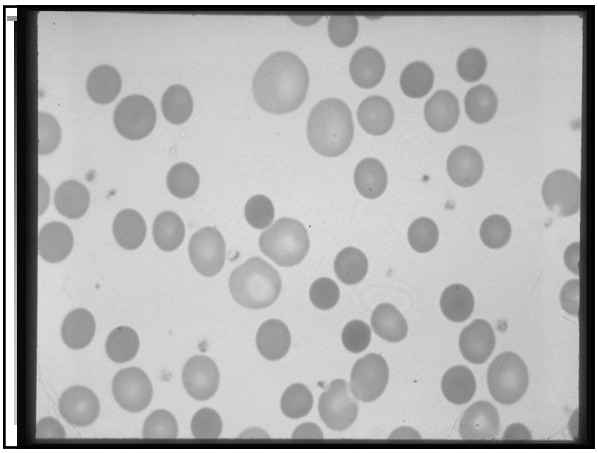
HEMOLYTIC ANEMIAS



HEMOLYTIC ANEMIA

- Anemia of increased destruction
  - Normochromic, normochromic anemia
  - Shortened RBC survival
  - Reticulocytosis - Response to increased RBC destruction
  - Increased indirect bilirubin
  - Increased LDH

HEMOLYTIC ANEMIA
Causes

- INTRACORPUSCULAR HEMOLYSIS
  - Membrane Abnormalities
  - Metabolic Abnormalities
  - Hemoglobinopathies
- EXTRACORPUSCULAR HEMOLYSIS
  - Nonimmune
  - Immune

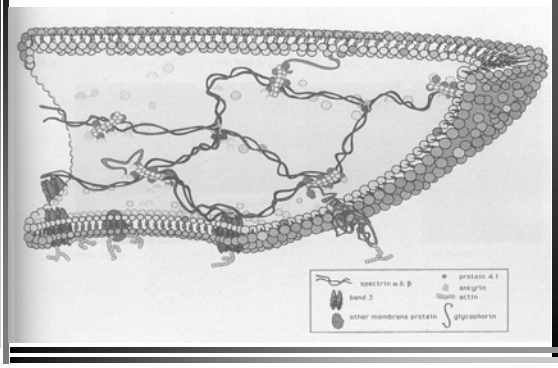
HEMOLYTIC ANEMIA
Testing

- Absent haptoglobin
- Hemoglobinuria
- Hemoglobinemia

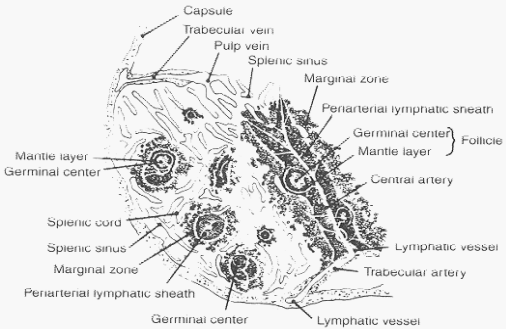
HEMOLYTIC ANEMIA
Membrane Defects

- Microskeletal defects
  - Hereditary spherocytosis
- Membrane permeability defects
  - Hereditary stomatocytosis
- Increased sensitivity to complement
  - Paroxysmal nocturnal hemoglobinuria

