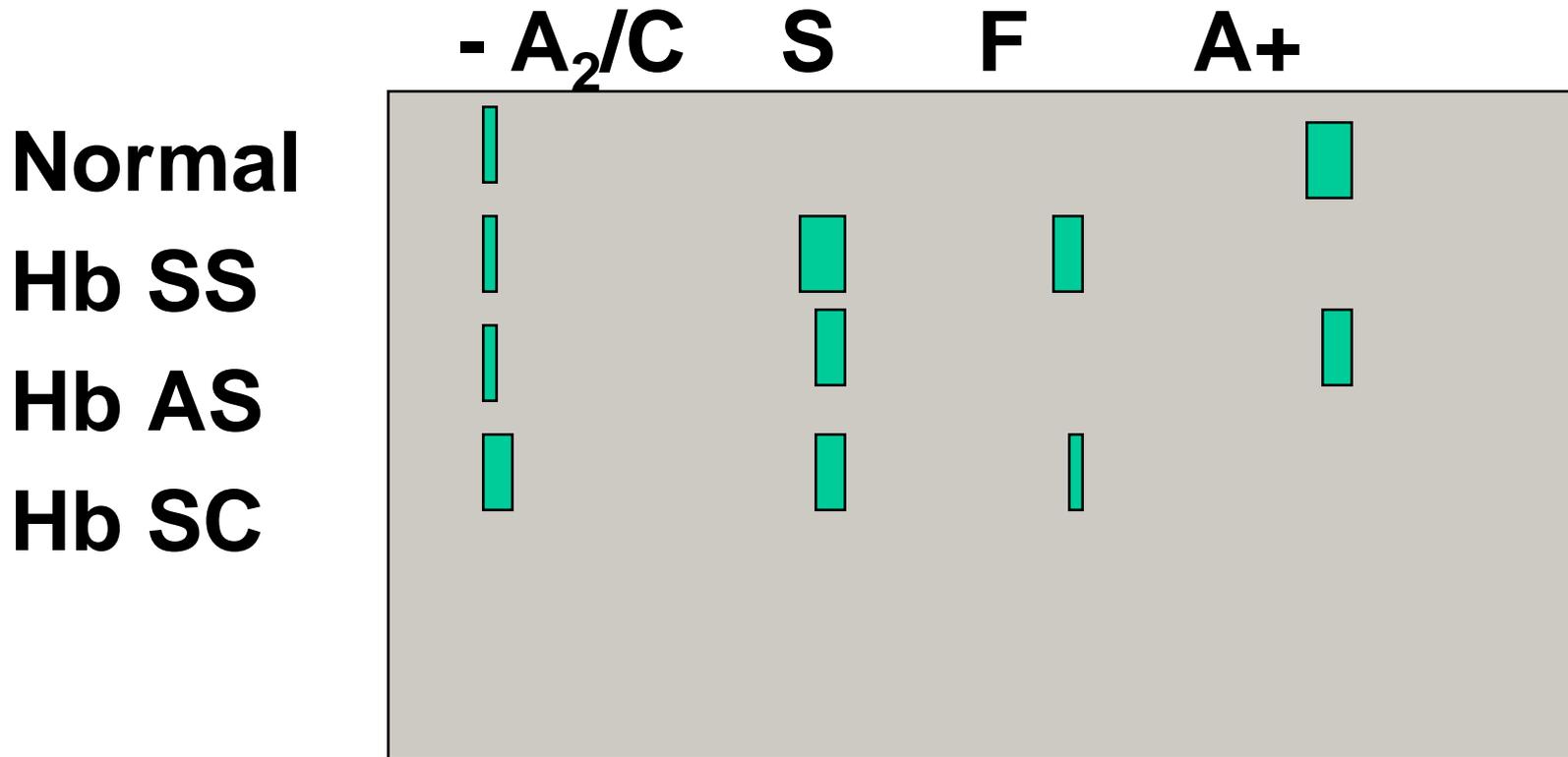
# Secondary Laboratory Investigation

## Cellulose Acetate Hb Electrophoresis



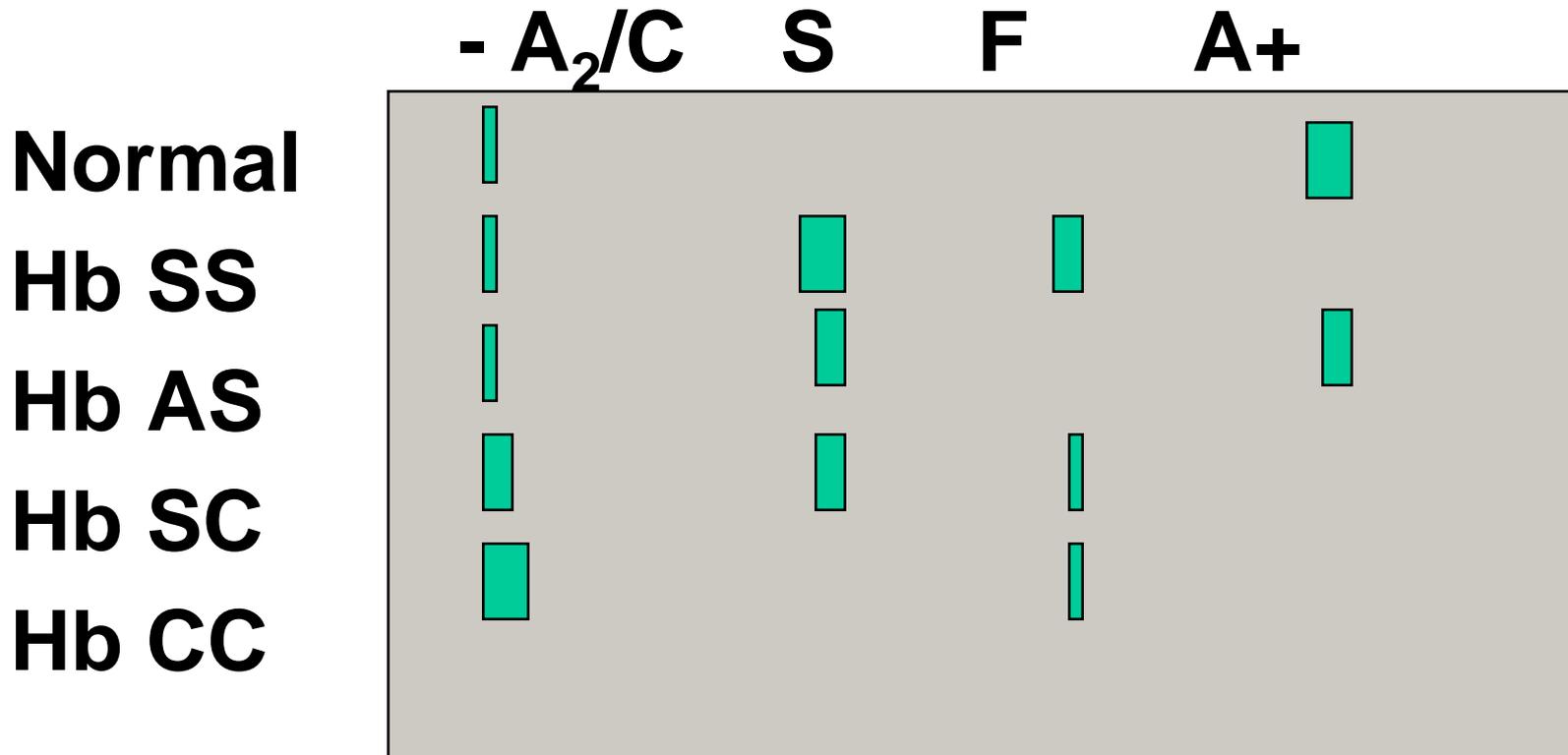
# Secondary Laboratory Investigation

## Cellulose Acetate Hb Electrophoresis



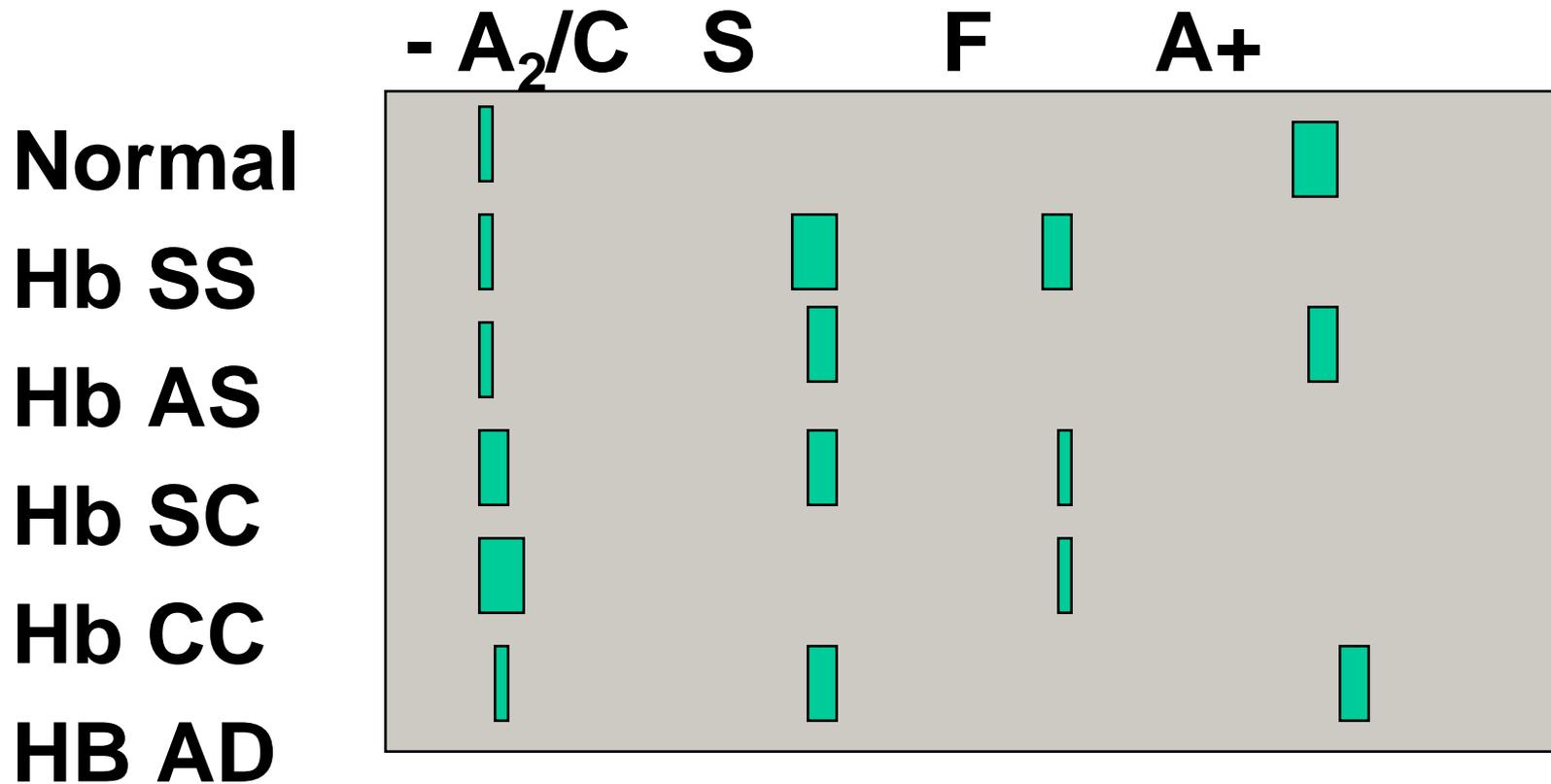
# Secondary Laboratory Investigation

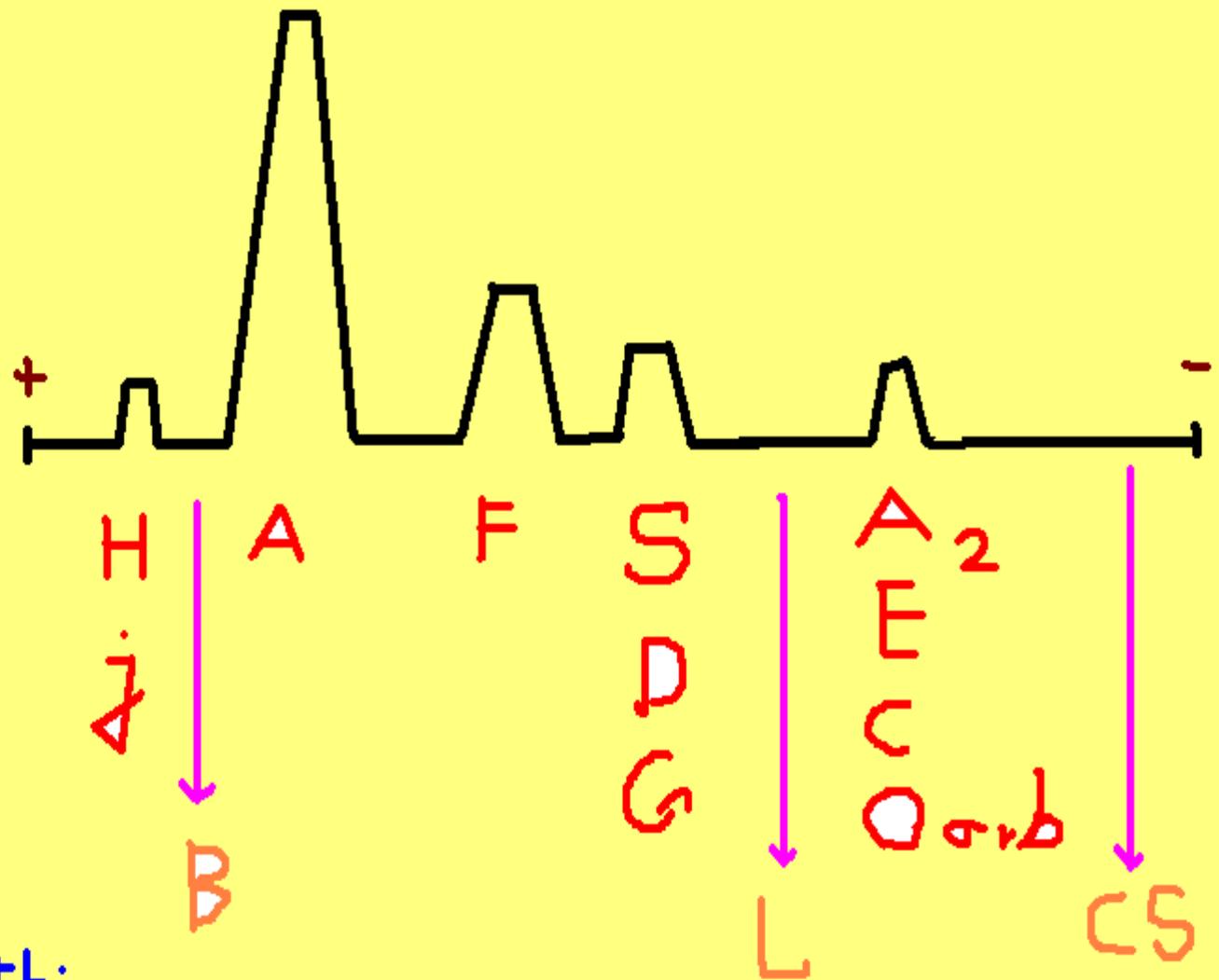
## Cellulose Acetate Hb Electrophoresis



# Secondary Laboratory Investigation

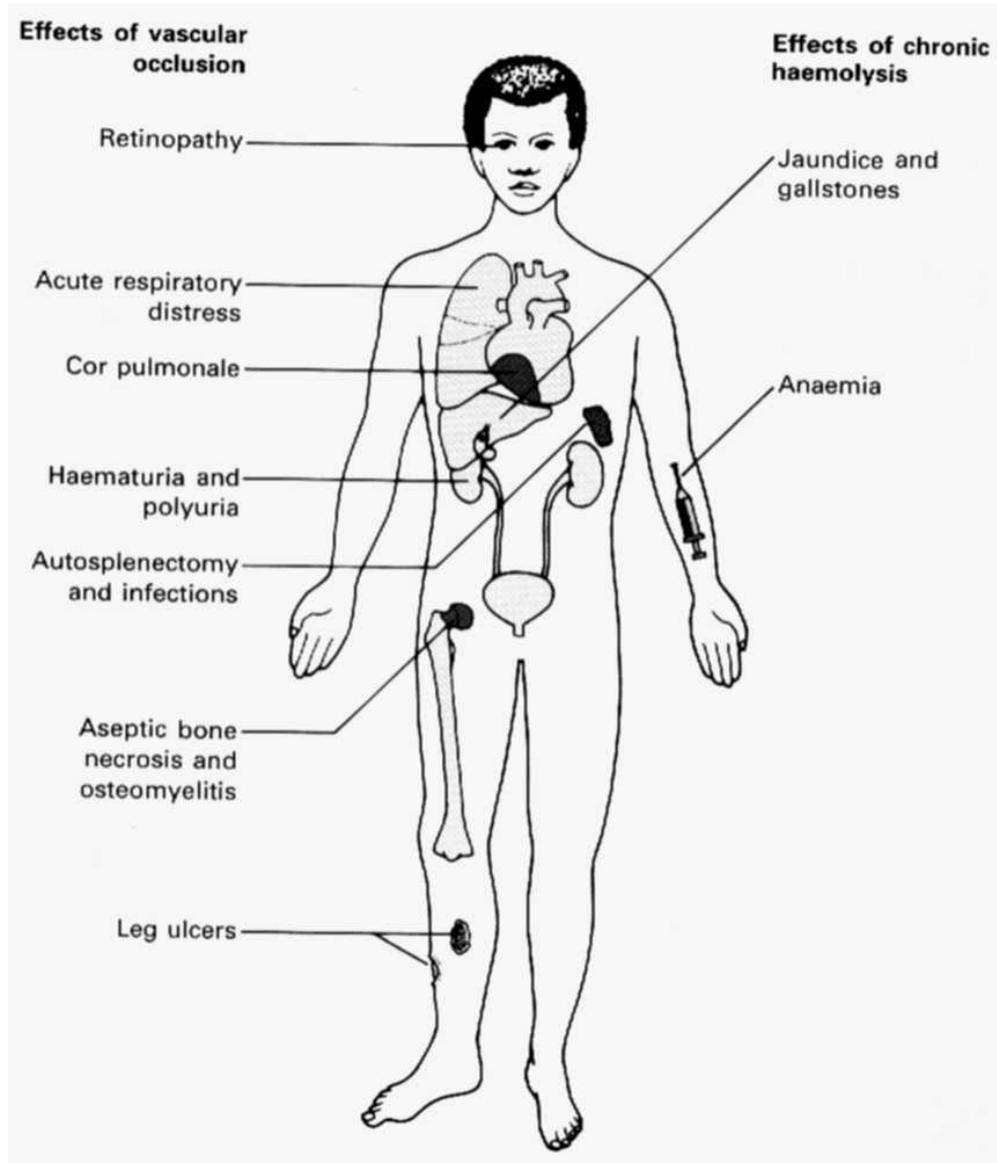
## Cellulose Acetate Hb Electrophoresis





D.v.Fathi

# Sickle cell



# سندرم قفسه سينه حاد



یک هفته بعد از درمان



# موقع ترخيص



# Daily Preventative Measures

1. Taking the **folic acid** (folate) daily to help make new red cells
2. Daily **penicillin until age six** to prevent serious infection
3. **Drinking** plenty of water daily (8-10 glasses for adults)
4. Avoiding **too hot or too cold** temperatures
5. Avoiding **over exertion and stress**
6. Getting plenty of rest
7. Getting regular check-ups from knowledgeable health care providers

# Alleviating Pain

- **Warmth**: increases blood flow
- **Massaging** and rubbing
- Heat from hot water bottles and deep heat creams
- **Bandaging** to support the painful region
- **Resting** the body
- Cognitive Behavioral Therapy
- Getting the sufferer to relax
  - deep breathing exercises
  - distracting the attention
  - by other psychological methods.
- Pain-killing medicines (**analgesics**): paracetamol, codeine **non-steroidal anti-inflammatory**, morphine if necessary

# Transfusion in Sickle Cell

- In severely **anemic patients, simple** transfusions should be used.
- Common causes of acute anemia:
  - acute splenic sequestration
  - transient red cell aplasia
  - Hyperhemolysis (infection, acute chest syndrome, malaria).
- If the patient is stable and the reticulocyte count high, transfusions can (and should) be deferred.

