2nd Lecture Objectives (Hereditary Spherocytosis)

1. To understand the definition of hemolytic anemia and recognize its different types according to their etiology
2. To be able to approaches to patient with hemolytic anemia (investigations and treatment)
3. To be able to approaches to patient with hereditary spherocytosis (investigations and treatment)
4. To be able to recognize the complications of hereditary spherocytosis and treating it

Hemolytic Anemia

Hemolysis is defined as the premature destruction of red blood cells (RBCs).

Anemia results when the rate of destruction exceeds the capacity of the marrow to produce RBCs.

Normal RBC survival time is **110–120 days**.

During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and the stimulation of marrow activity results in heightened RBC production.

This is reflected in an increased percentage of reticulocytes in the blood. Thus, hemolysis should be suspected as a cause of anemia if **an elevated reticulocyte count is present**.

The reticulocyte count also may be elevated as a response to blood loss or for a short period after replacement therapy for iron, vitamin B_{12}, or folate deficiency.

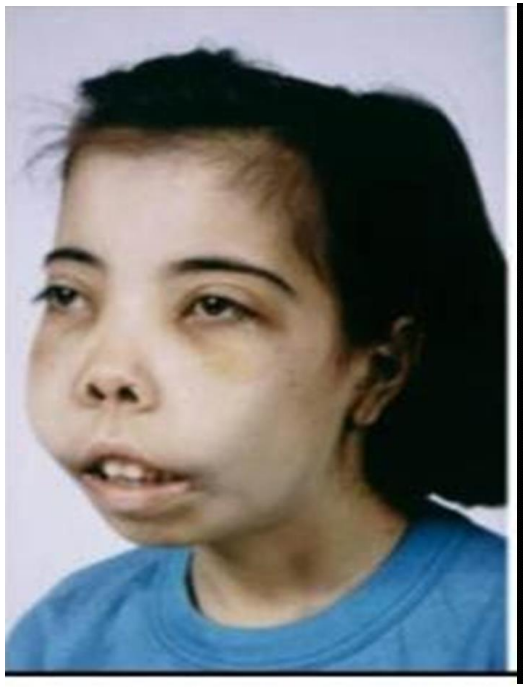
Several plasma, urinary, or fecal chemical alterations reflect the presence of hemolysis

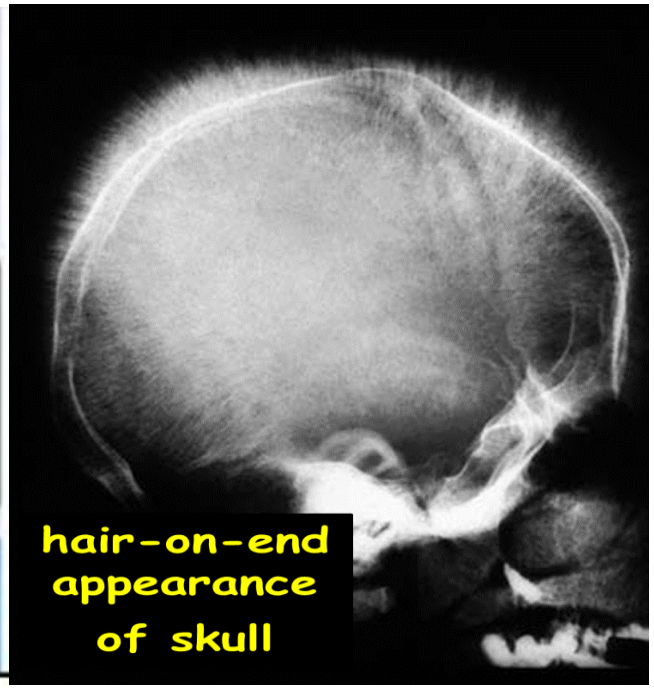
Accelerated Hemoglobin Catabolism

1. Increased unconjugated bilirubin.
2. Increased lactic acid dehydrogenase in serum.
3. Increased fecal and urinary urobilinogen.
4. Increased rate of carbon monoxide production.
5. Hemoglobinuria
6. Low or absent plasma haptoglobin.
7. Raised plasma hemoglobin level .
8. Raised plasma methemalbumin
9. Raised plasma methemoglobin (oxidized free plasma hemoglobin) .

