Hemolytic Anemias - Extracorpuscular defects

What is destroying this RBC?

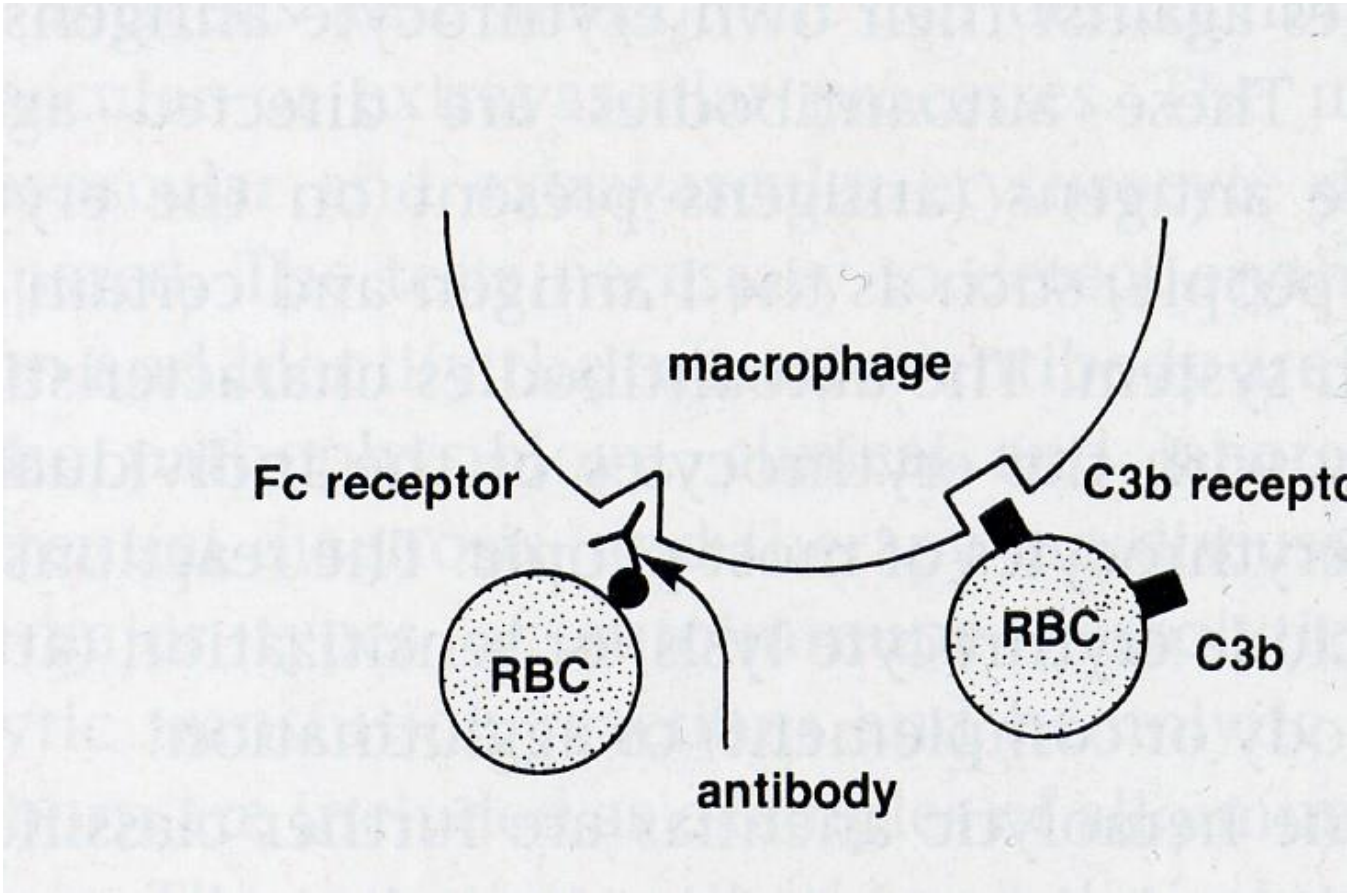
Extracorpuscular defects

- Immune hemolytic anemias
  - Theses anemias result from a shortened RBC survival mediated by the immune response, specifically humeral antibodies.
  - There are three broad categories:
    - Alloimmune in which the patient produces alloantibodies to foreign RBC antigens introduced through transfusion or pregnancy
      - Transfusion reaction
        - An immediate transfusion reaction is characterized by acute intravascular hemolysis, mostly associated with ABO IgM isoantibodies. The patient's antibodies destroy the donor's cells.