# Transfusion in Sickle Cell

*(exchange transfusion)*

- **Except in severe anemia**, exchange transfusion offers many benefits and is our first choice
- Phenotypically matched, leukodepleted packed cells are the blood product of choice.
- A posttransfusion hematocrit of 36 percent or less is recommended.
- **Avoid hyperviscosity**, which is dangerous to sickle cell patients.

# Developing Treatments

- **Hydroxyurea**
  - The first effective drug treatment for adults with severe sickle cell anemia reported in early 1995
  - Daily doses of the anticancer drug, hydroxyurea, reduced the frequency of painful crises, acute chest syndrome, needed fewer blood transfusions
  - Increases production of fetal hemoglobin in the blood
    - **Fetal hemoglobin seems to prevent sickling** of red cells
    - cells containing fetal hemoglobin tend to survive longer in the bloodstream

# معبد چغازنبیل-شوش



# Hereditary spherocytosis

- **most common** inherited red cell membrane disorder
  - **1/5000** in northern European populations
- **autosomal dominant**
- due to mutations of **RBC membrane cytoskeleton proteins**

# Hereditary spherocytosis

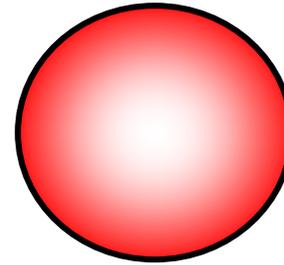
- Clinical features:
  - **severity varies**, usually mild to moderate anemia
  - **splenomegaly, cholelithiasis, jaundice** may occur
- Laboratory features
  - hemolytic anemia with spherocytes
  - **osmotic fragility test**
  - **MCHC ↑ 36**
  - **negative DAT**
- Treatment
  - usually none required
  - **splenectomy (P)** if severe
  - counsel patient and family about inheritance

# Normal

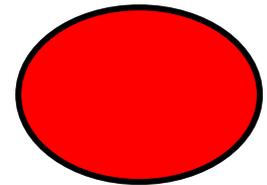
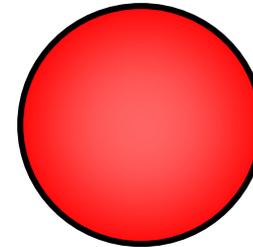
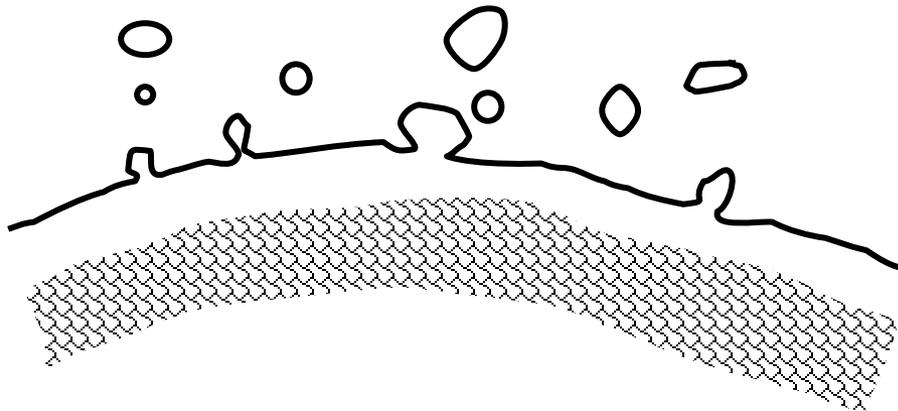
membrane



cytoskeleton



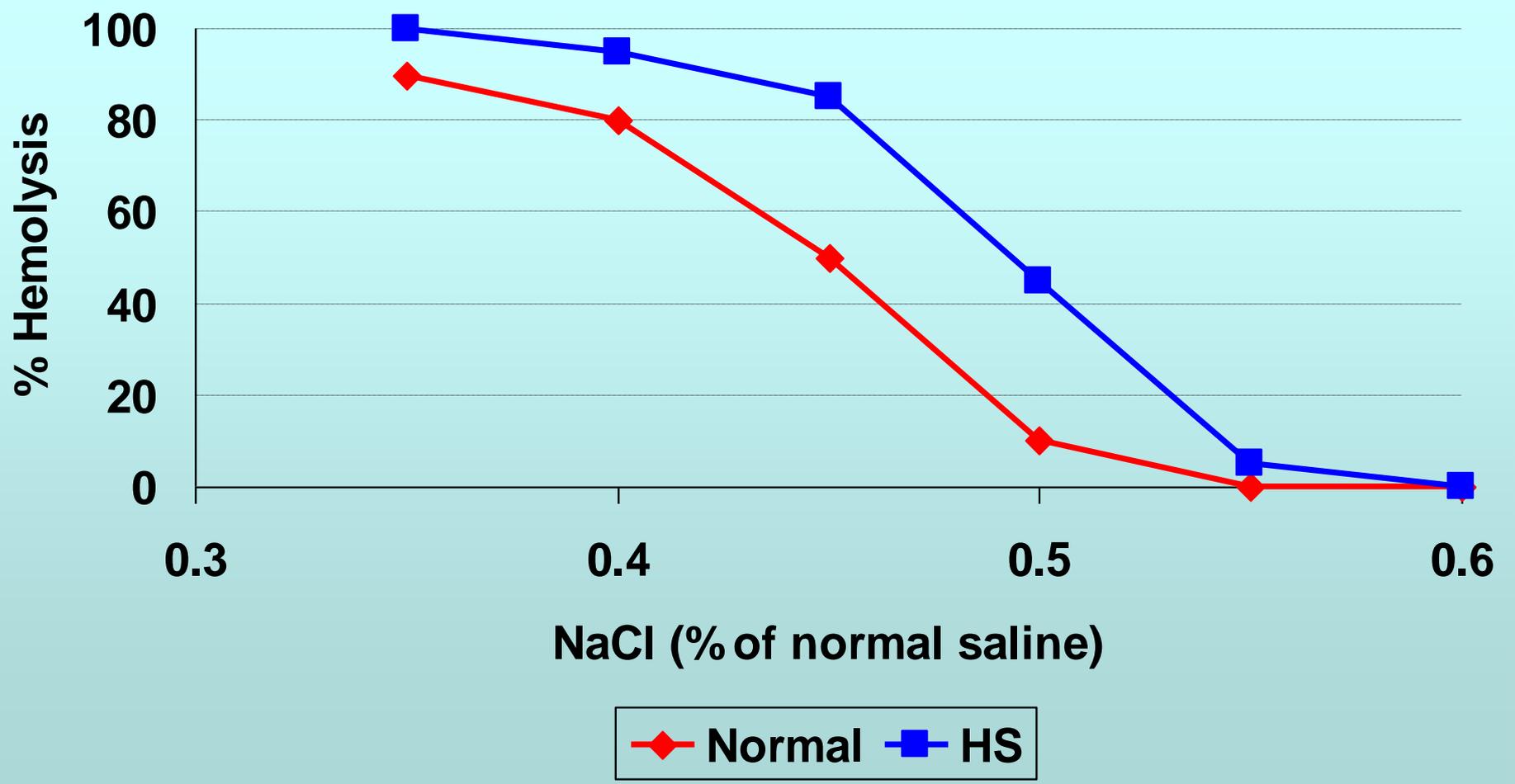
# Hereditary spherocytosis



loss of membrane = loss of SA = loss of deformability = increased splenic clearance