Increased Erythropoiesis

1. Reticulocytosis.
2. Erythroid hyperplasia of the bone marrow
3. Expansion of marrow space in chronic hemolysis resulting in:
   - Prominence of frontal bones
   - Broad cheek bones
   - Widened intratrabecular spaces, hair-on-end appearance of skull radiographs





Hemolytic anemias may be classified a

(1)cellular, resulting from intrinsic abnormalities of the

membrane or

Enzymes or

hemoglobin

(2)extracellular, resulting from

antibodies or

mechanical factors or

plasma factors

Hereditary Spherocytosis

It is the most common inherited abnormality of the red blood cell (RBC) membrane.
Hereditary spherocytosis has been described in most ethnic groups, but is most common among persons of Northern European origin.

ETIOLOGY

Autosomal dominant inheritance (75% of cases)
25% of patients have no previous family history(most represent new mutations)

The most common molecular defects are abnormalities of **spectrin** or **ankyrin,** which are major components of the cytoskeleton responsible for RBC shape.
The loss of membrane surface area without a proportional loss of cell volume causes sphering of the RBCs and an associated increase in cation permeability.
The decreased deformability of the spherocytic RBCs impairs cell passage from the splenic cords to the splenic sinuses, and the spherocytic RBCs are destroyed prematurely in the spleen.