Extracorpuscular defects

- A delayed transfusion reaction occurs 2-14 days after transfusion and usually is the result of an anamnestic response in which IgG antibodies are made in an individual who has been previously sensitized. Extravascular hemolysis of IgG coated antibodies occurs in the spleen.
- Hemolytic disease of the newborn
  - RBCs of the fetus are destroyed by maternal IgG antibodies that cross the placenta.
  - The baby is often born jaundiced, anemic and with hepatosplenomegaly.

Extravascular hemolysis



Extracorpuscular defects

- Autoimmune hemolytic anemia – This represents an abnormality in which the immune system's ability for self-recognition is lost and antibodies are made to the RBC antigens (autoantibodies). They bind to the RBCs and initiate hemolysis.
  - Warm autoimmune hemolytic anemia In this type of immune hemolytic anemia the serologic reactivity of IgG antibody is optimal at 37^0 C.
    - Primary, idiopathic - severe, but self-limiting anemias that may last several weeks to years.
    - Secondary – associated with some underlying disease (lymphoproliferative, neoplastic, SLE, RA, viral or bacterial infection, chronic inflammatory disease)

Extracorpuscular defects

- In both the primary and secondary form of the disease, most hemolysis is extravascular and complement is not necessary for cell destruction, though it may be involved (Ag-Ab complexes may be pitted from the cell membrane in the spleen or the cell itself may be ingested by phagocytic cells).
- The anemia is moderate to severe, the RBCs are normochromic, normocytic with polychromasia (increased reticulocytes).
- Spherocytes, schistocytes, etc. may be seen and are indicative of the hemolytic process.

Extracorpuscular defects

- The direct Coombs test is positive. This tests for RBCs sensitized with IgG Ab or complement. IgM antibodies will agglutinate RBCs in saline, but IgG antibodies are not large enough to overcome the zeta potential of the RBCs. In the direct Coombs test, antihuman globulin (AHG), which contains antibodies to human antibodies and complement, is added to cells suspected of having IgG or complement bound to them. When AHG binds to the IgG or complement that is bound to RBCs, it bridges the distance between the RBCs which leads to agglutination and a positive test.
- Treatment is glucocorticoids, splenectomy, or other immunosuppressive drugs.