RED CELL CYTOSKELETON



SPLENIC ARCHITECTURE

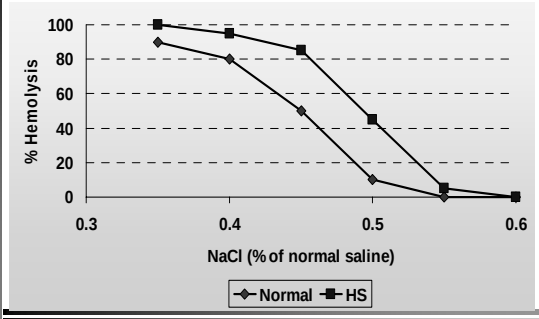


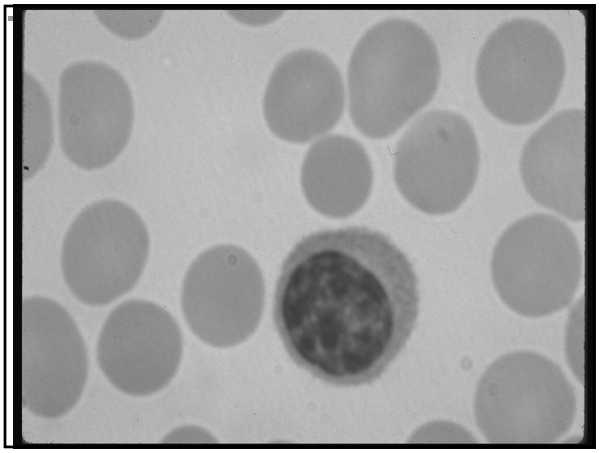
HEREDITARY SPHEROCYTOSIS

- Defective or absent spectrin molecule
- Leads to loss of RBC membrane, leading to spherocytosis
- Decreased deformability of cell
- Increased osmotic fragility
- Extravascular hemolysis in spleen

HEREDITARY SPHEROCYTOSIS

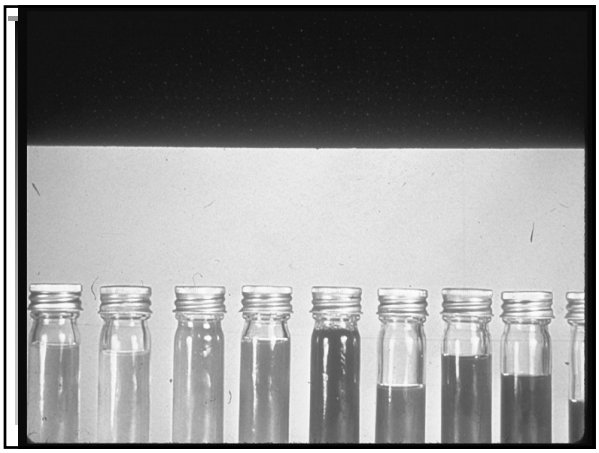
Osmotic Fragility





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)



HEMOLYTIC ANEMIA

Membrane abnormalities - Enzymopathies

- Deficiencies in Hexose Monophosphate Shunt
  - Glucose 6-Phosphate Dehydrogenase Deficiency
- Deficiencies in the EM Pathway
  - Pyruvate Kinase Deficiency

GPI BRIDGE

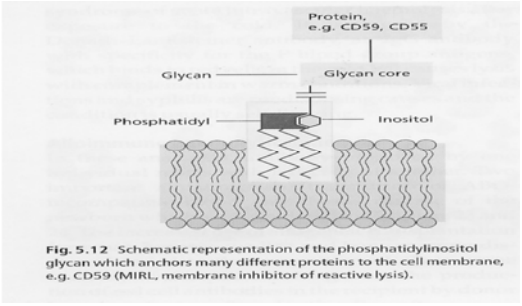


Fig. 5.12 Schematic representation of the phosphatidylinositol glycan which anchors many different proteins to the cell membrane, e.g. CD59 (MIRL, membrane inhibitor of reactive lysis).

G6PD DEFICIENCY – Function of G6PD

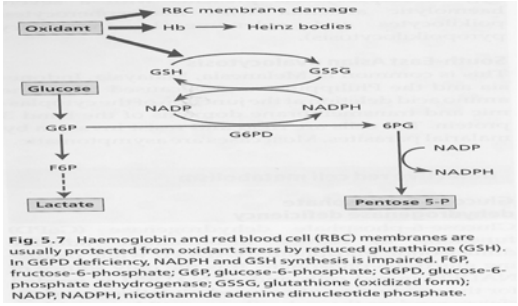


Fig. 5.7 Haemoglobin and red blood cell (RBC) membranes are usually protected from oxidant stress by reduced glutathione (GSH). In G6PD deficiency, NADPH and GSH synthesis is impaired. F6P, fructose-6-phosphate; G6P, glucose-6-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GSSG, glutathione (oxidized form); NADP, NADPH, nicotinamide adenine dinucleotide phosphate.