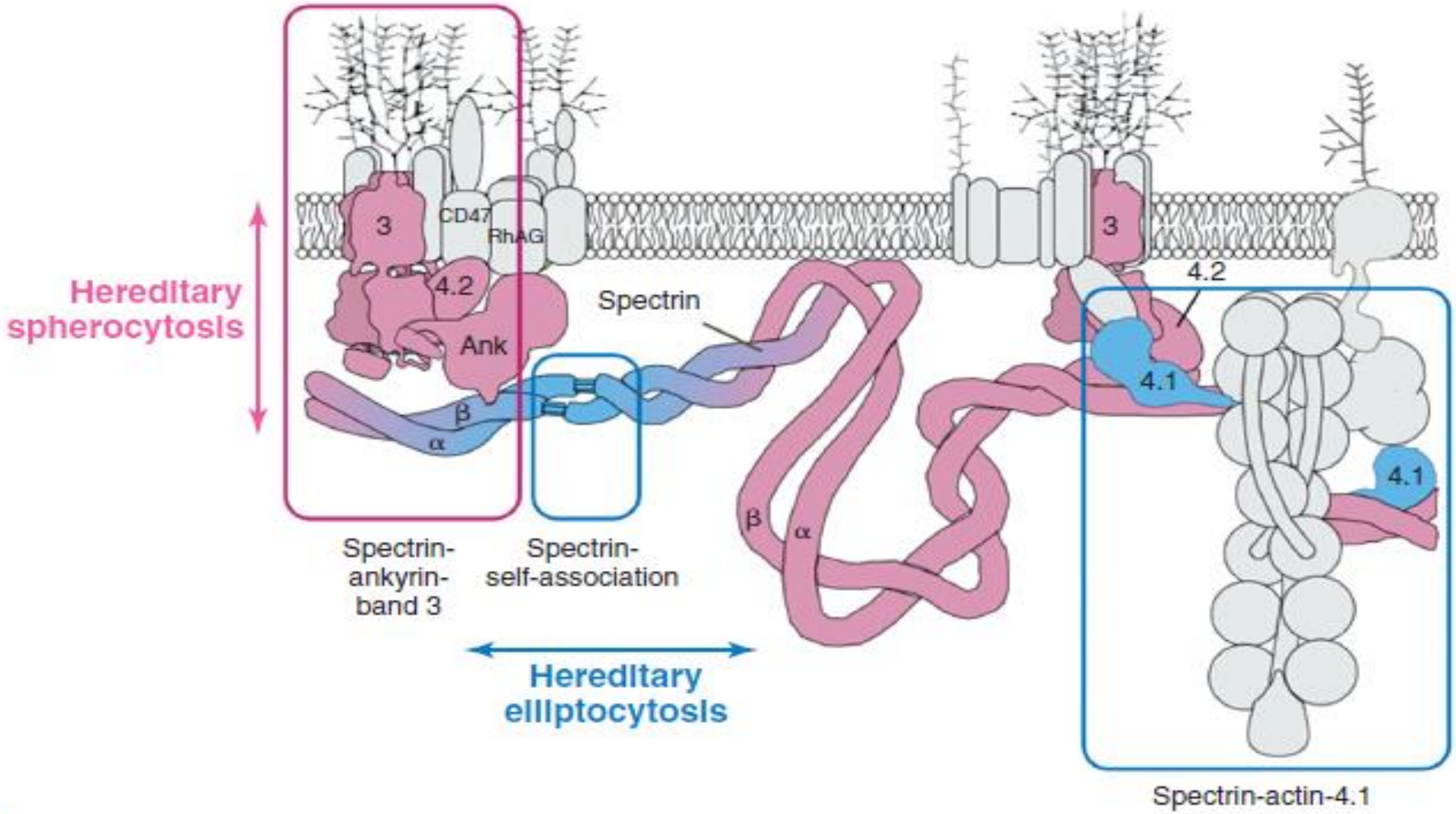
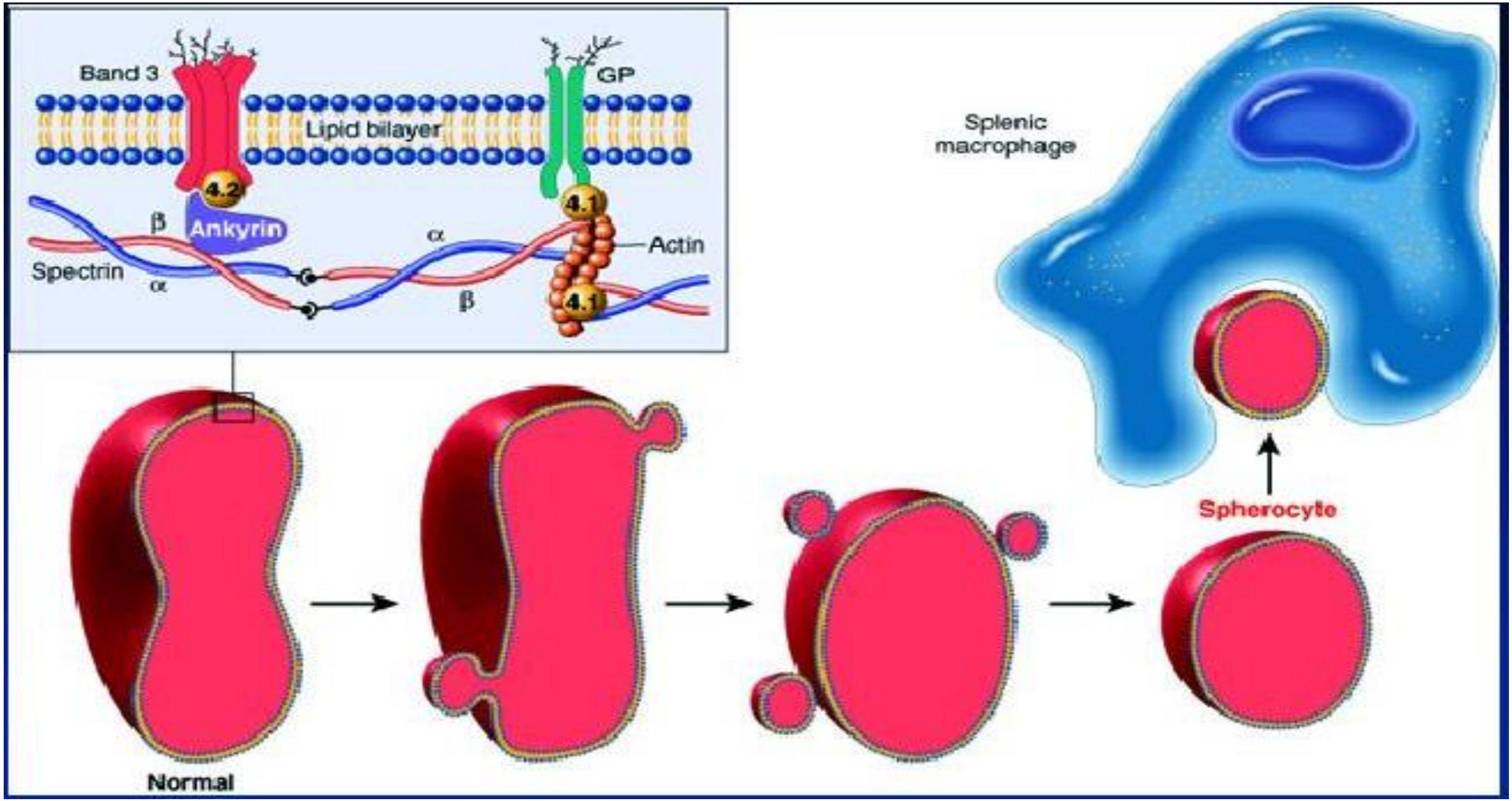