Zeta potential

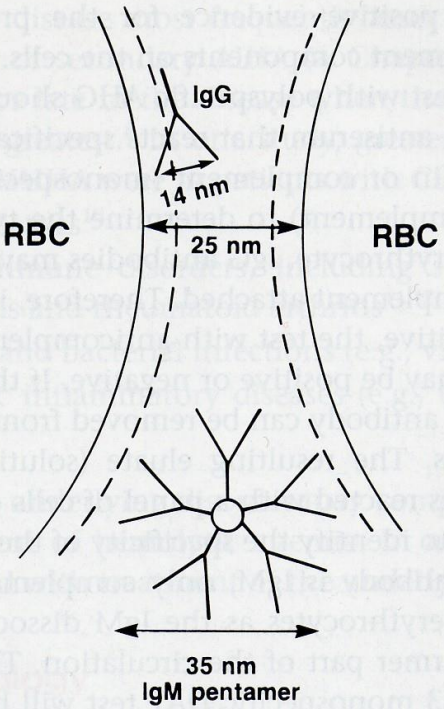
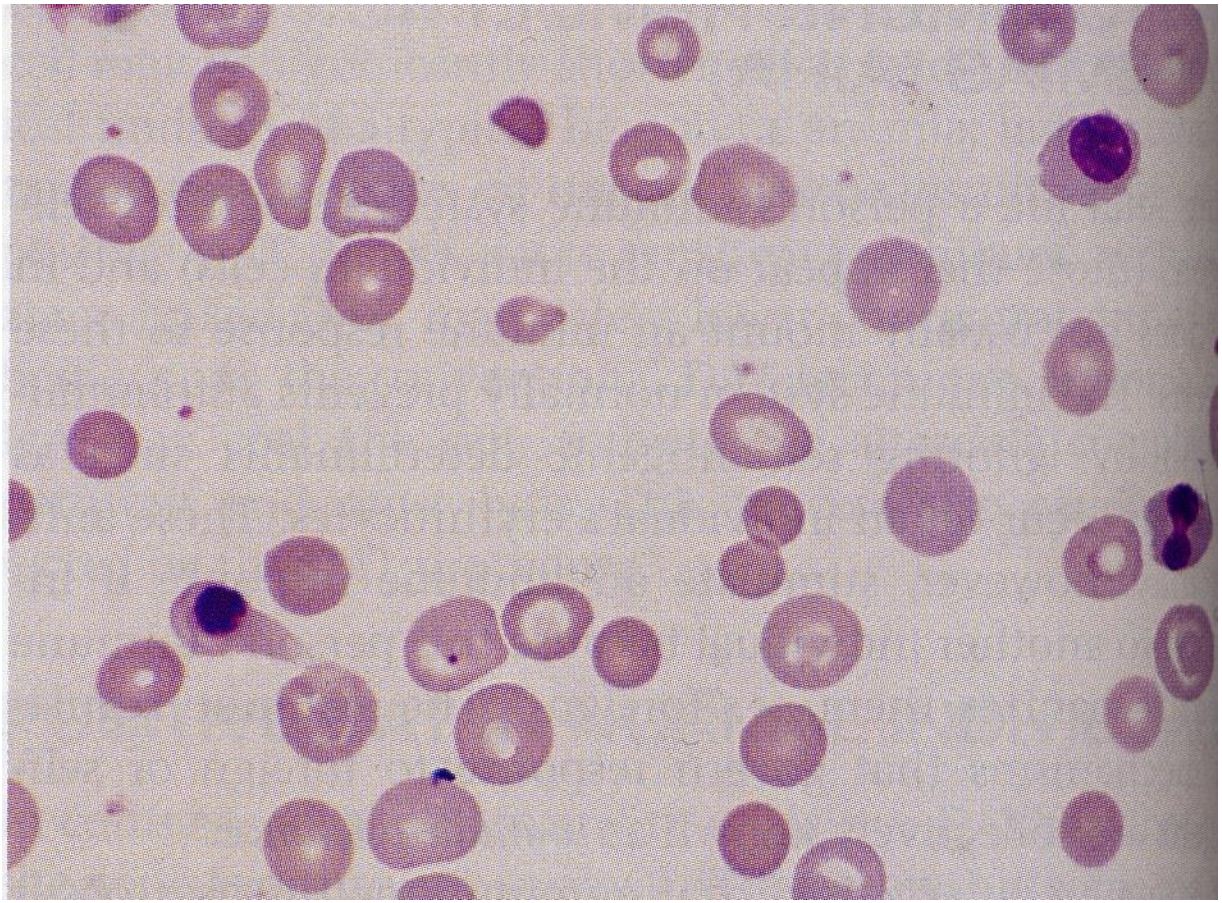


FIGURE 19-3 The zeta potential of erythrocytes keep the cells about 25 nm apart when suspended in saline. IgG antibodies have a span of about 14 nm, not enough to bridge the gap between cells and cause agglutination. IgM antibodies, however, are pentamers with a span of about 35 nm, a distance sufficient to bridge the space between cells and cause agglutination.

Warm autoimmune hemolytic anemia



Extracorpuscular defects

- Cold autoimmune hemolytic anemia – pathologic cold autoantibodies are usually IgM antibodies that fix complement and are optimally reactive below 37^0 C. It is normal to have benign cold autoantibodies, but their thermal amplitude and concentration are not high enough to cause problems. The pathologic forms can be divided into three types:
  - Cold agglutinin syndrome – This is idiopathic, chronic, usually in individuals older than 50, and usually due to an IgM monoclonal antibody.
  - Secondary, cold autoimmune hemolytic anemia – due to polyclonal IgM antibodies that develop with *Mycoplasma pneumonia* infections, infectious mononucleosis, or lymphoproliferative disease. Is usually transient.