Paroxysmal Nocturnal Hemoglobinuria

GPI Proteins

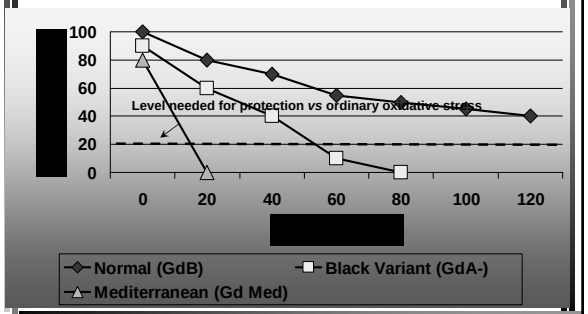
- GPI links a series of proteins to outer leaf of cell membrane via phosphatidyl inositol bridge, with membrane anchor via diacylglycerol bridge
- PIG-A gene, on X-chromosome, codes for synthesis of this bridge; multiple defects known to cause lack of this bridge
- Absence of decay accelerating factor leads to failure to inactivate complement & thereby to increased cell lysis

Glucose 6-Phosphate Dehydrogenase

Functions

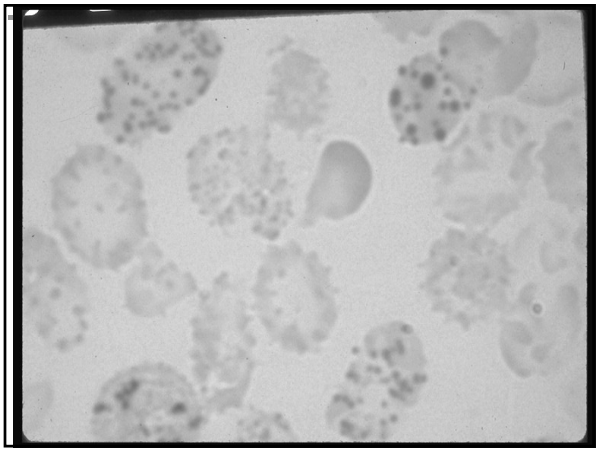
- Regenerates NADPH, allowing regeneration of glutathione
- Protects against oxidative stress
- Lack of G6PD leads to hemolysis during oxidative stress
  - Infection
  - Medications
  - Fava beans
- Oxidative stress leads to Heinz body formation, ➔ extravascular hemolysis

Glucose 6-Phosphate Dehydrogenase
Different Isozymes



EXTRACORPUSCULAR HEMOLYSIS
Nonimmune

- Mechanical
- Infectious
- Chemical
- Thermal
- Osmotic



Microangiopathic Hemolytic Anemia
Causes

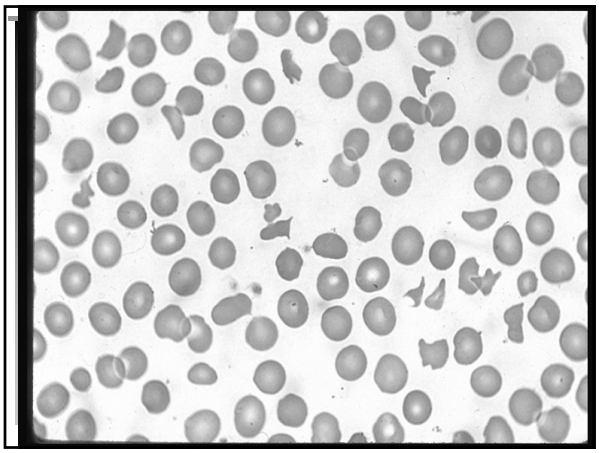
- Vascular abnormalities
  - Thrombotic thrombocytopenic purpura
  - Renal lesions
    - Malignant hypertension
    - Glomerulonephritis
    - Preeclampsia
    - Transplant rejection
  - Vasculitis
    - Polyarteritis nodosa
    - Rocky mountain spotted fever
    - Wegener's granulomatosis
    - Scleroderma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