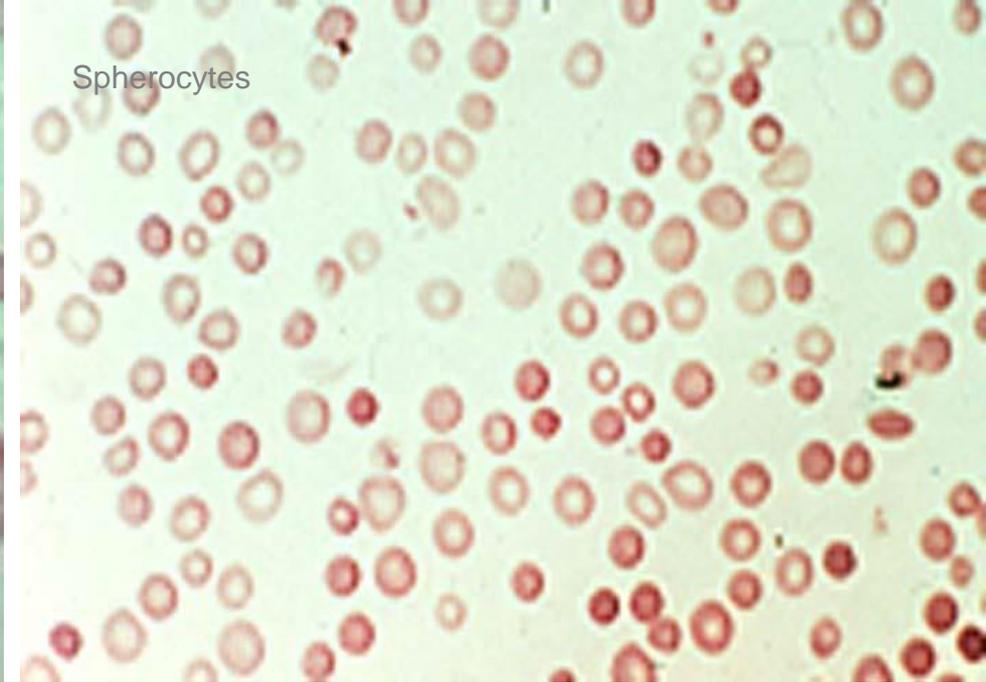


# HEREDITARY SPHEROCYTOSIS

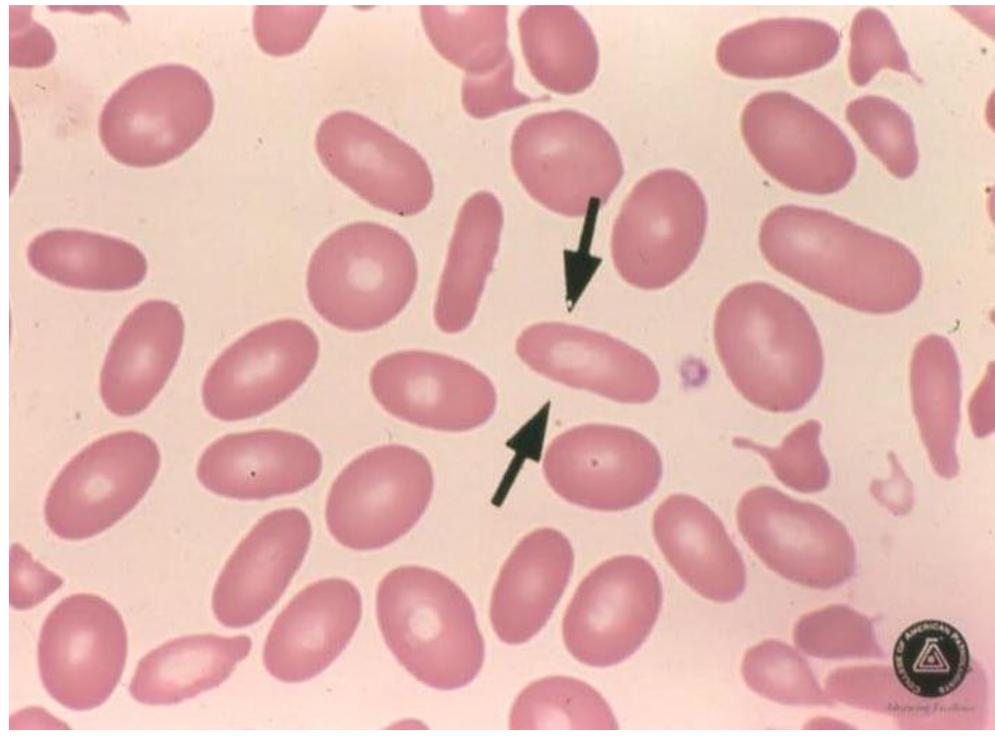


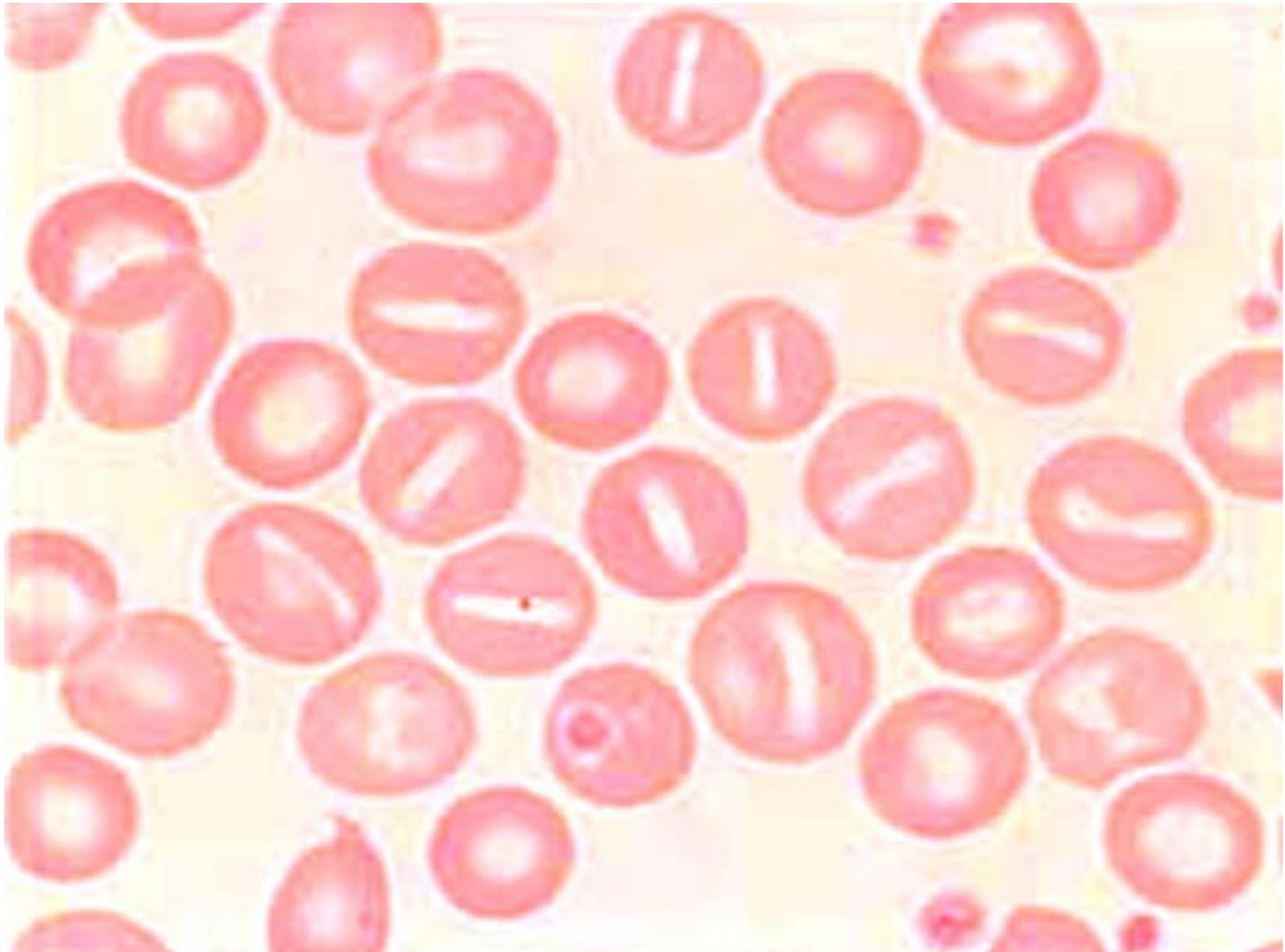


Spherocytes



Elliptocytes





Stomatocytes

# قلعه شوش



# G6PD deficiency

- **Most common** inherited red cell enzymopathy
  - up to 10% of those with African and Mediterranean descent
- **X-linked**
- hemolysis due to increased **oxidative** damage to red cells

# WHO working groups

- **Class I:** severely deficient, associated with **chronic nonspherocytic** hemolytic anemia
- **Class II:** severely deficient (1%-10% residual activity), associated with **acute intermittent** hemolytic anemia (G6PD Mediterranean)
- **Class III:** moderately deficient (10%-60% residual activity) - **intermittent hemolysis** usu assoc **with infection or drugs** (G6PD A)
- **Class IV:** **normal** activity (60%-150%)
- **Class V:** **increased** activity (>150%)

# Acute hemolytic anemia

Asymptomatic at steady state without anemia or abnormal morphology.

Sudden destruction of deficient erythrocytes **2-4 days after** offending "event" leads to **jaundice, pallor, dark urine**, +/- back pain. Abrupt drop in H/H to <4 g/dL and PBS with **microspherocytes**, cell fragments or bite cells. Sequestration of damaged red cells in liver and spleen.

Increase in **reticulocytes within 5 days**, maximal at 7-10 days with reversal of anemia even without removal of offending drug.

In G6PD Mediterranean, hemolysis more severe and can continue even after drug d/c'd.

# Favism

Results from ingestion of fava beans.

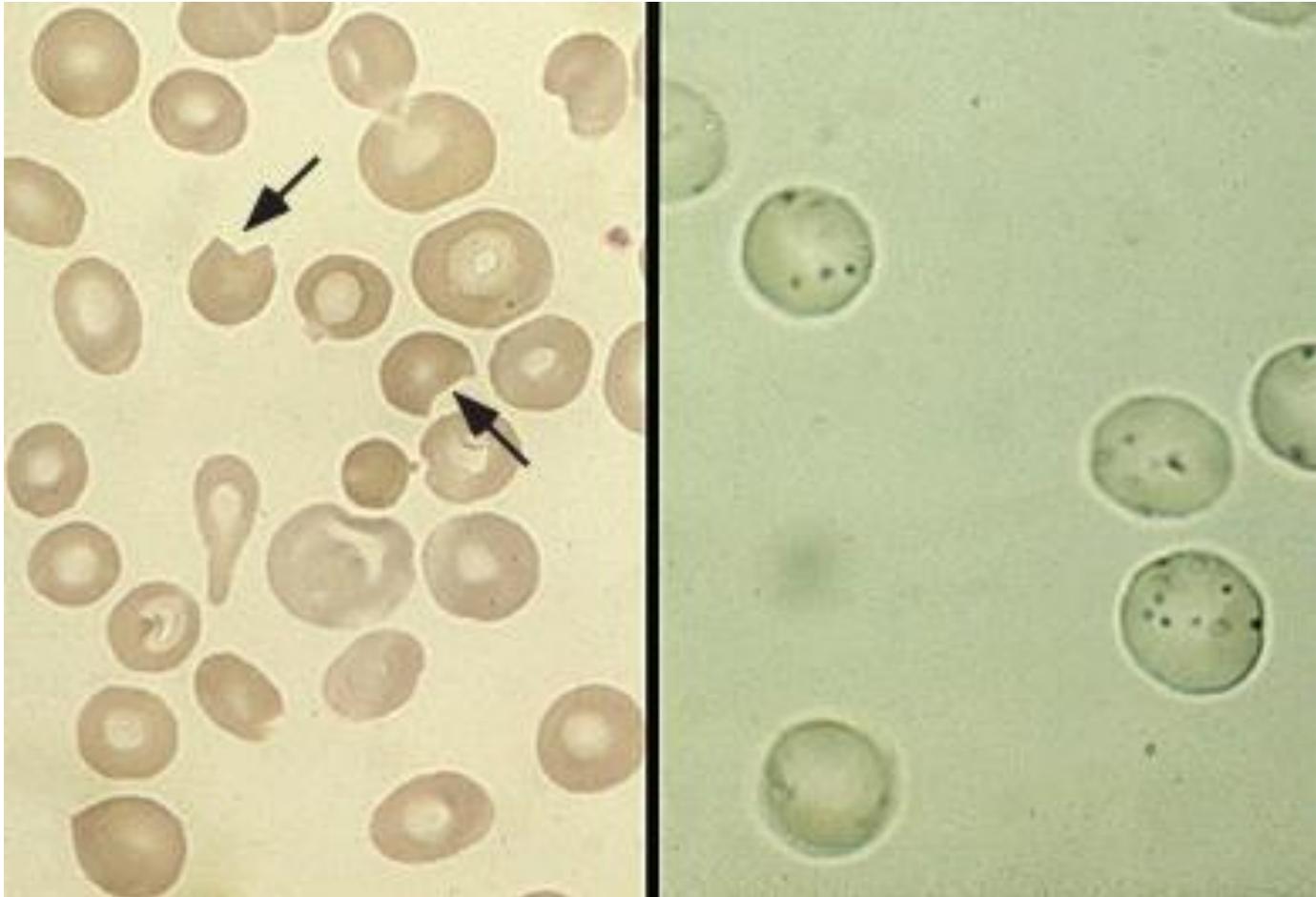
Peak incidence April/May coincident with **harvest** time.

