بسم الله الرحمن الرحيم

HEMOLYTIC ANEMIA

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Definition

- An essential feature of hemolytic anemia is a reduction in the normal red cell survival of 120 days. Premature destruction of red cells may result from:

  Corpuscular abnormalities

  membrane,enzymes, or hemoglobin;
  Extracorpuscular abnormalities,

  immune or nonimmune mechanisms.

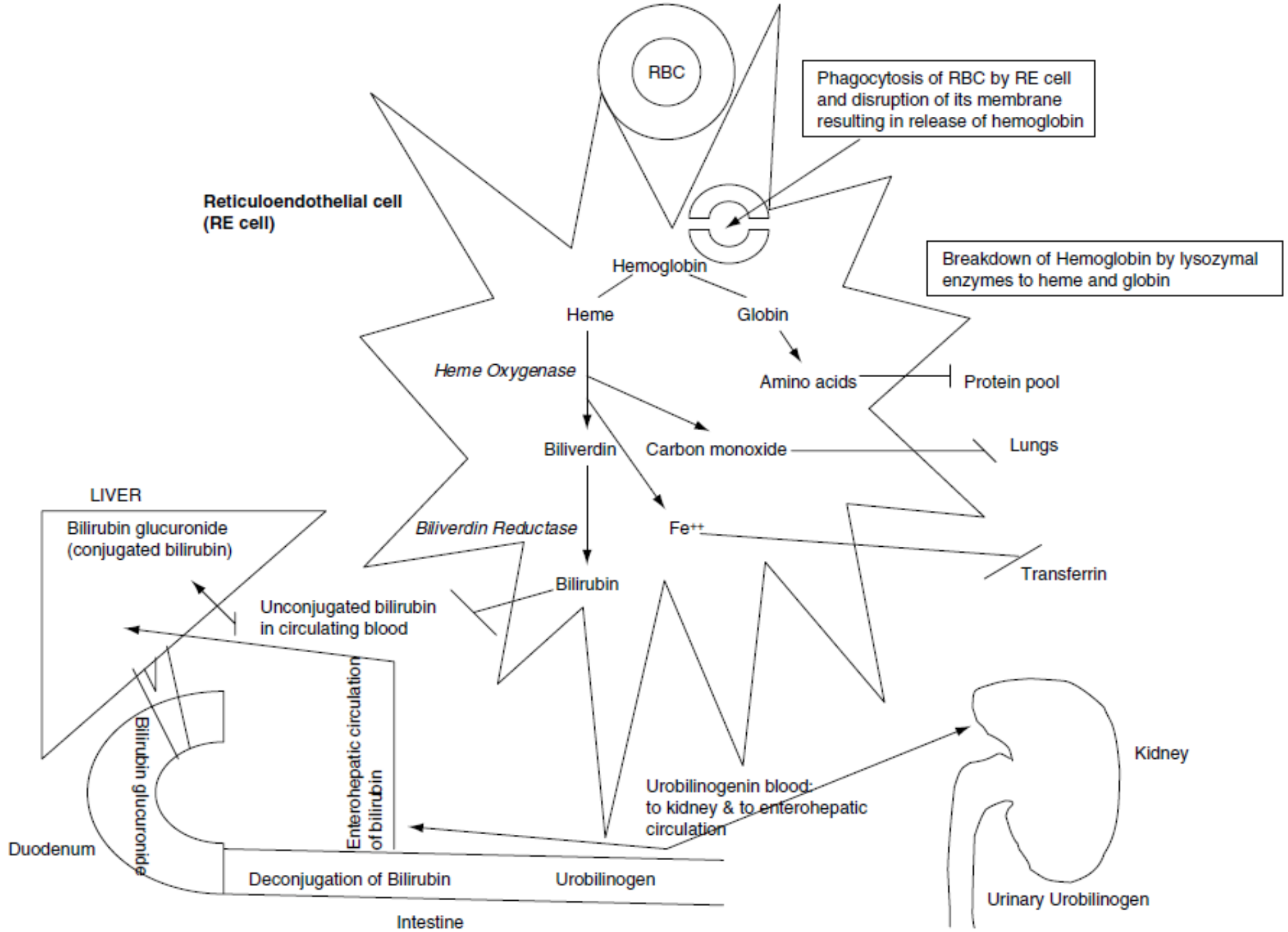
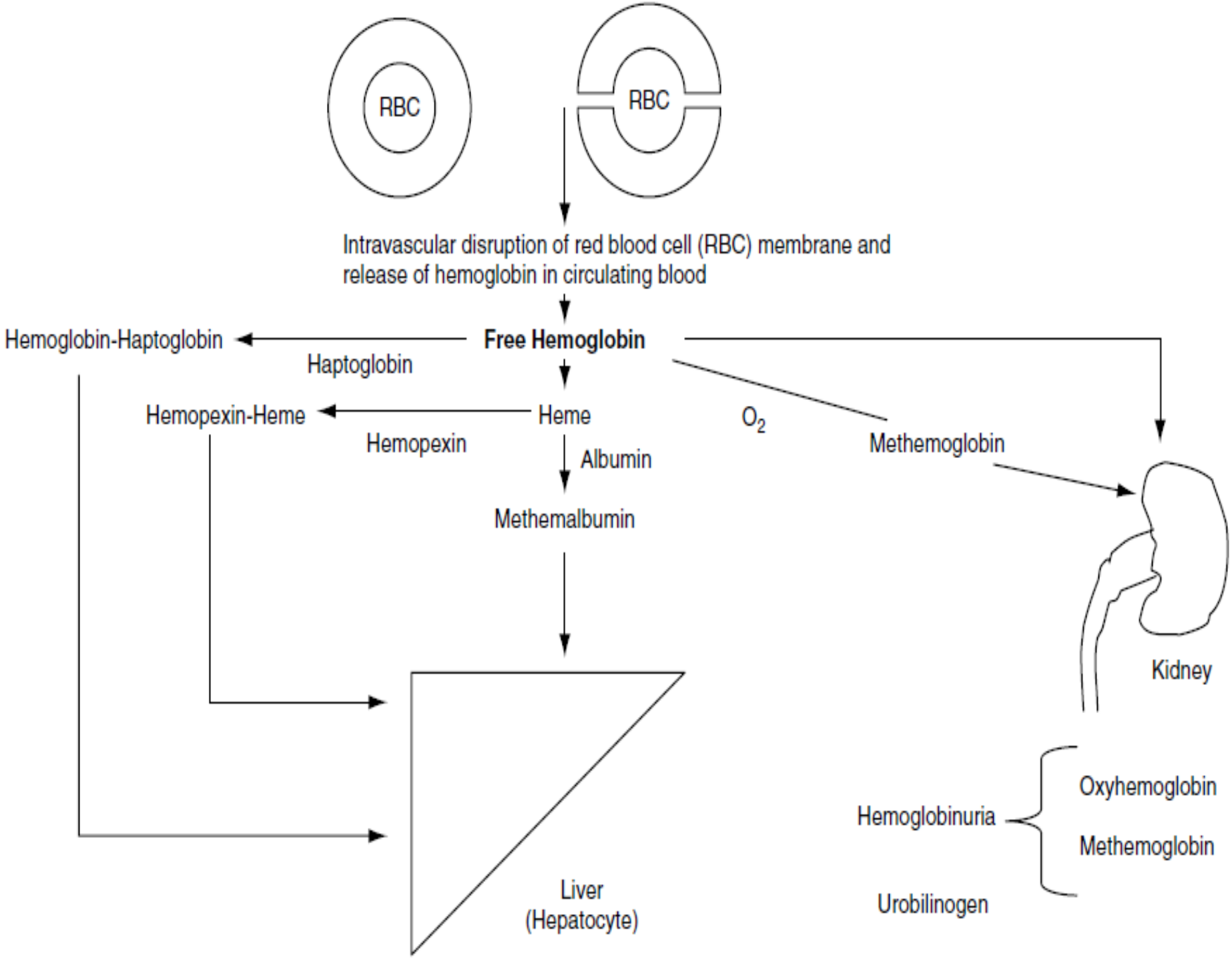