Figure 16-4 Membrane defects in hereditary spherocytosis and elliptocytosis. Hereditary spherocytosis is caused by a quantitative deficiency of spectrin, ankyrin, band 3, or protein 4.2, proteins involved in the "vertical" interactions that attach the membrane skeleton to the overlying lipid bilayer with its integral membrane proteins. Hereditary elliptocytosis is caused by functional defects in the "horizontal" protein interactions that hold the skeleton together. These are either defects near the head end of spectrin that impair self-association of spectrin dimers, or deficiency of protein 4.1R, a cofactor protein that bolsters the attachment of spectrin to actin. A more accurate model of the membrane is shown in Figure 15-6 of Chapter 15.


Band 3
GP
Lipid bilayer
4.2
4.1
β
Ankyrin
α
Actin
Spectrin
α
β
4.1
Splenic
macrophage
Spherocyte
Normal

CLINICAL MANIFESTATIONS

-Hereditary spherocytosis may be a cause of hemolytic disease in the newborn and may present as anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions.

-The severity of symptoms in infants and children is variable. Some children remain asymptomatic into adulthood, but others may have severe anemia, with pallor, jaundice, fatigue, and exercise intolerance.

After infancy, the spleen is usually enlarged, and pigmentary (bilirubin) gallstones may form as early as age 4–5 year

Severe cases may be marked by expansion of the diploë of the skull and the medullary region of other bones, but to a lesser extent than in thalassemia major

Complications

1. **Hemolytic crisis:** With more pronounced jaundice due to accelerated hemolysis (may be precipitated by viral infection).

2. **Aplastic crisis:** Dramatic fall in hemoglobin level (and reticulocyte count); usually due to maturation arrest and often associated with parvovirus B19 infection.

3. **Folate deficiency:** Caused by increased red cell turnover; may lead to superimposed megaloblastic anemia. Megaloblastic anemia may mask HS morphology as well as its diagnosis by osmotic fragility.

4. **Gallstones:** In approximately one-half of untreated patients; increased incidence with age, can occur as early as 4–5 years of age.