Usually male children, **ages 1-5**.

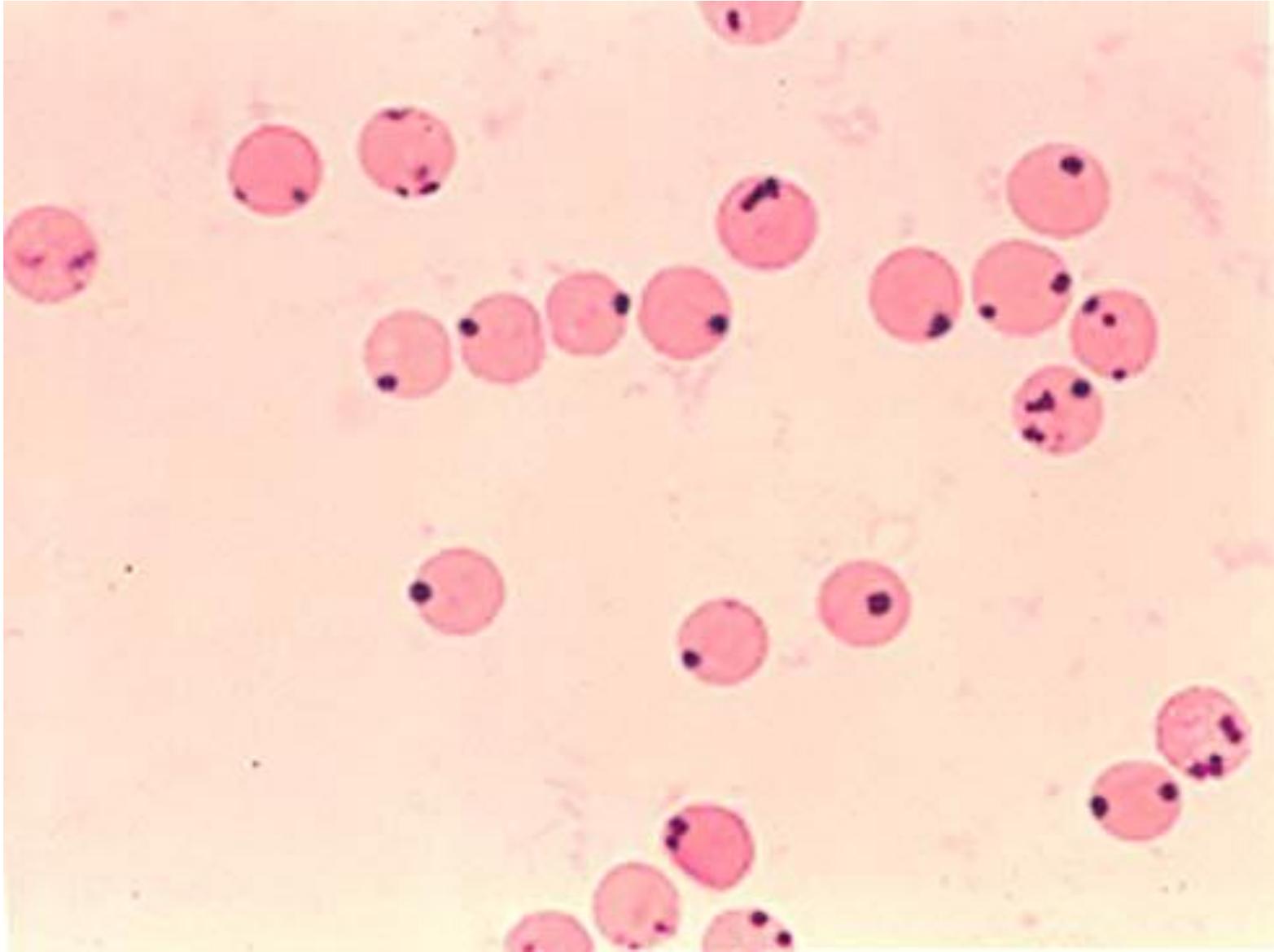
**5-24** hours after ingestion - HA, nausea, back pain, chills, **fever**, jaundice and hemoglobinuria. Acute fall in hemoglobin requiring transfusion.

Most commonly seen **with G6PD Mediterranean** variant.

# Peripheral Blood Smear



**Heinz body** preparation with Crystal violet  
Unstable hemoglobin



# Precipitants

**Infections** (salmonella, E.coli, beta-hemolytic strep, rickettsiae, viral hepatitis)

**Medications:**

- anti-malarials (primaquine)
- anti-bacterials (dapson, furazolidone, nitrofurantoin, sulfonamides, quinolones)
- others (acetanalide, methylene blue, naphthalene in moth balls and henna, toluidine blue, trinitrotoluene, rasburicase, vitamin k derivatives)
- possible association (phenazopyridine, ASA, doxorubicin, flutamide, probenecid, sulfasalazine, aminopyrine, aminosallylic acid, acetylphenylhydrazine)

**Metabolic abnormalities** (DKA)

# How do you treat it?

- **avoid** offending medications
- supportive care
- **hydration** to protect against renal failure
- **transfusions, folic acid**
- **splenectomy and vitamin E** (anti-oxidant) have been suggested but **not** been proven effective

\*\*\*because hemolysis is usually mild, **drugs** may be given if there **is important indication**

# سد شهيد عباسپور



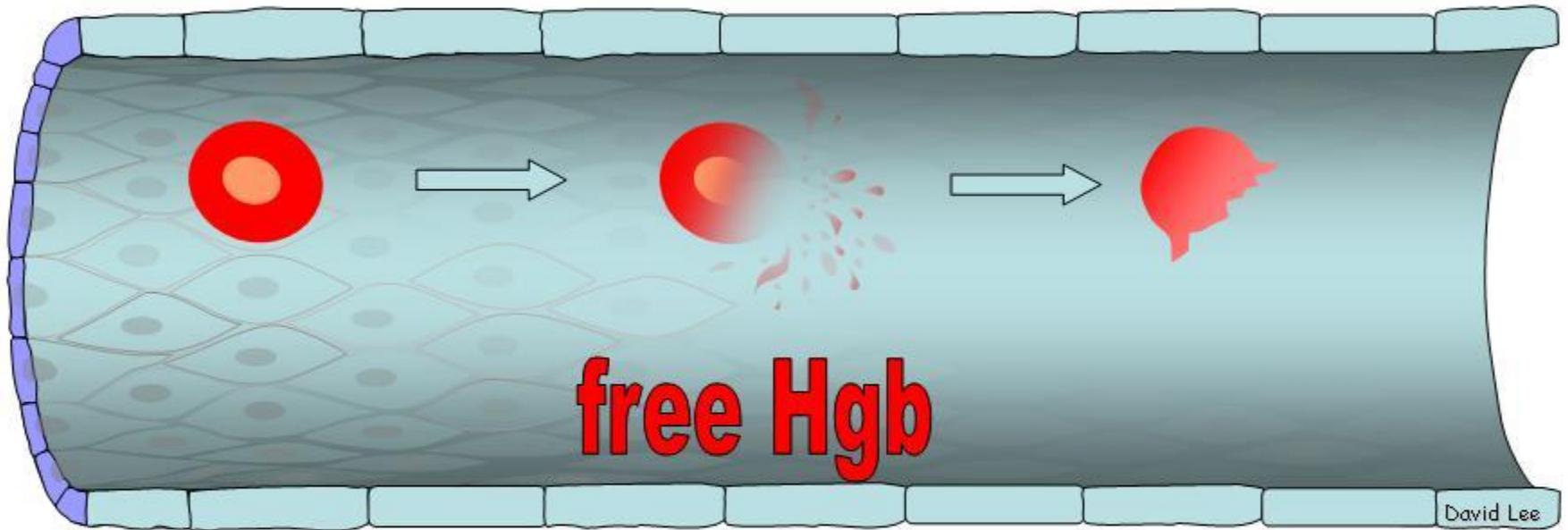
# Autoimmune hemolytic anemia (AIHA)

- **Warm autoimmune** hemolytic anemia (WAIHA)
- **Cold Agglutinin Syndrome (CAS)** and **Paroxysmal Cold Hemoglobinuria (PCH)**
- Mixed-type autoimmune hemolytic anemia
- Drug-induced immune hemolytic anemias

# Incidence of Autoimmune Hemolytic Anemias

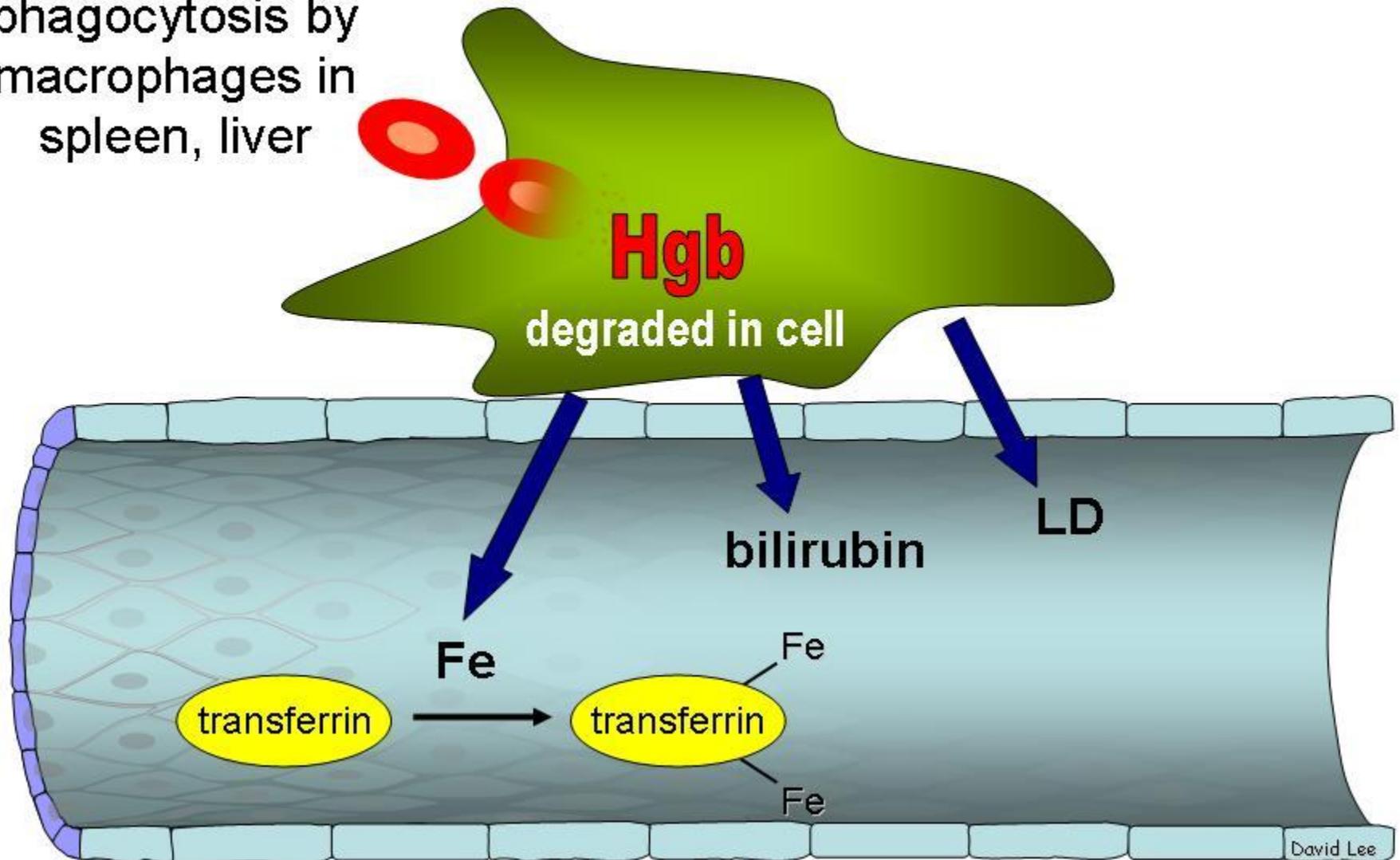
Warm Autoimmune Hemolytic Anemia	60-70%
Cold Agglutinin Syndrome	16-32%
Mixed-type Autoimmune Hemolytic Anemia	7-8%
Paroxysmal Cold Hemoglobinuria	Up to 2%
Drug-induced Immune Hemolytic Anemia	12-18%