Fig. 7-1. Extravascular hemoglobin catabolism following extravascular destruction of the RBC.


RBC
RBC
Intravascular disruption of red blood cell (RBC) membrane and release of hemoglobin in circulating blood
Free Hemoglobin
Hemoglobin-Haptoglobin
Haptoglobin
Hemopexin-Heme
Hemopexin
Heme
Albumin
Methemalbumin
O_2
Methemoglobin
Kidney
Hemoglobinuria
Oxyhemoglobin
Methemoglobin
Urobilinogen
Liver
(Hepatocyte)

APPROACH TO DIAGNOSIS

- The approach to the diagnosis of hemolytic anemia should include:
- 1. Consideration of the clinical features suggesting hemolytic disease
- 2. Laboratory demonstration of the presence of a hemolytic process
- 3. Determination of the precise cause of the hemolytic anemia by special hematologic investigations

Clinical Features

- 1. History of anemia, jaundice, or gallstones in family
- 2. Persistent or recurrent anemia associated with reticulocytosis
- 3. Anemia unresponsive to hematinics
- 4. Intermittent or persistent indirect hyperbilirubinemia
- 5. Splenomegaly
- 6. Hemoglobinuria
- 7. Presence of multiple gallstones
- 8. Chronic leg ulcers

Laboratory Findings

- Laboratory findings of hemolytic anemia consist of:
- 1. Reduced red cell survival and evidence of accelerated hemoglobin catabolism
- 2. Evidence of increased erythropoiesis.