HEMOLYTIC ANEMIA
Causes

- INTRACORPUSCULAR HEMOLYSIS
  - Membrane Abnormalities
  - Metabolic Abnormalities
  - Hemoglobinopathies
- EXTRACORPUSCULAR HEMOLYSIS
  - Nonimmune
  - Immune

Microangiopathic Hemolytic Anemia
Causes - #2

  - Vascular abnormalities
    - AV Fistula
    - Cavernous hemangioma
- Intravascular coagulation predominant
  - Abruptio placentae
  - Disseminated intravascular coagulation



IMMUNE HEMOLYTIC ANEMIA
Coombs Test - Direct

- Looks for immunoglobulin &/or complement of surface of red blood cell (normally neither found on RBC surface)
- Coombs reagent - combination of anti-human immunoglobulin & anti-human complement
- Mixed with patient's red cells; if immunoglobulin or complement are on surface, Coombs reagent will link cells together and cause agglutination of RBCs

IMMUNE HEMOLYTIC ANEMIA
General Principles

- All require antigen-antibody reactions
- Types of reactions dependent on:
  - Class of Antibody
  - Number & Spacing of antigenic sites on cell
  - Availability of complement
  - Environmental Temperature
  - Functional status of reticuloendothelial system
- Manifestations
  - Intravascular hemolysis
  - Extravascular hemolysis

IMMUNE HEMOLYTIC ANEMIA
Coombs Test - Indirect

- Looks for anti-red blood cell antibodies in the patient's serum, using a panel of red cells with known surface antigens
- Combine patient's serum with cells from a panel of RBC's with known antigens
- Add Coombs' reagent to this mixture
- If anti-RBC antigens are in serum, agglutination occurs

IMMUNE HEMOLYTIC ANEMIA
General Principles - 2

- Antibodies combine with RBC, & either
  1. Activate complement cascade, &/or
  2. Opsonize RBC for immune system
- If 1, if all of complement cascade is fixed to red cell, intravascular cell lysis occurs
- If 2, &/or if complement is only partially fixed, macrophages recognize Fc receptor of Ig &/or C3b of complement & phagocytize RBC, causing extravascular RBC destruction

HEMOLYTIC ANEMIA - IMMUNE

- Drug-Related Hemolysis
- Alloimmune Hemolysis
  - Hemolytic Transfusion Reaction
  - Hemolytic Disease of the Newborn
- Autoimmune Hemolysis
  - Warm autoimmune hemolysis
  - Cold autoimmune hemolysis

IMMUNE HEMOLYSIS
Drug-Related

- Immune Complex Mechanism
  - Quinidine, Quinine, Isoniazid
- "Haptenic" Immune Mechanism
  - Penicillins, Cephalosporins
- True Autoimmune Mechanism
  - Methyldopa, L-DOPA, Procaineamide, Ibuprofen

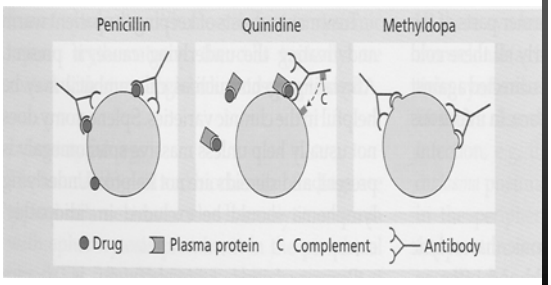
DRUG-INDUCED HEMOLYSIS
True Autoantibody Formation

- Certain drugs appear to cause antibodies that react with antigens normally found on RBC surface, and do so even in the absence of the drug