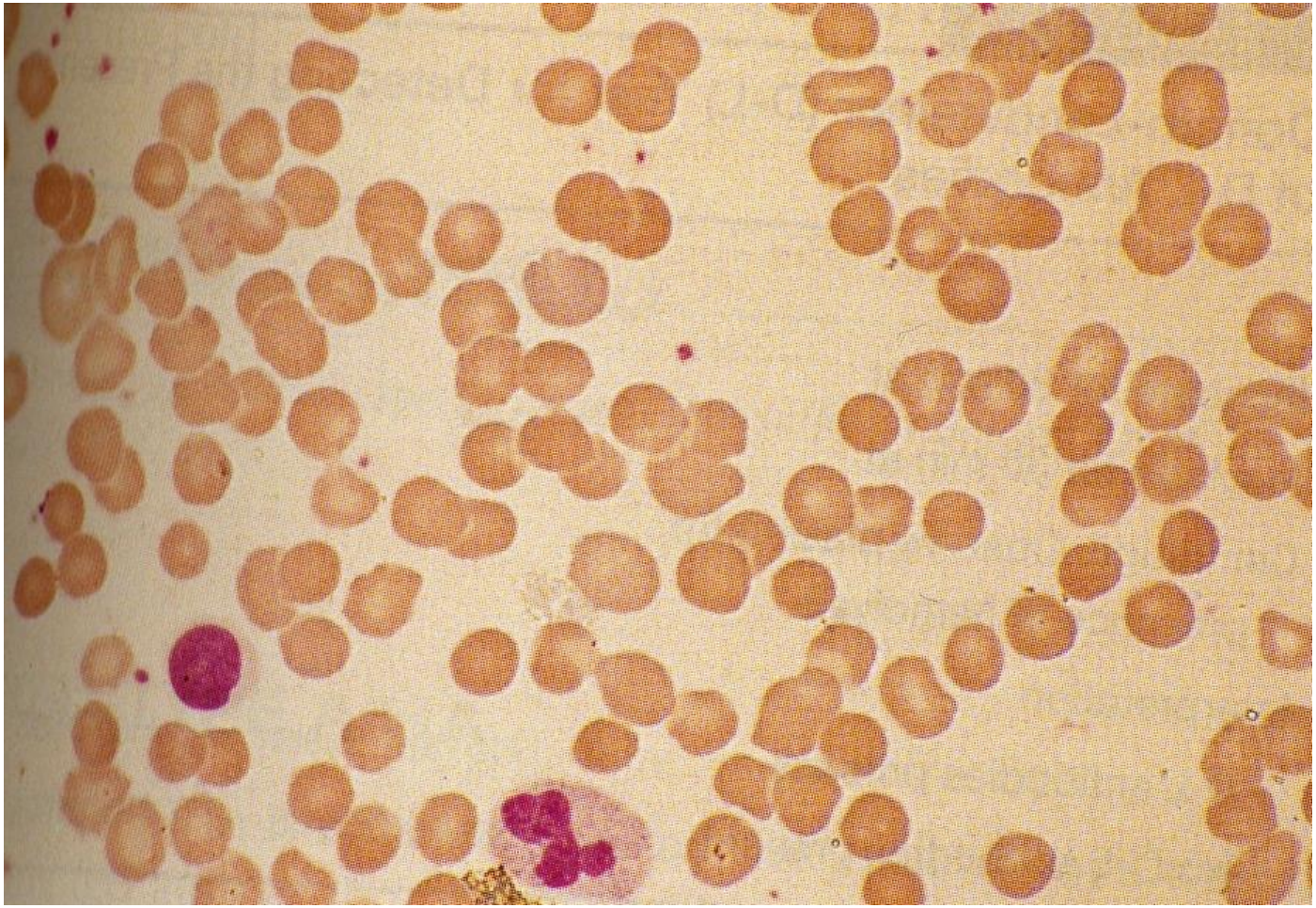
Extracorpuscular defects

- In both a and b the extent of the disease is related to the thermal amplitude of the antibody – if it reacts at 30-32^0 C, it can cause problems when the peripheral circulation cools to that temperature:
- IgM binds and fixes complement, upon warming the antibody dissociates, but complement remains bound leading to either intravascular or extravascular hemolysis.
- The patient may experience acrocyanosis of hands, feet, ears, and nose (with agglutination blood flow slows down, the skin turns white and then blue; upon warming, the skin turns red).
- Blood counts are difficult to perform unless the blood is warmed.
- The Coombs test with anti-complement antibody is positive.

Extracorpuscular defects

- The cold agglutinin test is positive at 0-20^0 C and usually up to 30^0 C. The titer is usually 1:1000 or greater.
- Paroxysmal cold hemoglobinuria – is found in association with viral disorders and syphilis and may be chronic.
- This is characterized by massive, intermittent, acute intravascular hemolysis and hemoglobinuria upon exposure to cold.
- It is caused by a biphasic IgG antibody that binds at low temperature and fixes complement.
- Upon warming, to body temperature, the intravascular hemolysis occurs and is accompanied by fever, shaking chills, and abdominal and back cramps.