Accelerated Hemoglobin Catabolism

- *Signs of extravascular hemolysis:*
- 1. Increased unconjugated bilirubin
- 2. Increased fecal and urinary urobilinogen
- 3. Increased rate of carbon monoxide production

Accelerated Hemoglobin Catabolism

- *Signs of intravascular hemolysis:*
- 1. Raised plasma hemoglobin level
- 2. Hemoglobinuria
- 3. Low or absent plasma haptoglobin
- 4. Raised plasma methemalbumin (albumin bound to heme; unlike haptoglobin,albumin does not bind intact hemoglobin)
- 5. Raised plasma methemoglobin (oxidized free plasma hemoglobin) and raised levels of hemopexin-heme complex in plasma.

Increased Erythropoiesis

- 1. *Reticulocytosis*
- 2. Increased mean (MCV) due to the presence of reticulocytosis and increased (RDW) as the hemoglobin level falls
- 3. Increased normoblasts in peripheral blood

Increased Erythropoiesis

- 5. Erythroid hyperplasia in bone marrow
- 6. Expansion of marrow space in chronic hemolysis resulting in:

  a. Prominence of frontal bones

  b. Broad cheekbones

  c. Widened intratrabecular spaces, hair-on-end appearance of skull radiographs

Determination of Cause

Table 7-5. Tests Used to Establish a Specific Cause of Hemolytic Anemia

- Corpuscular defects
  - Membrane
    - Blood smear: spherocytes, ovalocytes, pyknocytes, stomatocytes[a]
    - Osmotic fragility (fresh and incubated)[a]
    - Autohemolysis[a]
    - Cation permeability studies
    - Membrane phospholipid composition
    - Scanning electron microscopy
  - Hemoglobin defects
    - Blood smear: sickle cells, target cells (Hb C)[a]
    - Sickling test[a]
    - Hemoglobin electrophoresis[a]
    - Quantitative fetal hemoglobin determination[a]
    - Kleihauer–Betke smear[a]
    - Heat stability test for unstable hemoglobin
    - Oxygen dissociation curves
    - Rates of synthesis of polypeptide chain production
    - Fingerprinting of hemoglobin
  - Enzyme defects
    - Heinz-body preparation[a]
    - Osmotic fragility[a]
    - Autohemolysis test[a]
    - Screening test for enzyme deficiencies[a]
    - Specific enzyme assays[a]
  - Extracorpuscular defects
    - Coombs' test: IgG (gamma), C'3 (complement), broad-spectrum (both gamma and complement)[a]
    - Acidified serum lysis (Ham's) test[a]
    - Donath–Landsteiner test[a]
    - Flow cytometric analysis of red cells with monoclonal antibodies to GP1-linked surface antigens (for PNH)

Causes of Hemolytic Anemia Due to Corpuscular Defects

I. Membrane defects
   A. Primary membrane defects with specific morphologic abnormalities
      1. Hereditary spherocytosis
      2. Hereditary elliptocytosis/pyropoikilocytosis
      3. Hereditary stomatocytosis with:
         a. Increased osmotic fragility (high Na^+, low K^+)
         b. Decreased osmotic fragility (high Na^+, low K^+)
         c. Normal osmotic fragility
         d. Rh_{null}
      4. Congenital hemolytic anemia with dehydrated red cells (high Na^+, low K^+, decreased osmotic fragility)
   B. Secondary membrane defects: abetalipoproteinemia

II. Enzyme defects

A. Energy potential defects (Embden–Meyerhof: anaerobic; ATP-producing pathway deficiencies)
   1. Hexokinase
   2. Glucose phosphate isomerase
   3. Phosphofructokinase
   4. Triosephosphate isomerase
   5. Phosphoglycerate kinase
   6. 2,3-Diphosphoglyceromutase (polycythemia and no hemolysis)
   7. Pyruvate kinase

B. Reduction potential defects (hexose monophosphate: aerobic; NADPH-producing pathway deficiencies)
   1. G6PD[a]
   2. 6-Phosphogluconate dehydrogenase (6PGD)
   3. Glutathione reductase
   4. Glutathione synthetase
   5. 2,3-Glutamyl-cysteine synthetase

C. Abnormalities of erythrocyte nucleotide metabolism
   1. Adenosine triphosphatase deficiency
   2. Adenylate kinase deficiency
   3. Pyrimidine 5′-nucleotidase (P5N) deficiency
   4. Adenosine deaminase excess

Causes of Hemolytic Anemia Due to Corpuscular Defects

III. Hemoglobin defects
   A. Heme: congenital erythropoietic porphyria
   B. Globin
      1. Qualitative: hemoglobinopathies (e.g., Hb S, C, H, M)
      2. Quantitative: α- and β-thalassemias