# Intravascular hemolysis



# Extravascular hemolysis

phagocytosis by  
macrophages in  
spleen, liver

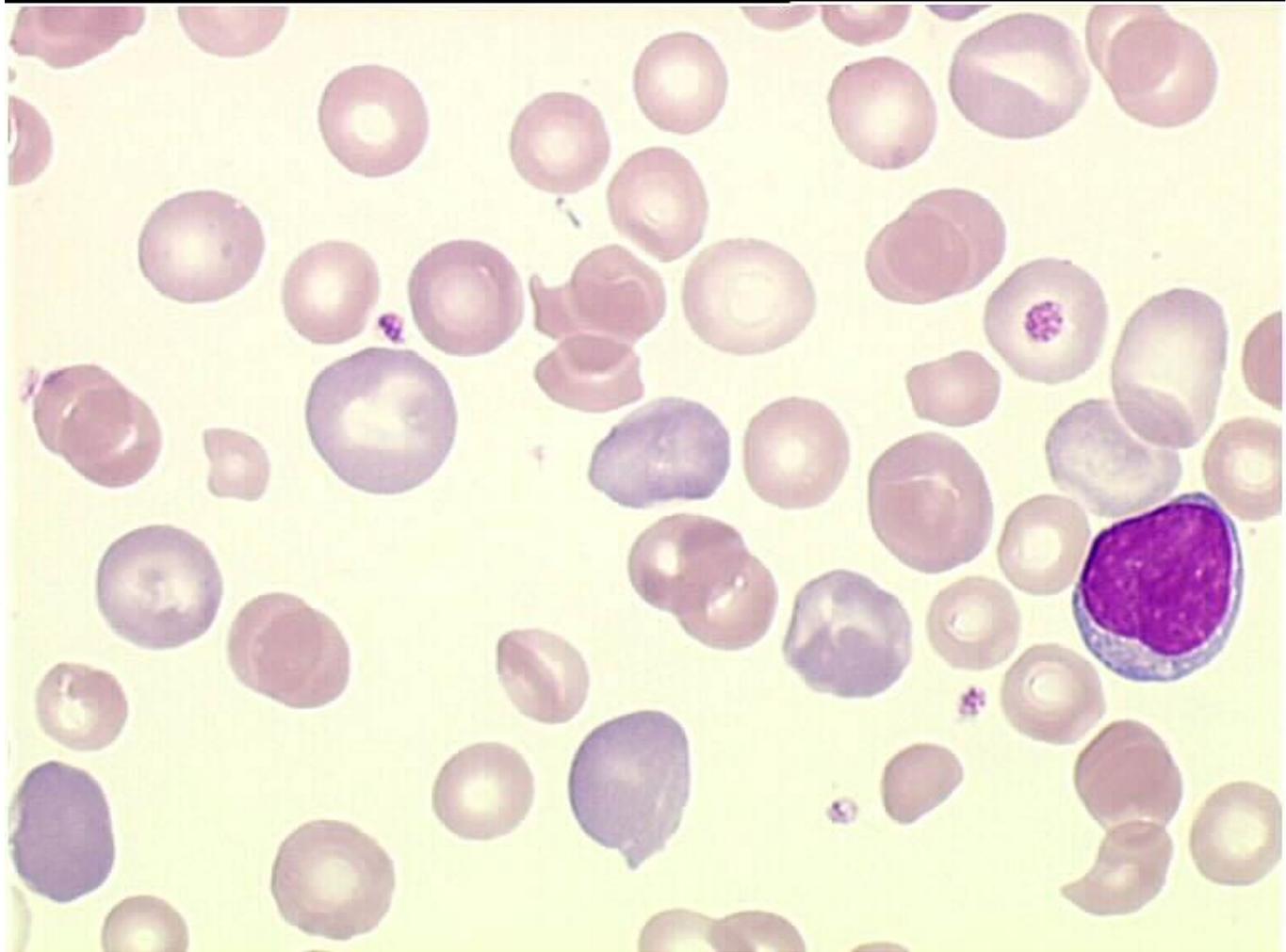


**TABLE 2. HOW TO DISTINGUISH BETWEEN EXTRAVASCULAR AND INTRAVASCULAR HEMOLYSIS**

<b>Test</b>	<b>Extravascular hemolysis</b>	<b>Intravascular hemolysis</b>
peripheral blood film	no red cell fragments	fragments frequently present
serum LD	↑	↑ ↑
serum bilirubin (unconjugated)	↑	↑
serum haptoglobin	normal or ↓/absent	↓/absent
hemoglobinuria	absent	present
free hemoglobin in plasma	absent	present
urine hemosiderin	absent	present

# Warm Autoimmune Hemolytic Anemia

- WAIHA
- **IgG** (sometimes occurs along with **IgA and IgM**)
- Primary or idiopathic
- **Secondary** to patients with lymphoma, SLE, and chronic lymphocytic leukemia (CLL)
- DAT
  - Positive with **polyspecific AHG** (anti-IgG and anti-C3d); variable reactions with monospecific
  - Rarely is the DAT negative (low levels of IgG, etc)

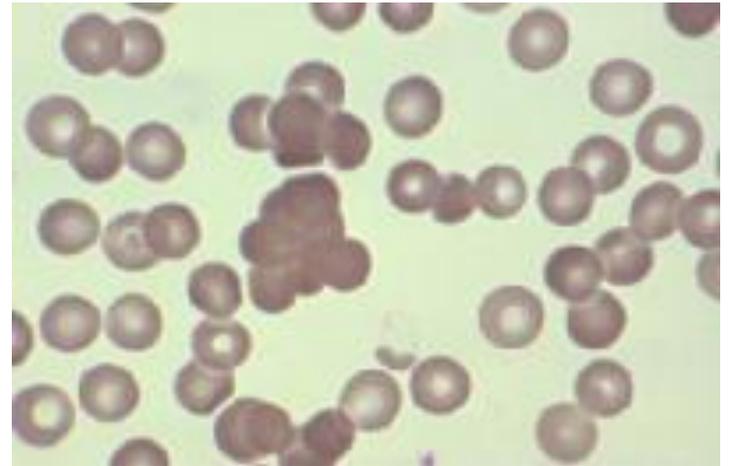
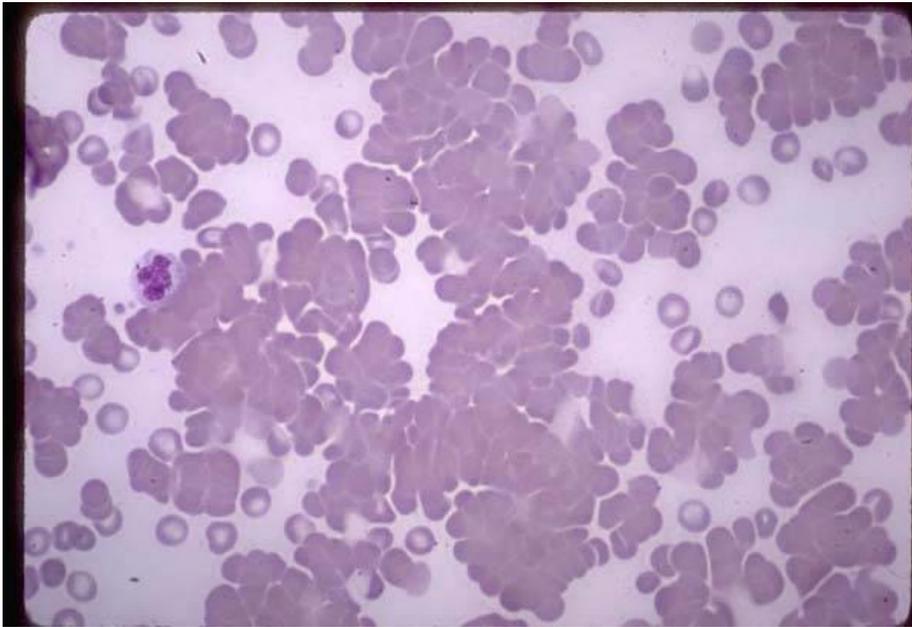




# Cold autoantibodies

- Bind best at temperatures less than 4°C
- Most frequently **IgM**, rarely IgA or IgG
- Antibodies are usually:
  - **CAS** - **anti-I**, followed by anti-i and anti-IH
  - **PCH** - **anti-P** is more common
    - there may also be an IgG biphasic hemolysin in PCH
- As previously stated, strong antibodies may interfere with ABO and Rh typings
- Thiol reagents (dithiothreitol or 2-mercaptoethanol) can be used to treat the cells and abolish autoagglutination

# Peripheral Smear



# Treatment

- WAIHA
  - **Prednisone**: corticosteroid used as antiinflammatory
  - **Splenectomy** may be required if no response to steroids
  - **Azothioprine**: when previous treatments fail; immunosuppressive antimetabolite
- CAS or PCH
  - **Chlorambucil** or **cyclophosphamide** (cytotoxic)
  - Transfusion (using blood warming devices)
- Drug-Induced
  - Discontinue drug
  - Transfuse only if insufficient oxygen delivery occurs

# Treatment cont in CAS .

## **Prednisone**

- **Not** useful for cold agglutinin disease
- Can be used if IgG co-antibodies

## **Splenectomy**

- **Not** useful because **the liver** is the main site of immune clearance
- Can be used if IgG co-antibodies are present

# Plasmapheresis

- Adjunctive treatment to **remove IgM** antibody
- Effect is short lived with 5 day half life
- Used for severe hemolysis in acute infection when thermal amplitude is high
- Used in preparation for surgery
- Severe acrocyanosis

# Rituximab

## **Rituximab anti-CD20 monoclonal antibody**

- Mostly case reports and small prospective trials
- Prospective uncontrolled study of 27 patients treated with Rituxan. (Berensten)
  - 54% response rate with 1 complete remission, 19 partial responses over 11 months.
- Prospective study of 20 patient, phase II trial. 5 doses over 22 days, followed 48 weeks. (Schollkopf)
  - 45% response to treatment with 1 CR, 8 PR

# Other Agents

- Cyclophosphamide, azathioprine, interferon, and fludarabine have been used to suppress IgM synthesis
- Generally not useful, response rates <20%
- One on-going phase II trial using Rituxan and fludarabine “preliminary results encouraging” (Berensten)
- **Chemotherapy** should be used to treat underlying lymphoma or malignancy

# Paroxysmal Nocturnal Hemoglobinuria

- Clonal cell disorder
- Ongoing **Intra- & Extravascular hemolysis**; classically at night
- Testing
  - Acid hemolysis (Ham test)
  - Sucrose hemolysis
  - **CD-59 negative** (Product of PIG-A gene)
- Acquired deficit of GPI-Associated proteins (including Decay Activating Factor)

# آبشارهای شوشتر – از نمای خانه مرعشی



# Microangiopathic Hemolytic Anemia

## *Causes*

- Vascular abnormalities
  - Thrombotic thrombocytopenic purpura
  - Renal lesions
    - Malignant hypertension
    - Glomerulonephritis
    - Preeclampsia
    - Transplant rejection
  - Vasculitis
    - Polyarteritis nodosa
    - Rocky mountain spotted fever
    - Wegener's granulomatosis