Cold autoimmunne hemolytic anemia



Extracorpuscular defects

- Drug induced immune hemolytic anemia – many different drugs can cause this and 3-4 different mechanisms may be involved.
  - Immune complex mechanism
    - The drug binds to plasma proteins and antibodies are made against the drug.
    - The antibodies bind to the drug to form an immune complex which adsorbs nonspecifically to the patients RBCs, complement is fixed, and acute intravascular hemolysis occurs.

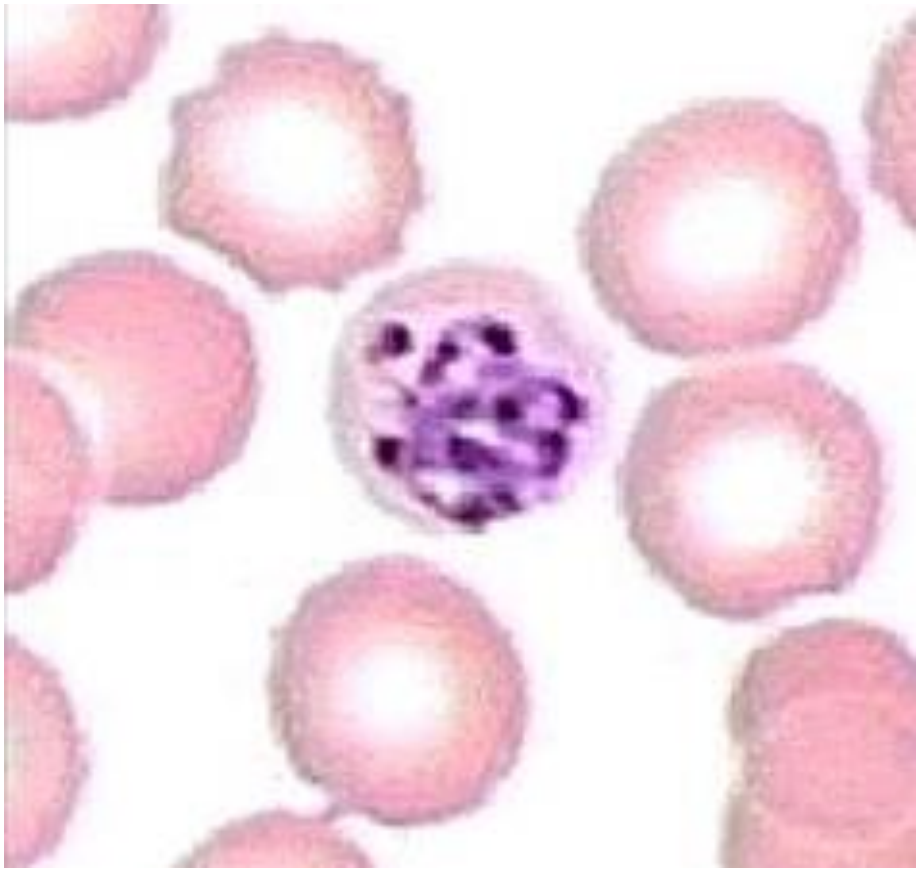
Extracorpuscular defects

- Drug adsorption (hapten) mechanism
  - The drug binds nonspecifically to proteins on the RBC membrane, antibodies are made (usually IgG), they bind to the drug and extravascular hemolysis occurs.
- Membrane modification mechanism
  - The drug modifies the RBC membrane so that normal plasma proteins bind nonimmunologically.
  - In rare instances a cross reacting antibody causes a hemolytic anemia.
- Methyldopa induced mechanism
  - The drug induces formation of autoantibodies causing extravascular destruction.
  - It may change autoproteins so that they are no longer recognized as self, or it may cause a direct loss of T suppressor cells.