IV. Congenital dyserythropoietic anemias
   A. Type I
   B. Type II
   C. Type III
   D. Type IV

Causes of Hemolytic Anemia Due to Extracorpuscular Defects

I. **Immune**
   A. Isoimmune
      1. Hemolytic disease of the newborn
      2. Incompatible blood transfusion
   B. Autoimmune: IgG only; complement only; mixed IgG and complement
      1. Idiopathic
         a. Warm antibody
         b. Cold antibody
         c. Cold–warm hemolysis (Donath–Landsteiner antibody)
      2. Secondary
         a. Infection, viral: infectious mononucleosis—Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis, herpes simplex, measles, varicella, influenza A, coxsackie virus B, human immunodeficiency virus (HIV); bacterial: streptococcal, typhoid fever, *Escherichia coli* septicemia, *Mycoplasma pneumoniae* (atypical pneumonia)
         b. Drugs and chemicals: quinine, quinidine, phenacetin, *p*-aminosalicylic acid, sodium cephalothin (Keflin), penicillin, tetracycline, rifampin, sulfonamides, chlorpromazine, pyradone, dipyrone, insulin; lead
         c. Hematologic disorders: leukemias, lymphomas, lymphoproliferative syndrome, associated idiopathic thrombocytopenic purpura (Evans syndrome), paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria
         d. Immunopathic disorders: systemic lupus erythematosus, periarteritis nodosa, scleroderma, dermatomyositis, rheumatoid arthritis, ulcerative colitis, agammaglobulinemia, Wiskott–Aldrich syndrome, dysgammaglobulinemia, IgA deficiency, thyroid disorders, giant cell hepatitis, Evans syndrome, autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency
         e. Tumors: ovarian teratomata, dermoids, thymoma, carcinoma, lymphomas

Causes of Hemolytic Anemia Due to Extracorpuscular Defects

II. Nonimmune
   A. Idiopathic
   B. Secondary
      1. Infection, viral: infectious mononucleosis, viral hepatitis; bacterial: streptococcal, *E. coli* septicemia, *Clostridium perfringens, Bartonella bacilliformis;* parasites: malaria, histoplasmosis
      2. Drugs and chemicals: phenylhydrazine, vitamin K, benzene, nitrobenzene, sulfones, phenacetin, acetinalimide; lead
      3. Hematologic disorders: leukemia, aplastic anemia, megaloblastic anemia, hypersplenism, pyknocytosis
      4. Microangiopathic hemolytic anemia: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, chronic relapsing schistocytic hemolytic anemia, burns, post cardiac surgery, march hemoglobinuria
      5. Miscellaneous: Wilson disease, erythropoietic porphyria, osteopetrosis, hypersplenism

Hereditary Spherocytosis

- Genetics
- 1. Autosomal dominant inheritance (75% of cases). The severity of anemia and the degree of spherocytosis may not be uniform within an affected family.
- 2. No family history in 25% of cases. Some show minor laboratory abnormalities,suggesting a carrier (recessive) state. Others are due to a *de novo mutation.*
- 3. Most common in people of northern European heritage, with an incidence of 1 in 5000.

Pathogenesis

- In hereditary spherocytosis (HS), the primary defect is membrane instability due to

  dysfunction or deficiency of a red cell skeletal protein. A variety of membrane skeletal

  protein defects have been found in different families.

Pathogenesis

- Deficiency of these membrane skeletal proteins in HS results in vertical defect,

  which causes progressive loss of membrane lipid and surface area. The loss of surface

  area results in characteristic microspherocytic morphology of HS red cells

- The sequelae are as follows:
- 1. Sequestration of red cells in the spleen (due to reduced erythrocyte deformability)
- 2. Depletion of membrane lipid
- 3. Decrease in membrane surface area relative to volume, resulting in a decrease in surface area-to-volume ratio
- 4. Tendency to spherocytosis
- 5. Influx and efflux of sodium increased; cell dehydration

Hematology

- 1. *Anemia: Mild to moderate*
- 2. MCV usually decreased; mean corpuscular hemoglobin concentration (MCHC) raised and RDW elevated.*
- 3. Reticulocytosis (3–15%).
- 4. *Blood film: Microspherocytes† (vary in number); hyperdense cells,‡ polychromasia.*
- 5. Coombs' test negative.
- 6. Increased red cell osmotic fragility (spherocytes lyse in higher concentrations of saline than normal red cells) occasionally only demonstrated after incubation of blood sample at 37°C for 24 hours. In spite of normal osmotic fragility, increased MCHC or an increase of hyperdense red cells is highly suggestive of HS.

Biochemistry

- 1. Raised bilirubin, mainly indirect reacting
- 2. Obstructive jaundice with increased direct-reacting bilirubin; may develop due to gallstones.