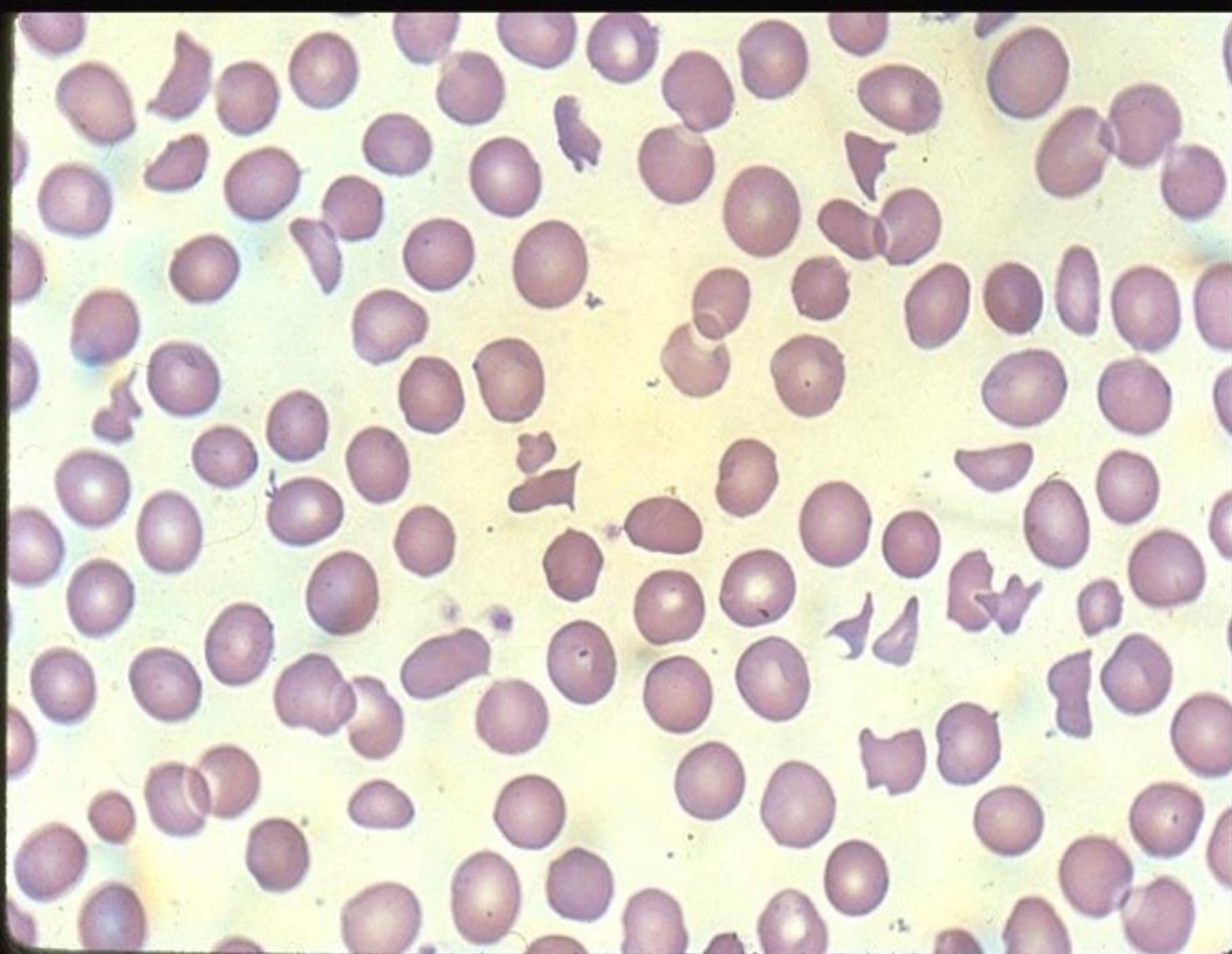
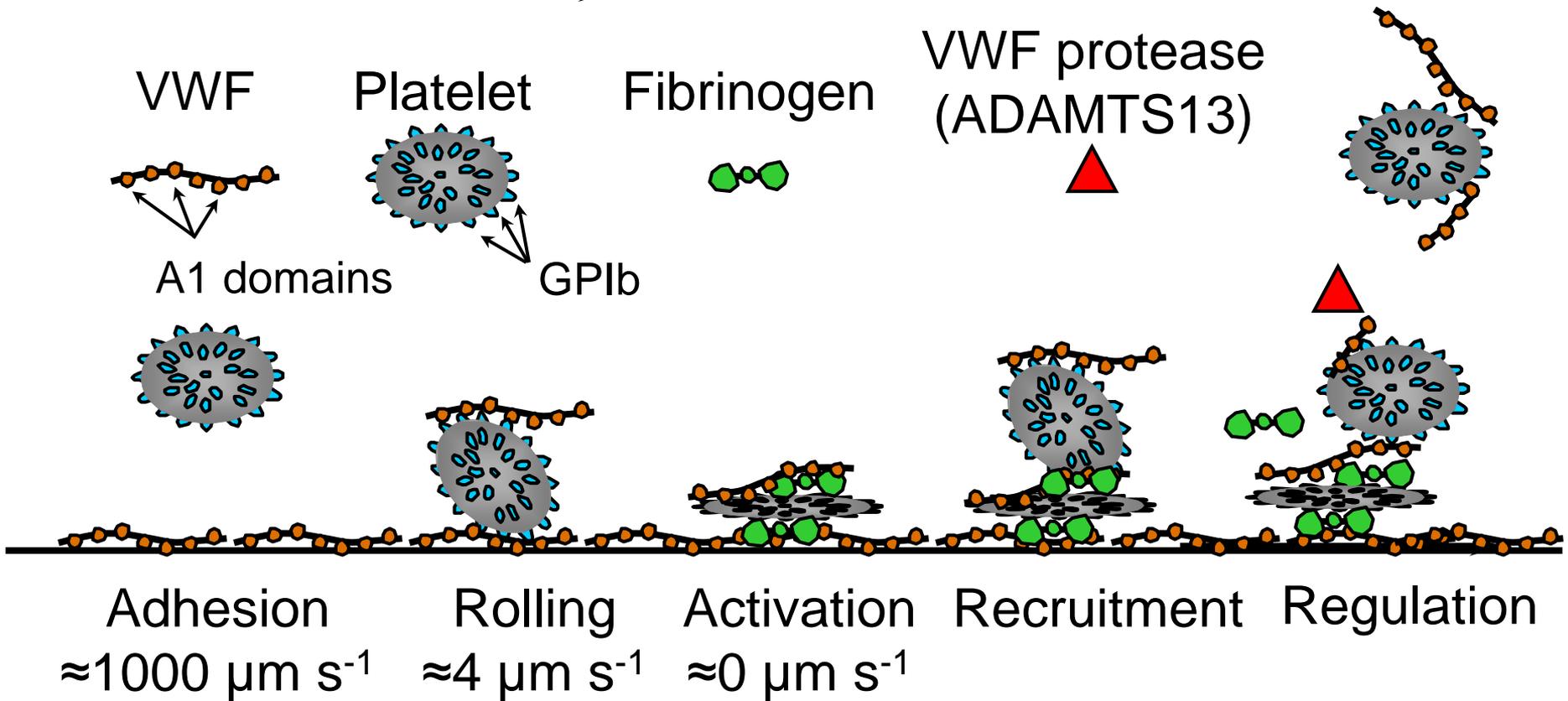