Extracorpuscular defects

- Nonimmune hemolytic anemias
  - Caused by antagonists in blood or abnormalities in plasma lipids.
    - Chemicals and drugs
      - Include drugs that cause oxidative injury
      - Inhalation of arsine gas
      - Lead intoxication (in addition to interfering with heme synthesis, lead can cause membrane damage by interfering with energy production)
      - Injection of large volumes of water.
    - Animal venoms – bees, wasps, spiders, scorpions in susceptible individuals, rarely snakebites
    - Infectious agents – malarial parasites, Babesiosis, *Clostridium perfringens, Bartonella bacilliformis*

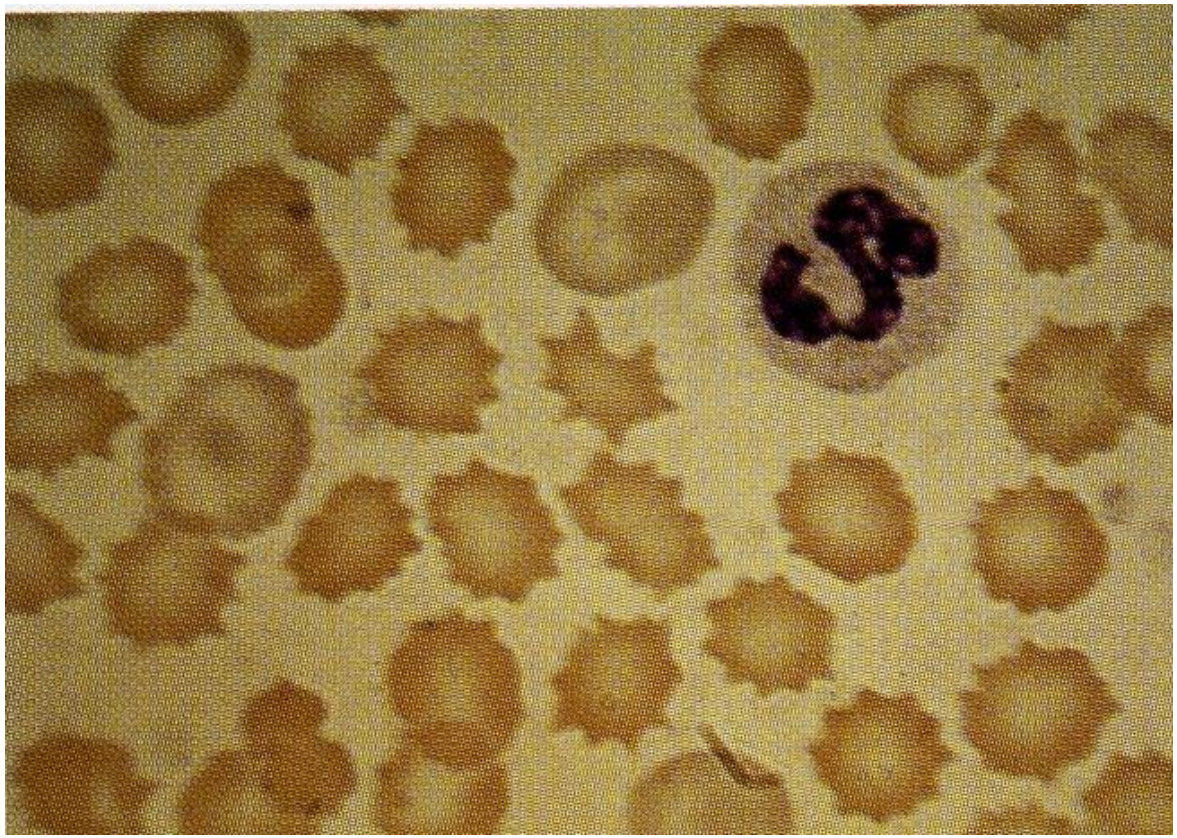
Plasmodium



Extracorpuscular defects

- Abnormal plasma lipid composition – note that these were also included in iintracorpuscular problems, because they lead to intrinsic problems with the RBC.
  - Spur cell anemia – associated with severe hepatocellular disease which leads to increased serum lipoproteins, increased membrane cholesterol, decreased deformability and decreased survival
  - Abetalippoproteinemia – leads to an increased cholesterol/phospholipid ratio, acanthocytes, and decreased survival.
- Caused by physical injury to RBCs
  - Microangiopathic hemolytic anemia
    - Caused by microcirculatory lesions that cause the RBCs to tear due to sheer stress
      - Disseminated cancer