Clinical Features

- 1. Anemia and jaundice:
- 2. Splenomegaly.
- 3. Presents in newborn (50% of cases) with hyperbilirubinemia, reticulocytosis,

  normoblastosis, spherocytosis, negative Coombs' test, and splenomegaly.
- 4. Presents before puberty in most patients.
- 5. Diagnosis sometimes made much later in life by chance.

Table 7-6. Classification of Spherocytosis and Indications for Splenectomy

Classification	Trait	Mild spherocytosis	Moderate spherocytosis	Severe spherocytosis[a]
Hemoglobin (g/dL)	Normal	11–15	8–12	6–8
Reticulocyte count (%)	≤3	3.1–6	≥6	≥10
Bilirubin (mg/dL)	≤1.0	1.0–2.0	≥2.0	≥3.0
Reticulocyte production index	<1.8	1.8–3	>3	
Spectrin per erythrocyte[b] (percentage of normal)	100	80–100	50–80	40–60
Osmotic fragility				
Fresh blood	Normal	Normal to slightly increased	Distinctly increased	Distinctly increased
Incubated blood	Slightly increased	Distinctly increased	Distinctly increased	Distinctly increased
Autohemolysis				
Without glucose (%)	>60	>60	0–80	50
With glucose (%)	<10	≥10	≥10	≥10
Splenectomy	Not necessary	Usually not necessary during childhood and adolescence	Necessary during school age before puberty	Necessary, not before 3 years of age
Symptoms	None	None	Pallor, erythroblastopenic crises, splenomegaly, gallstones	Pallor, erythroblastopenic crises, splenomegaly, gallstones

Diagnosis

- 1. Clinical features and family history
- 2. Hematologic features.

Complications

- 1. *Hemolytic crisis:* (may be precipitated by infection)
- 2. *Erythroblastopenic crisis: Dramatic fall in hemoglobin level (and reticulocyte count);*usually due to maturation arrest and often associated with giant pronormoblasts in the recovery phase; usually 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
- 4. *Gallstones: In approximately one-half of untreated patients; increased incidence* with age.