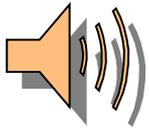


Fig. 15.27 Thrombotic thrombocytopenic purpura: massive area of

# VWF and Platelet Adhesion

*Blood Flow* →





ADAMTS13 & Inhibitor assay may become Useful to Quid Therapy

ADAMTS13 → Nor  
Inhibitor → Nor



Idiopathic

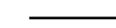


Plasma exchange

ADAMTS13 → ↓  
Inhibitor → Nor



Inherited



Plasma Infusion

ADAMTS13 → ↓  
Inhibitor → ↑

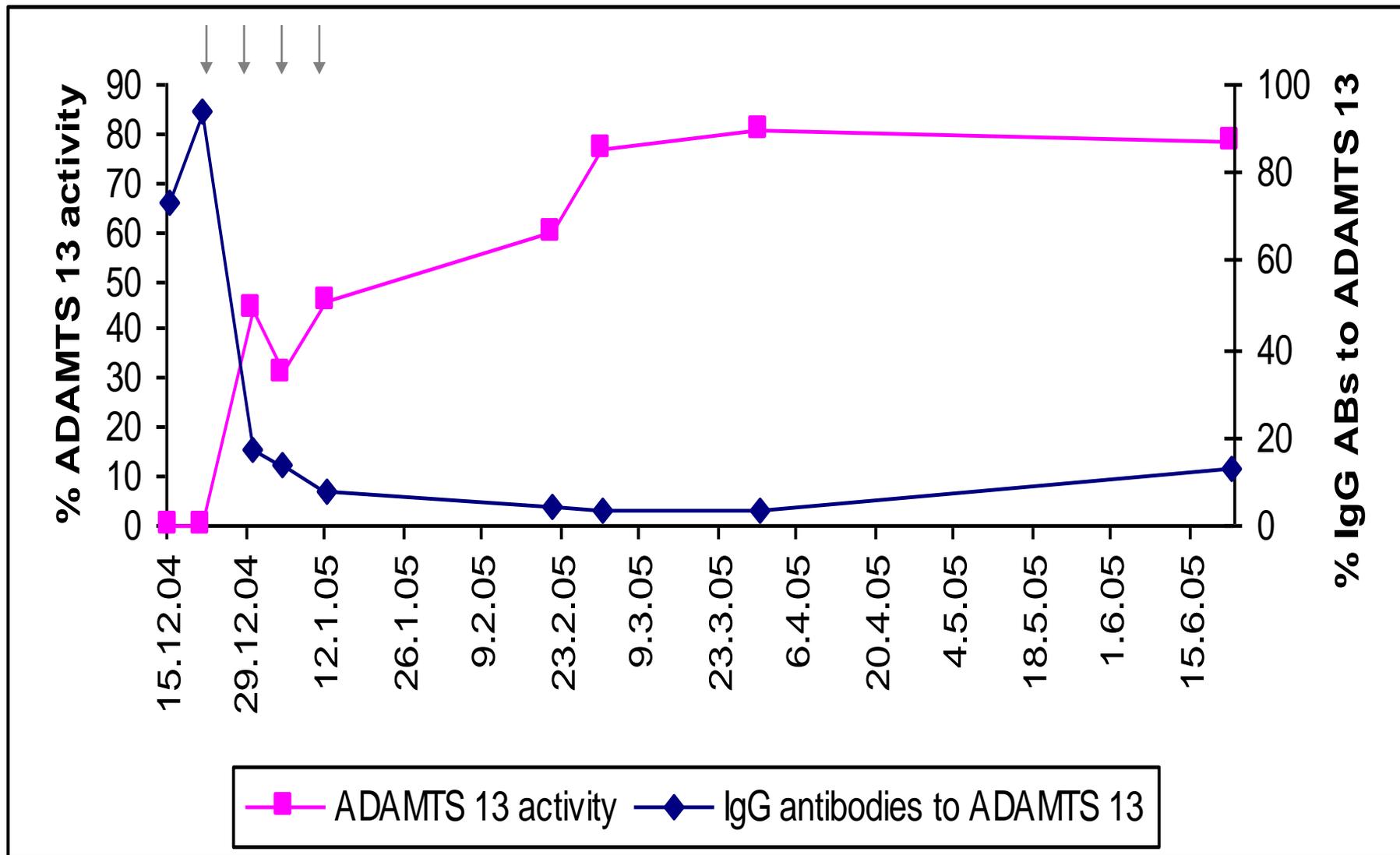


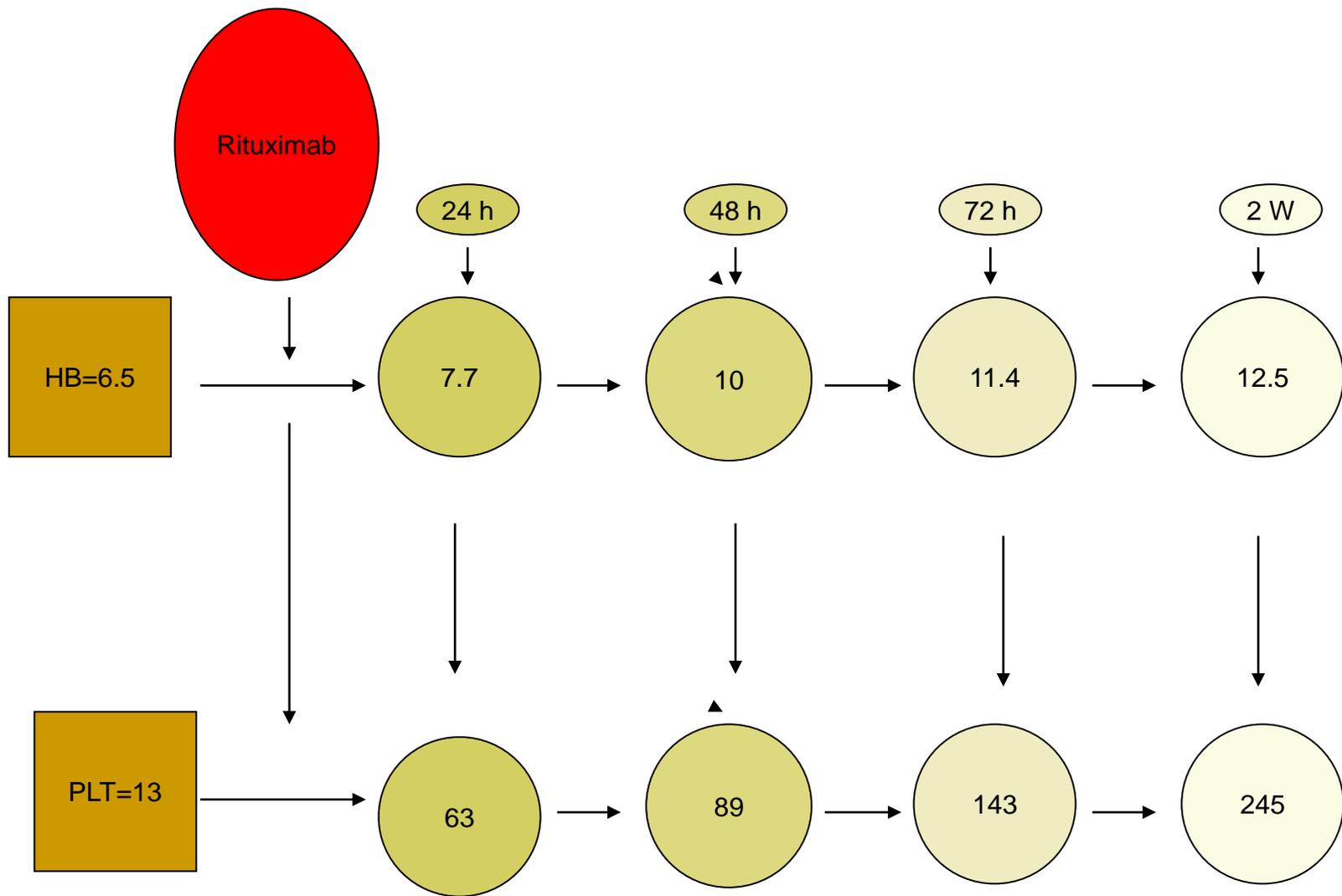
Secondary



Plasma exchange+Immunosuppression

# Effect of Rituximab in acute refractory TTP



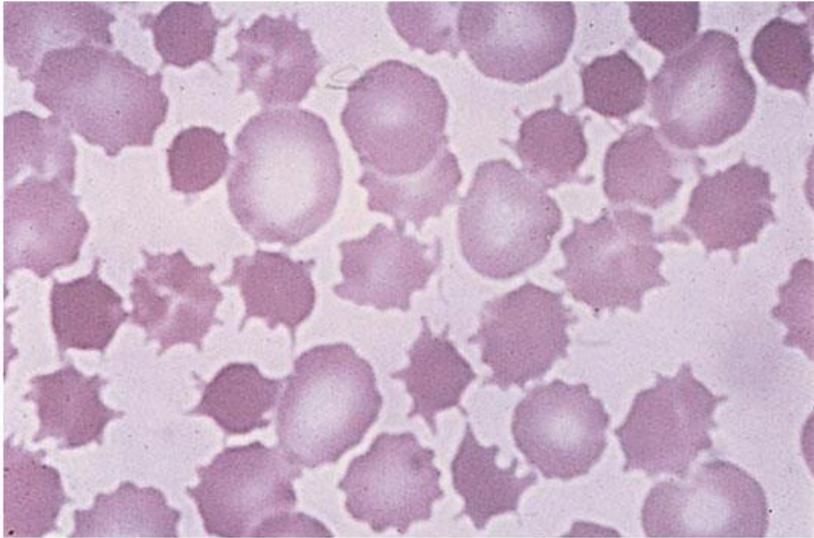




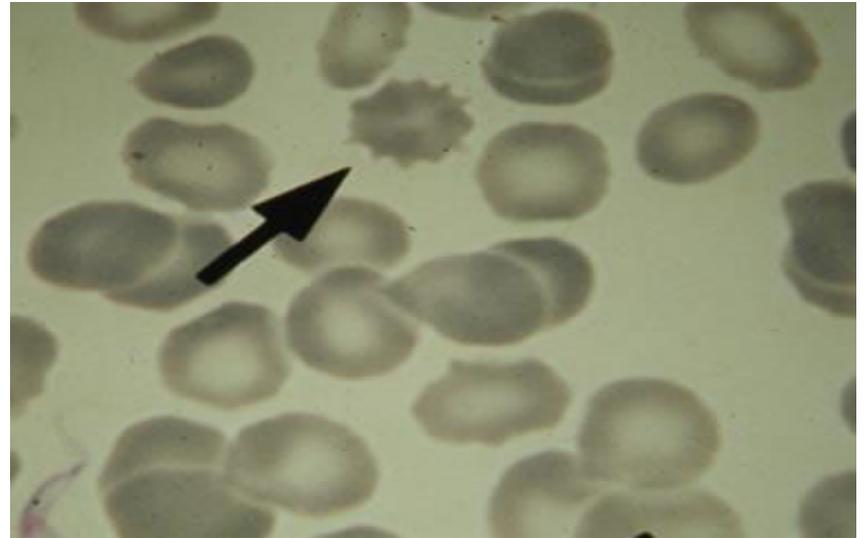
# بند میزان-کارون



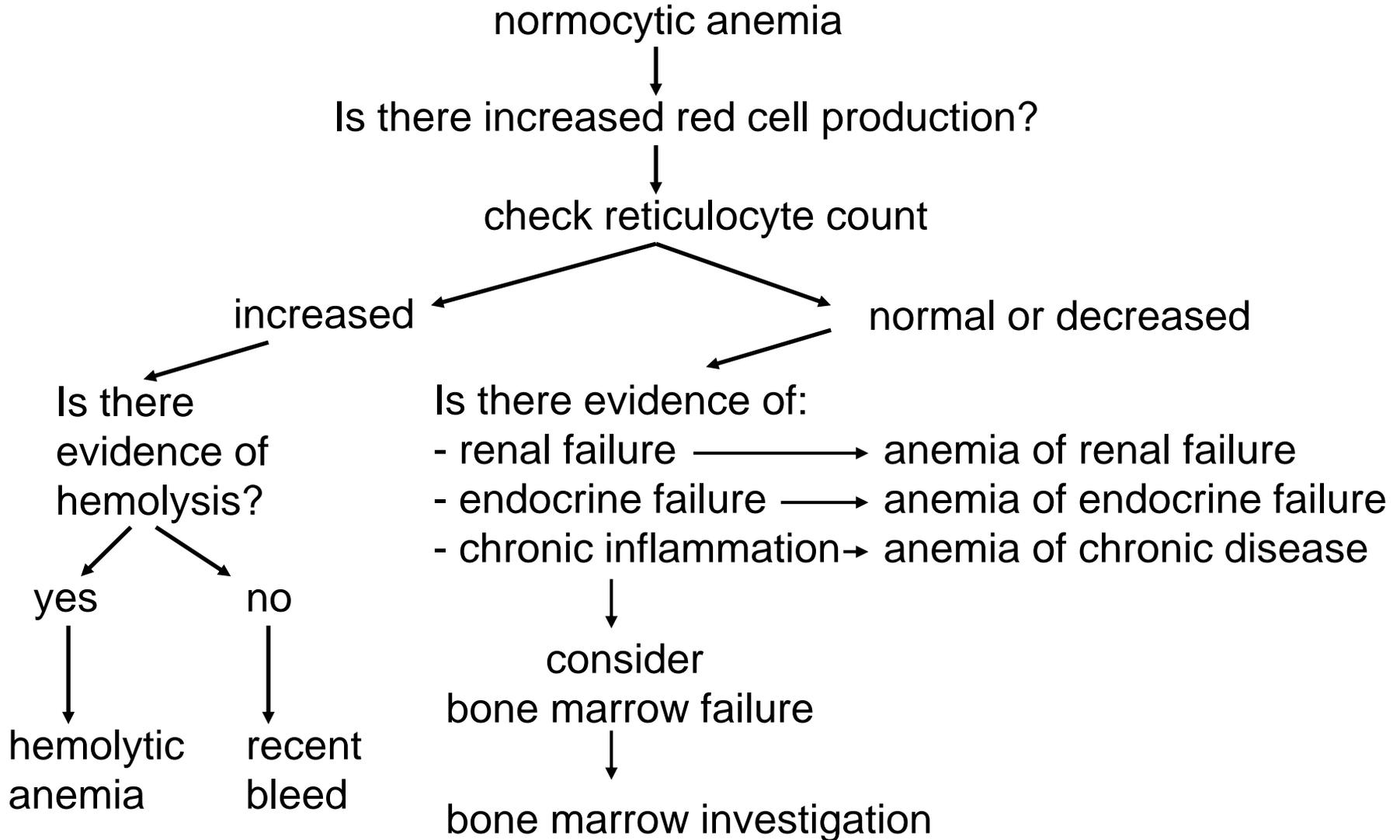
**acanthocyte**



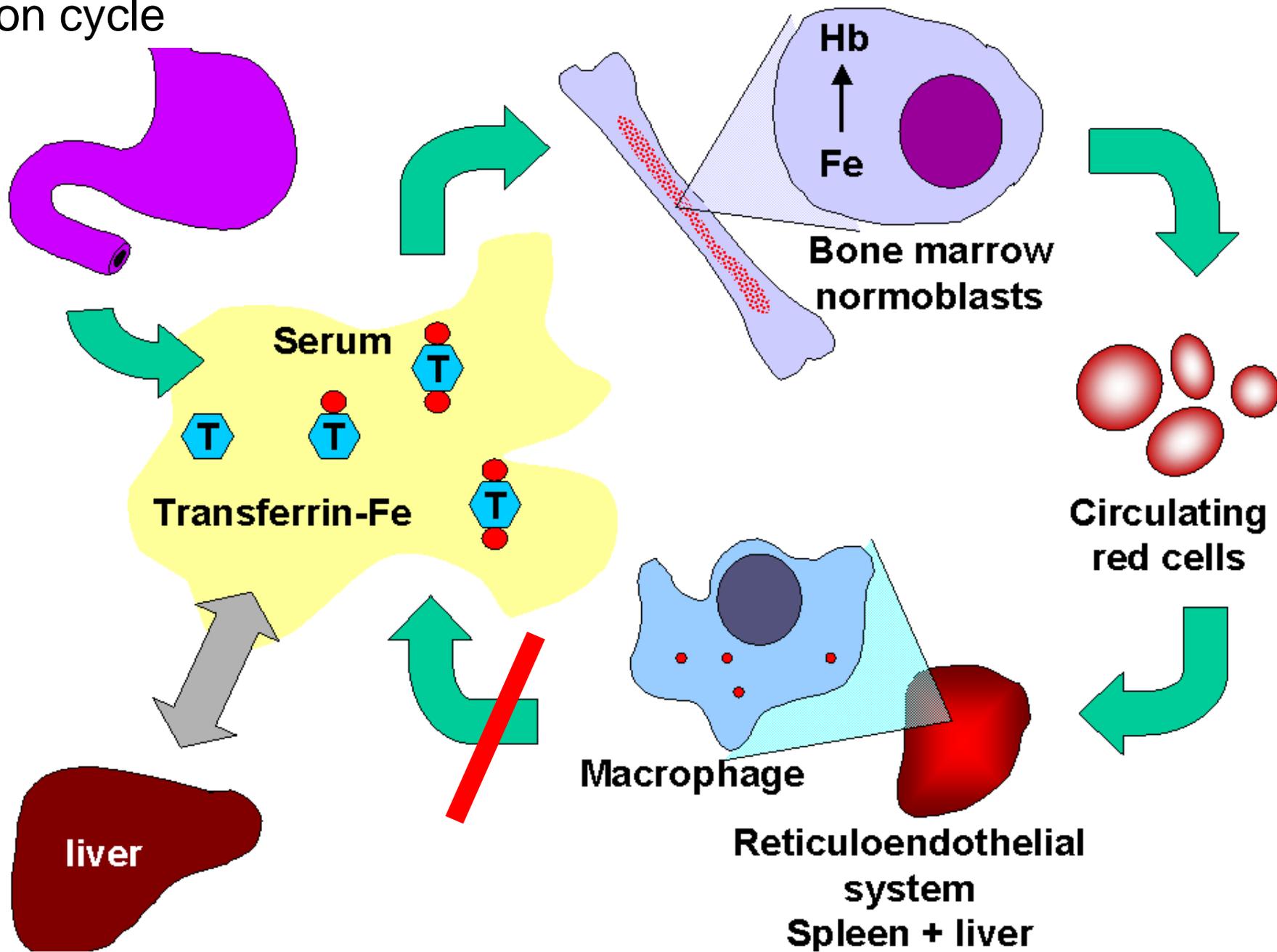
**Bur cell**



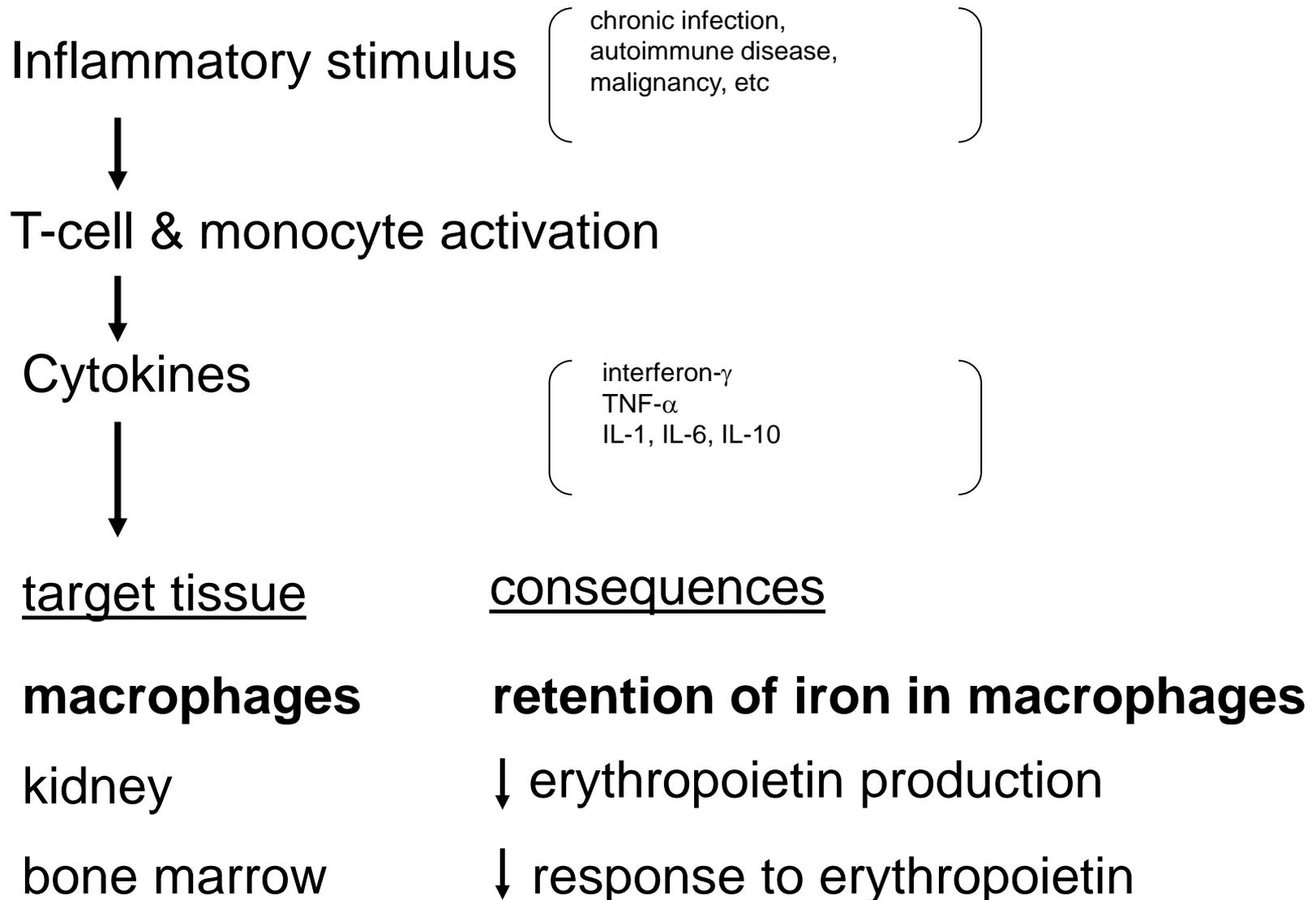
# Approach to normocytic anemia



# Iron cycle



# Pathophysiology of anemia of chronic disease



# Anemia of chronic disease

- Treatment
  - treat the **underlying** cause
  - **erythropoietin** can be effective, but is expensive
- **Iron** therapy has **no role** in the treatment of ACD

# اصفهان- باغ گلها



# Aplastic Anemia

Failure of the bone marrow precursors to produce mature cells. Characterized by hypocellular marrow and pancytopenia.

## Etiology:

- Acquired: **More common**
- Inherited: **Fanconi anemia**

## Acquired:

### 1. Drugs

- Cytotoxic drugs
- Chloramphenicol
- Anti-convulsant
- 2-3 months usually between exposure and the development of aplastic anemia.
- Antibiotics
- Anti-inflammatory
- Sulphonamides

# Aplastic Anemia: (Cont.)

## Acquired:

- Radiations
- Chemicals e.g., Benzene and pesticides
- Viruses:
  - Hepatitis A, Non-A and Non-B
  - Herpes simplex
  - E-B virus
  - Parvovirus: Transient
    - Important clinically in patients with hemolytic anemias
    - 5-10% of cases of AA in the West and 10-20% in the Far East.
    - 2-3 months between exposure to the virus and the development of AA.
- Immune: SLE, RA (rheumatoid arthritis)
- Pregnancy
- **Idiopathic: 75%**
- PNH

# Clinical Features

- Non-specific:
  - Bruising, petechiae
  - Manifestations of anemia
  - Infections
- Hematological findings:

## Peripheral blood:

- Pancytopenia: **initially only 1 or 2 parameters.** ANC < 500, retic < 1. Plat. < 30. No gross morphological abnormalities.
- Anemia is usually NCNC.
- Reticulocytopenia.
- **10% Ham's test is +** (complement mediated lysis)

# Treatment

- Withdrawal of etiological agents.
- Supportive.
- Restoration of marrow activity:
  - Bone marrow transplant
  - Immunosuppressive treatment
    - Prednisolone
    - Cyclosporin
    - Splenectomy
    - Antilymphocyte glob.
    - Anti T cells abs.
  - Androgens
  - Growth factors

# Clinical Course

- Usually fatal in constitutional type.

In the acquired type depends on severity: defined by retic count, months or years depending on the severity.

- Stable course: constant over a long period.
- Progressive, fluctuating.
- Unstable: Associated with abnormal clones.

# Inherited Anemia

## Fanconi's Anemia:

- The **most common** type of inherited aplastic anemias.
- Associated with anomalies e.g., skeletal, skin.
- **Autosomal recessive.**
- Marrow failure is at the level of CFU-GM.

## Genetics:

- Increased sensitivity of the cells to **chromosomal damage** by DNA cross linking agents.
- 5 genes are responsible A → E.
- IV54 mutation, is associated with multiple dysmorphism, severe pancytopenia, higher incidence of **AML**.

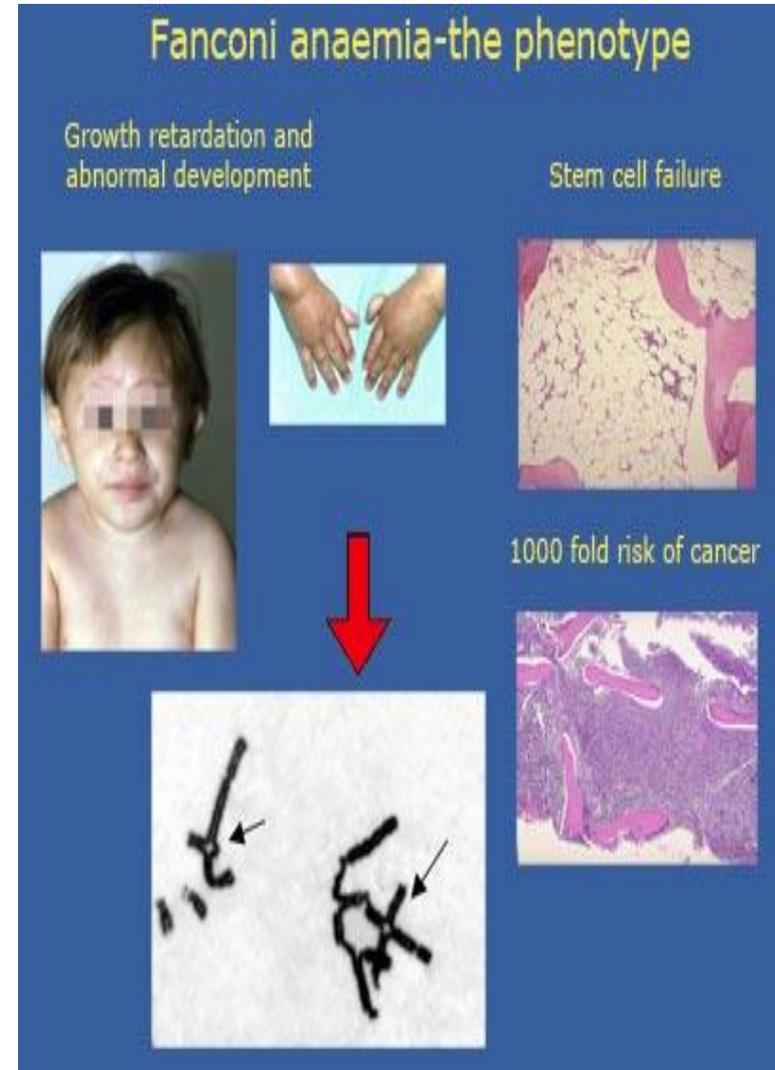
# Clinical Features of Fanconi's Anemia

## Common Findings:

- Low birth weight
- Short stature
- Microcephaly
- Microphthalmia
- Microstomia
- **Skeletal abnormalities**, particularly of thumbs and radii
- Hypoplastic hypothenar eminences
- Generalized increased **pigmentation of skin**
- Patches of hypopigmentation