DRUG-INDUCED HEMOLYSIS
Immune Complex Mechanism

- Drug & antibody bind in the plasma
- Immune complexes either
  - Activate complement in the plasma, or
  - Sit on red blood cell
- Antigen-antibody complex recognized by RE system
- Red cells lysed as "innocent bystander" of destruction of immune complex
- REQUIRES DRUG IN SYSTEM

DRUG-INDUCED HEMOLYSIS - Mechanisms



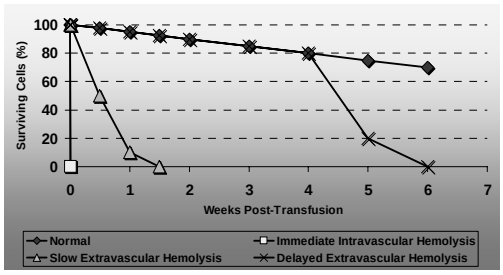
DRUG-INDUCED HEMOLYSIS
Haptenic Mechanism

- Drug binds to & reacts with red cell surface proteins
- Antibodies recognize altered protein, ± drug, as foreign
- Antibodies bind to altered protein & initiate process leading to hemolysis

ALLOIMUNE HEMOLYSIS
Hemolytic Transfusion Reaction

- Caused by recognition of foreign antigens on transfused blood cells
- Several types
  - Immediate Intravascular Hemolysis (Minutes) - Due to preformed antibodies; life-threatening
  - Slow extravascular hemolysis (Days) - Usually due to repeat exposure to a foreign antigen to which there was a previous exposure; usually only mild symptoms
  - Delayed sensitization - (Weeks) - Usually due to 1st exposure to foreign antigen; asymptomatic

INCOMPATIBLE RBC TRANSFUSION
Rate of Hemolysis



ALLOIMMUNE HEMOLYSIS
Hemolytic Disease of the Newborn - #2

- Can cause severe anemia in fetus, with erythroblastosis and heart failure
- Hyperbilirubinemia can lead to severe brain damage (kernicterus) if not promptly treated
- HDN due to Rh incompatibility can be almost totally prevented by administration of anti-Rh D to Rh negative mothers after each pregnancy

ALLOIMMUNE HEMOLYSIS
Testing Pre-transfusion

- ABO & Rh Type of both donor & recipient
- Antibody Screen of Donor & Recipient, including indirect Coombs
- Major cross-match by same procedure (recipient serum & donor red cells)

AUTOIMMUNE HEMOLYSIS

- Due to formation of autoantibodies that attack patient's own RBC's
- Type characterized by ability of autoantibodies to fix complement & site of RBC destruction
- Often associated with either lymphoproliferative disease or collagen vascular disease

ALLOIMMUNE HEMOLYSIS
Hemolytic Disease of the Newborn

- Due to incompatibility between mother negative for an antigen & fetus/father positive for that antigen. Rh incompatibility, ABO incompatibility most common causes
- Usually occurs with 2nd or later pregnancies
- Requires maternal IgG antibodies *vs.* RBC antigens in fetus

AUTOIMMUNE HEMOLYSIS
Warm Type

- Usually IgG antibodies
- Fix complement only to level of C3,if at all
- Immunoglobulin binding occurs at all temps
- Fc receptors/C3b recognized by macrophages; therefore,
- Hemolysis primarily extravascular
- 70% associated with other illnesses
- Responsive to steroids/splenectomy

AUTOIMMUNE HEMOLYSIS

Cold Type

- Most commonly IgM mediated
- Antibodies bind best at 30º or lower
- Fix entire complement cascade
- Leads to formation of membrane attack complex, which leads to RBC lysis in vasculature
- Typically only complement found on cells
- 90% associated with other illnesses
- Poorly responsive to steroids, splenectomy; responsive to plasmapheresis

HEMOLYTIC ANEMIA

Summary

- Myriad causes of increased RBC destruction
- Marrow function usually normal
- Often requires extra folic acid to maintain hematopoiesis
- Anything that turns off the bone marrow can result in acute, life-threatening anemia