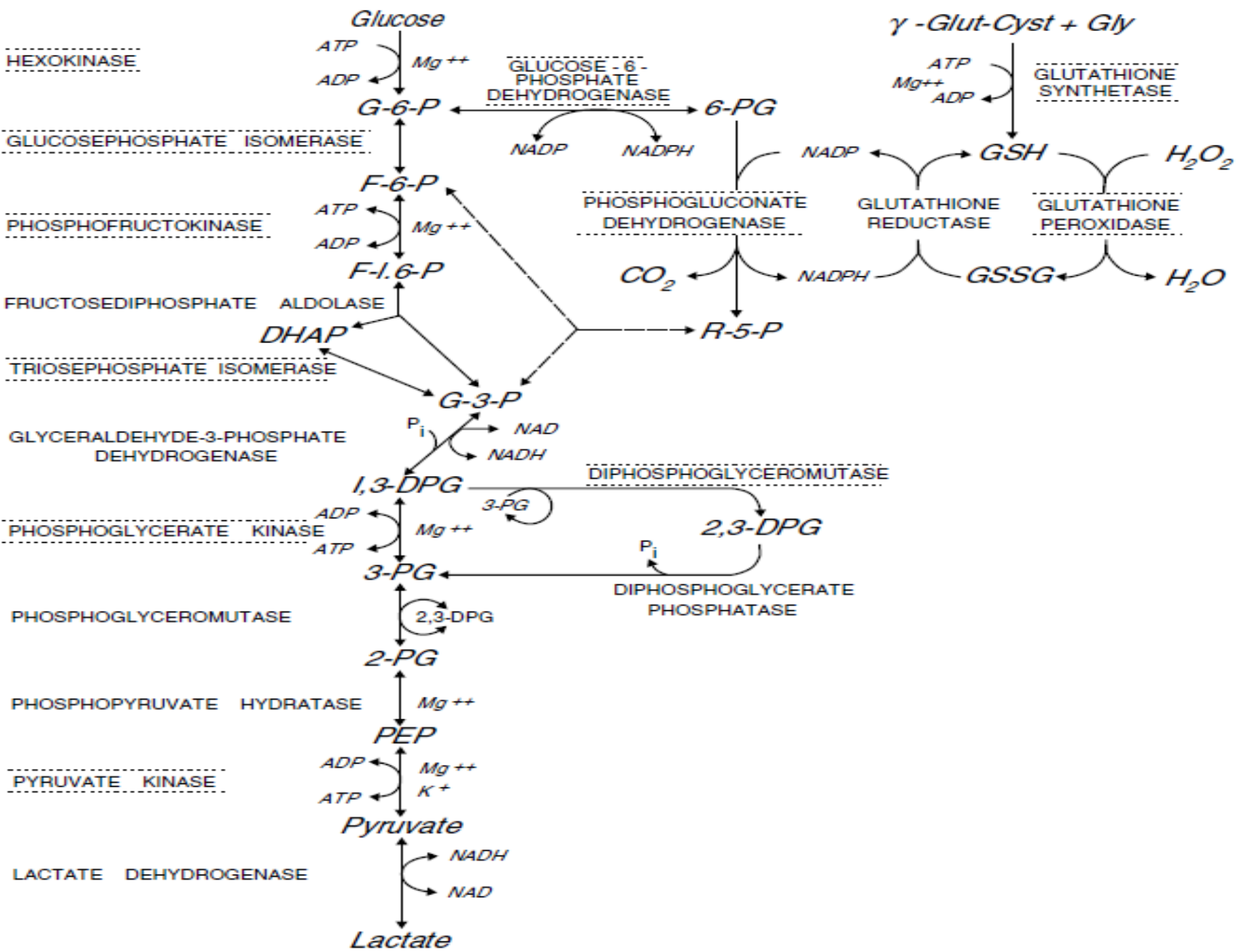
Treatment

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

Enzyme Defects

- There are two major biochemical pathways in the red cell:
- The Embden–Meyerhof anaerobic pathway (energy potential of the cell) and
- The hexose monophosphate shunt

  (reduction potential of the cell)


Glucose
ATP
ADP
Mg ++
HEXOKINASE
G-6-P
GLUCOSE - 6 - PHOSPHATE DEHYDROGENASE
6-PG
NADP
NADPH
GLUCOSEPHOSPHATE ISOMERASE
F-6-P
ATP
ADP
Mg ++
PHOSPHOFRUCTOKINASE
F-I.6-P
FRUCTOSEDIPHOSPHATE ALDOLASE
DHAP
TRIOSEPHOSPHATE ISOMERASE
G-3-P
Pi
NAD
NADH
GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE
I,3-DPG
DIPHOSPHOGLYCEROMUTASE
3-PG
ADP
Mg ++
ATP
PHOSPHOGLYCERATE KINASE
2,3-DPG
Pi
3-PG
DIPHOSPHOGLYCERATE PHOSPHATASE
PHOSPHOGLYCEROMUTASE
2,3-DPG
2-PG
PHOSPHOPYRUVATE HYDRATASE
Mg ++
PEP
ADP
ATP
Mg ++
K +
PYRUVATE KINASE
Pyruvate
NADH
NAD
LACTATE DEHYDROGENASE
Lactate
PHOSPHOGLUCONATE DEHYDROGENASE
CO2
NADPH
R-5-P
γ -Glut-Cyst + Gly
ATP
Mg++
ADP
GLUTATHIONE SYNTHETASE
GSH
NADP
GLUTATHIONE REDUCTASE
GSSG
H2O2
GLUTATHIONE PEROXIDASE
H2O

Glucose-6-Phosphate Dehydrogenase Deficiency

- Glucose-6-phosphate dehydrogenase (G6PD) is the first enzyme in the pentose phosphate pathway of glucose metabolism. Deficiency diminishes the reductive energy of the red cell and may result in hemolysis, the severity of which depends on the quantity and type of G6PD and the nature of the hemolytic agent .

Genetics

- 1. Sex-linked recessive mode of inheritance by a gene located on the X chromosome(similar to hemophilia).
- 2. Disease is fully expressed in hemizygous males and homozygous females.
- 3. Variable intermediate expression is shown by heterozygous females (due to random deletion of X chromosome, according to Lyon hypothesis).

The molecular basis of G6PD deficiency

- 1. Deletions of G6PD genes are incompatible with life
- 2. Point mutations are responsible for G6PD deficiencies. They result in:

  a. *Sporadic mutations:* Have no causal relationship with malarial selection. These patients manifest with chronic nonspherocytic hemolytic anemia (CNSHA WHO Class I).

  b. *Polymorphic mutations: These mutations have resulted from malaria selection;*hence, they correlate with specific geographic areas. They are usually WHO Class II or III and not Class I.

WHO Class	Variant	Magnitude of enzyme deficiency	Severity of hemolysis
I	Harilaou, Tokyo, Guadalajara, Stonybrook, Minnesota	2% of normal activity	Chronic nonspherocytic hemolytic anemia
II	Mediterranean	3% of normal activity	Intermittent hemolysis
III	A^-	10–60% of normal activity	Intermittent hemolysis usually associated with infections or drugs
IV	B (Normal)	100% of normal activity	No hemolysis

Pathogenesis

- 1. Diminished NADPH/NADP and GSH/GSSG ratios
- 2. Impaired elimination of oxidants (e.g., H2O2)
- 3. Oxidation of hemoglobin
- 4. Red cell integrity impaired, especially on exposure to oxidant drugs and chemicals

Clinical Features

- Episodes of hemolysis may be produced by:
  - Drugs
  - Fava bean
  - Infection (in more susceptible subjects).