- Cryptorchism
- Abnormalities of renal anatomy
  - Horseshoe kidneys
  - Pelvic kidney
- Strabismus
- Hyper-reflexia

## Uncommon associations:

- Mental retardation
- Vascular malformations
- Growth hormone deficiency



# Diamond Blackfan Anaemia

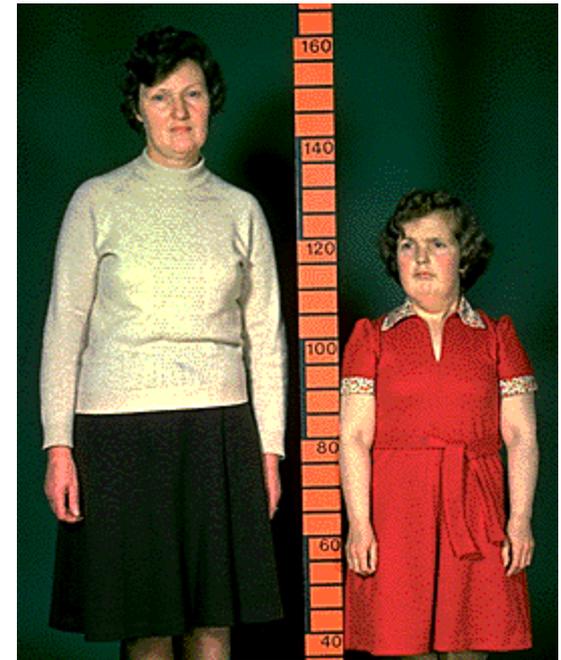
- Diamond Blackfan anaemia (DBA) is a blood condition resulting from a failure within the bone marrow
- **The hallmark** of this rare anaemia is the **inability** to **produce red blood cells**
- The majority of DBA cases are diagnosed between **4 months–2 years** of age
- This extremely rare condition affects 600–700 individuals worldwide

# Diamond Blackfan Anaemia

## *Physical Examination*

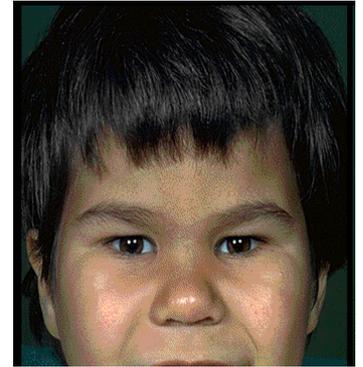
30%–50% of patients with DBA have associated congenital abnormalities

- Craniofacial abnormalities
- Neck anomalies
- Thumb abnormalities
- Genitourinary malformations
- Pre- and postnatal growth failure



# Diamond Blackfan Anaemia

- Children are reported to have **typical** facies with tow-colored hair, snub nose, wide set eyes, thick upper lip and an intelligent expression, although facies with different appearances have been reported in other children<sup>1</sup>
- Physical anomalies are more common in males<sup>2</sup>
- Growth retardation occurs in 30% of affected patients<sup>2</sup>
  - Often associated with other congenital abnormalities and the need for ongoing therapy



# Diamond Blackfan Anaemia

## *Treatment*

- The mainstays of therapy of DBA are **corticosteroids** and blood transfusion<sup>1</sup>
  - However, 1 study reported remissions in 22% of patients<sup>2</sup>
- **Transfusion** therapy is the mainstay of treatment for patients in whom **steroid therapy is ineffective** or in whom corticosteroid toxicity is prohibitive<sup>2</sup>
- **Bone marrow transplantation** has been employed with success in steroid refractory patients<sup>2</sup>
- Prognosis is dependent on transfusion dependence and subsequent complications of iron overload<sup>2</sup>

# Congenital Dyserythropoietic Anaemia (CDA)

- The CDAs (types I, II, III, and IV) form a rare group of disorders that result in anaemia caused by ineffective erythropoiesis and may present in childhood<sup>1</sup>
- Loci of the genes for types I, II, and III have been identified but only 1 gene, associated with type I CDA, has thus far been identified. This gene has been termed codanin-1, and may be involved in nuclear envelope integrity<sup>2</sup>
- In one retrospective study of 98 subjects with CDA type II<sup>3</sup>
  - Mean age at presentation was 5 years (range: 1 month–25 years), although the mean age at the time of correct diagnosis was 16 years (range: 4 months–65 years)<sup>3</sup>
  - Anaemia and jaundice were present in 66% and 53% of subjects, respectively

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In a second study of 48 patients with type II CDA

- Majority of patients had **splenomegaly** within the first 3 decades of life
- Absence of splenomegaly in an adolescent should raise doubts regarding the diagnosis
- **Gallstones** were found in 22 of 39 patients before the age of 40 years, appearing during childhood or adolescence a small percentage of the time; cholecystectomy was performed at a median age of 26 years
- In a patient with **congenital haemolytic anaemia, inadequate reticulocyte response suggests this diagnosis**, while the presence of **binucleated normoblasts** on the peripheral blood smear is noted as being **highly specific**

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## *Treatment*

Therapy depends on the type, and may include

- **Splenectomy** (effective **in type II** CDA but **not in type I**)<sup>1</sup>
- **Interferon  $\alpha$**  (effective in most patients with **type I**)<sup>2</sup>
- **Transfusion** in symptomatic patients<sup>2</sup>

**Thanks for your attention**