LABORATORY FINDINGS

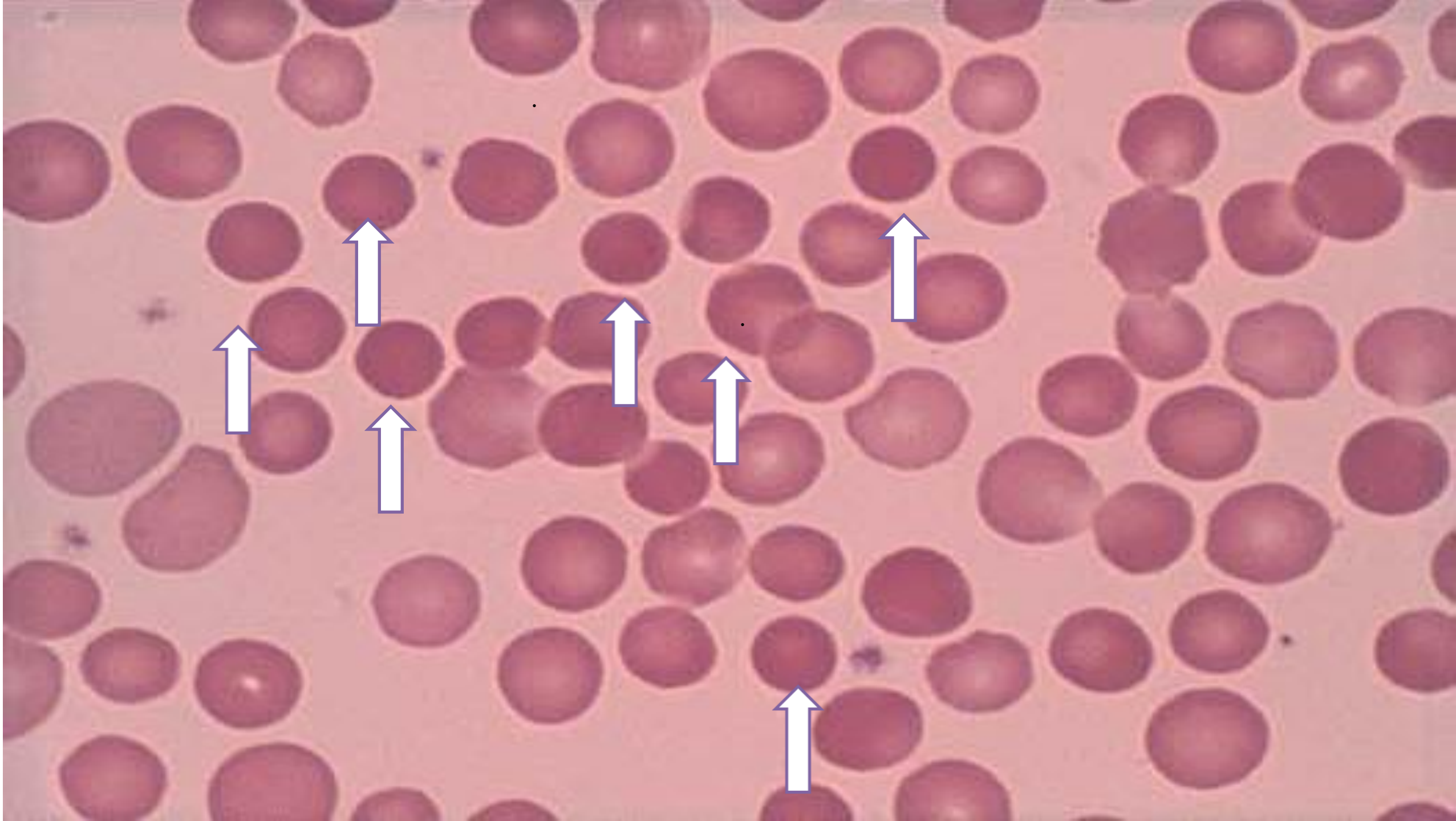
1. **The hemoglobin level** usually is 6–10 g/dL, but it can be in the normal range. The **reticulocyte percentage** often is increased to (3-15%).