1. Drug-induced hemolysis

- a. Typically in African Americans but also in Mediterranean types
- b. List of drugs
- c. Acute self-limiting hemolytic anemia with hemoglobinuria
- d. Heinz bodies in circulating red cells
- e. Blister cells, fragmented cells, and spherocytes
- f. Reticulocytosis
- g. Hemoglobin normal between episodes

Table 7-7. Agents Capable of Inducing Hemolysis in G6PD-Deficient Subjects[a]

Clinically significant hemolysis	Usually not clinically significant hemolysis
Analgesics and antipyretics	
Acetanilid	Acetophenetidin (phenacetin)
	Acetylsalicylic acid (large doses)
	Antipyrine[a,b]
	Aminopyrine[b]
	p-Aminosalicyclic acid
Antimalarial agents	
Pentaquine	Quinacrine (Atabrine)
Pamaquine	Quinine[b]
Primaquine	Chloroquine[c]
Quinocide	Pyrimethamine (Daraprim)
	Plasmoquine
Sulfonamides	
Sulfanilamide	Sulfadiazine
N-Acetylsulfanilamide	Sulfamerazine
Sulfapyridine	Sulfisoxazole (Gantrisin)[c]
Sulfamethoxypyridazine (Kynex)	Sulfathiazole
Salicylazosulfapyridine (Azulfidine)	Sulfacetamide
Nitrofurans	
Nitrofurazone (Furacin)	
Nitrofurantoin (Furadantin)	
Furaltadone (Altafur)	
Furazolidone (Furoxone)	
Sulfones	
Thiazolsulfone (Promizole)	
Diaminodiphenylsulfone (DDS, dapsone)	Sulfoxone sodium (Diasone)
Miscellaneous	
Naphthalene	
Phenylhydrazine	Menadione
Acetylphenylhydrazine	Dimercaprol (BAL)
Toluidine blue	Methylene blue
Nalidixic acid (NegGram)	Chloramphenicol[b]
Neoarsphenamine (Neosalvarsan)	Probenecid (Benemid)
Infections	Quinidine[b]
Diabetic acidosis	Fava beans[b]

2. Favism

- a. Acute life-threatening hemolysis, often leading to acute renal failure caused by ingestion of fava beans
- b. Associated with Mediterranean and Canton varieties
- c. Blood transfusion required

3. Neonatal jaundice

- a. Usually associated with Mediterranean and Canton varieties
- b. Infants may present with pallor, jaundice (can be severe and produce kernicterus*),

  and dark urine.
- In a majority of neonates, the jaundice is not

  hemolytic but hepatic in origin.

4. Chronic nonspherocytic hemolytic anemia

- a. Occurs mainly in people of northern European origin
- b. Hematologic picture
  - (1) Chronic nonspherocytic anemia
  - (2) Reticulocytosis
  - (3) Shortened red cell survival
  - (4) Slight jaundice
  - (5) Mild splenomegaly.

Treatment

- 1. Avoidance of agents that are deleterious in G6PD deficiency
- 2. Indication for transfusion:
  a. Hemoglobin (Hb) level below 7 g/dL
  b. Persistent hemoglobinuria and Hb below 9 g/dL
- 3. Chronic nonspherocytic hemolytic anemia (NSHA):
  a. In patients with severe chronic anemia: transfuse red blood cells to maintain Hb level 8–10 g/dL and iron chelation, when needed
  b. Indications for splenectomy
    (1) Hypersplenism
    (2) Severe chronic anemia
    (3) Splenomegaly causing physical impediment

EXTRACORPUSCULAR HEMOLYTIC ANEMIAS

- Immune Hemolytic Anemia

  isoimmune or autoimmune.

  Isoimmune hemolytic anemia results from a mismatched blood transfusion or from hemolytic disease in the newborn.

  In autoimmune hemolytic anemia (AIHA), shortened red cell survival is caused by the action of immunoglobulins, with or without the participation of complement on the red cell membrane. The red cell autoantibodies may be of the warm type, the cold type, or the cold–warm Donath–Landsteiner type.

Warm Autoimmune Hemolytic Anemia

- Antibodies of the IgG class are most commonly responsible for AIHA in children.
- The antigen to which the IgG antibody is directed is one of the Rh erythrocyte antigens in more than 70% of cases. This antibody usually has its maximal activity at 37°C, and the resultant hemolysis is called warm antibody-induced hemolytic anemia.
- Rarely, warm reacting IgM antibodies may be responsible for hemolytic anemia.