Spur cell anemia

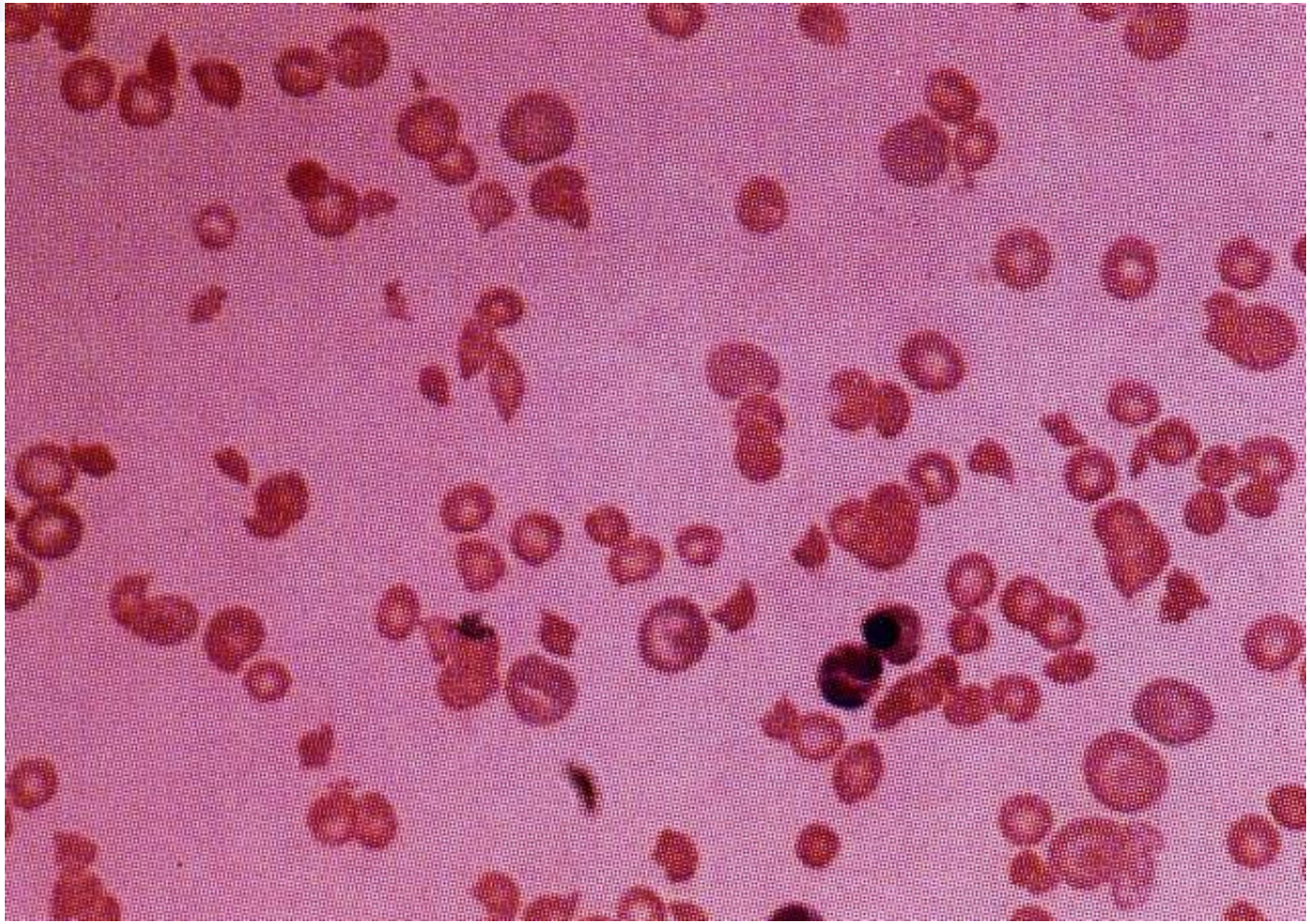


Extracorpuscular defects

- uremic syndrome
- Idiopathic thrombotic thrombocytopenic purpura – microthrombi are deposited in the microvasculature
- Malignant hypertension
- Disseminated intravascular coagulation.

- Macroangiopathic hemolytic anemia
  - Due to abnormalities in heart or large vessels causing RBC hemolysis
    - Prosthetic heart valves
- March hemoglobinemia
  - Transient hemolytic anemia occurring after strenuous exercise with contact with a hard surface (running, marching)
- Thermal injury

TTP



Thermal injury