2. **MCV** usually decreased; **(MCHC) raised (36–38 g/dL)** and
3. **RDW elevated(greater than 14)**

   The presence of **elevated RDW and MCHC** makes the likelihood of HS very high, because these two tests used together are very specific for HS

3. **The RBCs** on the blood film vary in size and include polychromatophilic reticulocytes and spherocytes.

   The spherocytes are smaller in diameter and appear hyperchromic on the blood film as a result of the high hemoglobin concentration. The central pallor is less conspicuous than in normal cells.



4.Osmotic fragility test: the RBCs are incubated in progressive dilutions of an iso-osmotic buffered salt solution. Exposure to hypotonic saline causes the RBCs to swell, and the spherocytes lyse more readily than biconcave cells in hypotonic solutions. This feature is accentuated by depriving the cells of glucose overnight at 37°C, known as the *incubated osmotic fragility test*. Unfortunately, this test is not specific for hereditary spherocytosis, and results may be abnormal in immune and other hemolytic anemias. A normal test result also may be found in 10–20% of patients.

5.Hypertonic Cryohemolysis Test. This method is based on the fact that HS red cells are particularly sensitive to cooling at 0°C in hypertonic solutions, which causes the cells to lyse and release hemoglobin.

6.Autohemolysis The autohemolysis of erythrocytes after 48 hours at 37°C is normally less than 5% in the absence of glucose or less than 1% in the presence of glucose. Autohemolysis of spherocytes increases to 15% to 45% in the absence of glucose.In HS, the degree of autohemolysis is reduced by the addition of glucose

7.Eosin-5-maleimide dye staining is a fluorescent dye that is used to detect red cell membrane defects by flow cytometry ,it is the test of choice to diagnose HS but is only available in special reference laboratories

8.Genetic analysis for the α- and β-spectrin, ankyrin, and band 3 mutations is available, but rarely necessary to be performed for diagnosis.

DIFFERENTIAL DIAGNOSIS

large numbers of spherocytes are seen on the blood film in:

Isoimmune and autoimmune hemolysis.
Isoimmune hemolytic disease of the newborn, particularly due to ABO incompatibility, mimics hereditary spherocytosis.
The detection of antibody on an infant's RBCs using a direct antiglobulin (Coombs) test should establish the diagnosis of immune hemolysis.
Autoimmune hemolytic anemia also are characterized by spherocytes, and there may be evidence of previously normal values for hemoglobin, hematocrit, and reticulocyte count.

Rare causes of spherocytosis include
thermal injury,
clostridial septicemia with exotoxemia, and
Wilson disease,
(each of which may present as **transient hemolytic anemia**)

TREATMENT

1. **Folic acid** supplement (1 mg/day).

2. Leukocyte-depleted **packed red cell transfusion** for severe erythroblastopenic crisis.

3. **Splenectomy** for moderate-to-severe cases .

Most patients with less than 80% of normal spectrin content require splenectomy.

Splenectomy should be carried out early in severe cases but not before 5 years of age.

Although spherocytosis persists postsplenectomy, the red cell life span normalizes and complications are prevented,especially transient erythroblastopenia and hyperbilirubinemia.

Patients are at risk of sepsis after splenectomy, especially for those under 5 years of age.

Laparoscopic splenectomy is safe in children., duration of hospital stay, and more rapid return to a regular diet and daily activities. It is not known whether accessory spleens are readily identified with the laparoscope although the magnification afforded by the laparoscope might be advantageous in some cases.

In **partial splenectomy**, up to 90% of the splenic mass is removed with small studies suggesting that the technique leaves enough splenic tissue to protect against infection.
The technique is not widely utilized but its use should certainly be entertained in **transfusion-dependent patients who are under 5 years of age.**

4. Ultrasound should be carried out before splenectomy to exclude the presence of gallstones. If present, **cholecystectomy** is also indicated.

Do you have any Questions?