Clinical Features

- 1. Severe, life-threatening condition
- 2. Sudden onset of pallor, jaundice, dark urine
- 3. Splenomegaly
- 4. Laboratory findings

  a. Hemoglobin level: very low

  b. Reticulocytosis: common

  c. Smear: prominent spherocytes, polychromasia, macrocytes,

  f. Direct Coombs' test: positive

  g. Hyperbilirubinemia

  h. Haptoglobin level: markedly decreased

  i. Hemoglobinuria, increased urinary urobilinogen

Management

- 1. Hemoglobin level (q4h)
- 2. Reticulocyte count (daily)
- 3. Splenic size (daily)
- 4. Hemoglobinuria (daily)
- 5. Haptoglobin level (weekly)
- 6. Coombs’ test (weekly).

Treatment

Blood Transfusion

- 1. If a specific antibody is identified, a compatible donor may be selected. The antibody usually behaves as a panagglutinin, and no totally compatible blood can be found.
- 2. Washed packed red cells should be used from donors whose erythrocytes show the least agglutination in the patient's serum.
- 3. The volume of transfused blood should only be of sufficient quantity to relieve any cardiopulmonary embarrassment from the anemia.

Corticosteroid Therapy

- 1. Hydrocortisone 8–40 mg/kg/day IV in divided doses (q8h) or prednisone2–10 mg/kg/day PO is administered.
- 2. High-dose corticosteroid therapy should be maintained for several days.
- Thereafter, corticosteroid therapy in the form of prednisone should be slowly tapered off over a 3- to 4-week period.
- a. The dose of prednisone should be tailored to maintain the hemoglobin at a reasonable level; when the hemoglobin stabilizes, the corticosteroids should be discontinued.
- b. Lack of response for 21 days should be considered a steroid failure and other modalities should be considered.

Intravenous Gammaglobulin

- Intravenous gammaglobulin (IVGG) in a dose of 5 g/kg, a much larger dose than used in idiopathic thrombocytopenic purpura or autoimmune neutropenia, may be effective.

Splenectomy

- 1. Splenectomy may be beneficial in some patients.
- 2. Splenectomy is indicated if the hemolytic process continues to be brisk despite high-dose corticosteroid therapy and IVGG for 3–4 weeks and the necessity of frequent packed red cell transfusions to maintain a reasonable hemoglobin level.
- 3. The results of splenectomy are unpredictable, but it is usually beneficial

Cytotoxic Agents

- 1. Antimetabolites: azathioprine, 6-mercaptopurine, and thioguanine
- 2. Alkylating agents: chlorambucil and cyclophosphamide
- 3. Mitotic inhibitors: vincristine and vinblastine.
- These agents have been used with variable success, but their use has not been completely evaluated.
- This type of therapy should be used only in patients refractory to steroids and splenectomy

Plasmapheresis

- Plasmapheresis has been successful in slowing the rate of hemolysis in patients with severe IgG-induced immune hemolytic anemia. Plasmapheresis has been more effective in IgM-induced hemolytic anemia.

Immunosuppressive Therapy

- Cyclosporine A, an immunosuppressive agent that has been used extensively in the treatment of rejection in organ transplantation and more recently in autoimmune diseases and aplastic anemia, may have a role in the treatment of immune-mediated hemolysis.
- The potential role of monoclonal antibodies (anti-Fc antibodies) in the treatment of immune-mediated hemolysis has yet to be fully evaluated.

Hormonal Therapy

- There has been recent success with danazol (synthetic androgen), which has a masculinizing effect. Danazol's early effect appears to be due to decreased expression of macrophage Fc-receptor activity and danazol may become an alternative to corticosteroid therapy in some patients with IgG-induced immune hemolytic anemia.
- The effect of these agents in IgM-induced hemolysis is untested.

Cold Autoimmune Hemolytic Anemia

- Most IgM autoantibodies that cause immune hemolytic anemia in humans are cold agglutinin.
- The destruction of red blood cells is usually triggered by cold exposure.
- Cold hemagglutinin disease usually occurs during *Mycoplasma pneumoniae* infection. It may also occur with other infections, such as infectious mononucleosis,cytomegalovirus, and mumps. Cold hemagglutinin disease or IgM-induced hemolysis
- is usually due to reaction with antigens of the I/i system.

Clinical Features

- This disease may be idiopathic but is more frequently seen in conjunction with infections such as *M. pneumoniae (atypical pneumonia) and less commonly with lymphoproliferative* disorders. The hematologic features in cold autoimmune hemolytic anemia are similar to those in warm autoimmune hemolytic anemia.

Treatment

- Treatment consists of control of the underlying disorder.
- Transfusions may be necessary;again, identification of compatible blood may prove difficult.
- Warming theblood to 37°C during administration by means of a heating coil or water bath is indicated.

Treatment

- If the anemia is severe, a trial of cytotoxic drug therapy is appropriate. Alkylating agents such as cyclophosphamide and chlorambucil may be capable of lowering the titer of cold agglutinins and, less commonly, reducing the degree of hemolysis.
- Treatment with corticosteroids or splenectomy is generally not effective.
- Plasmapheresis is a valuable approach to reducing the level of cold agglutinins.

THANK YOU