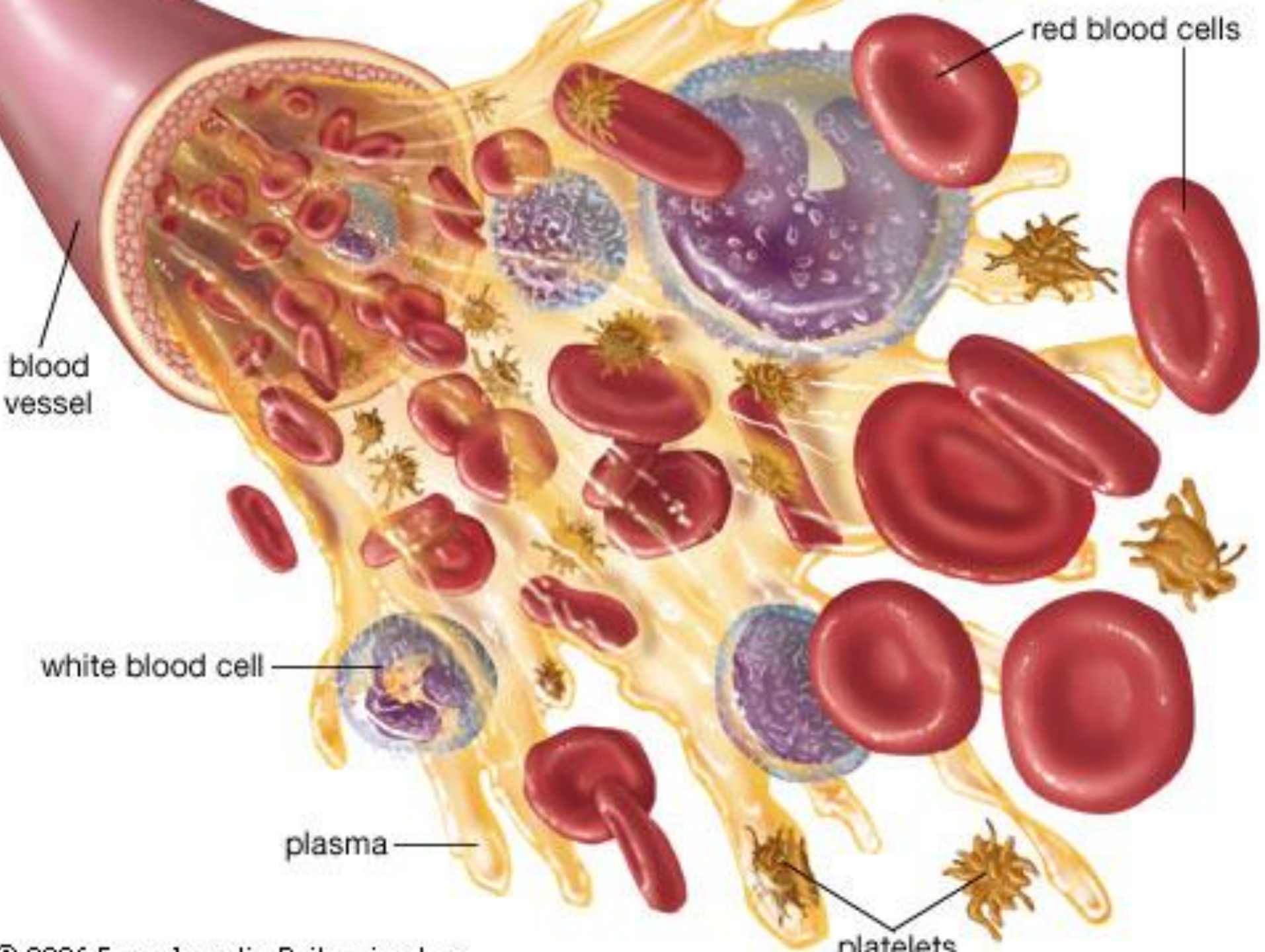
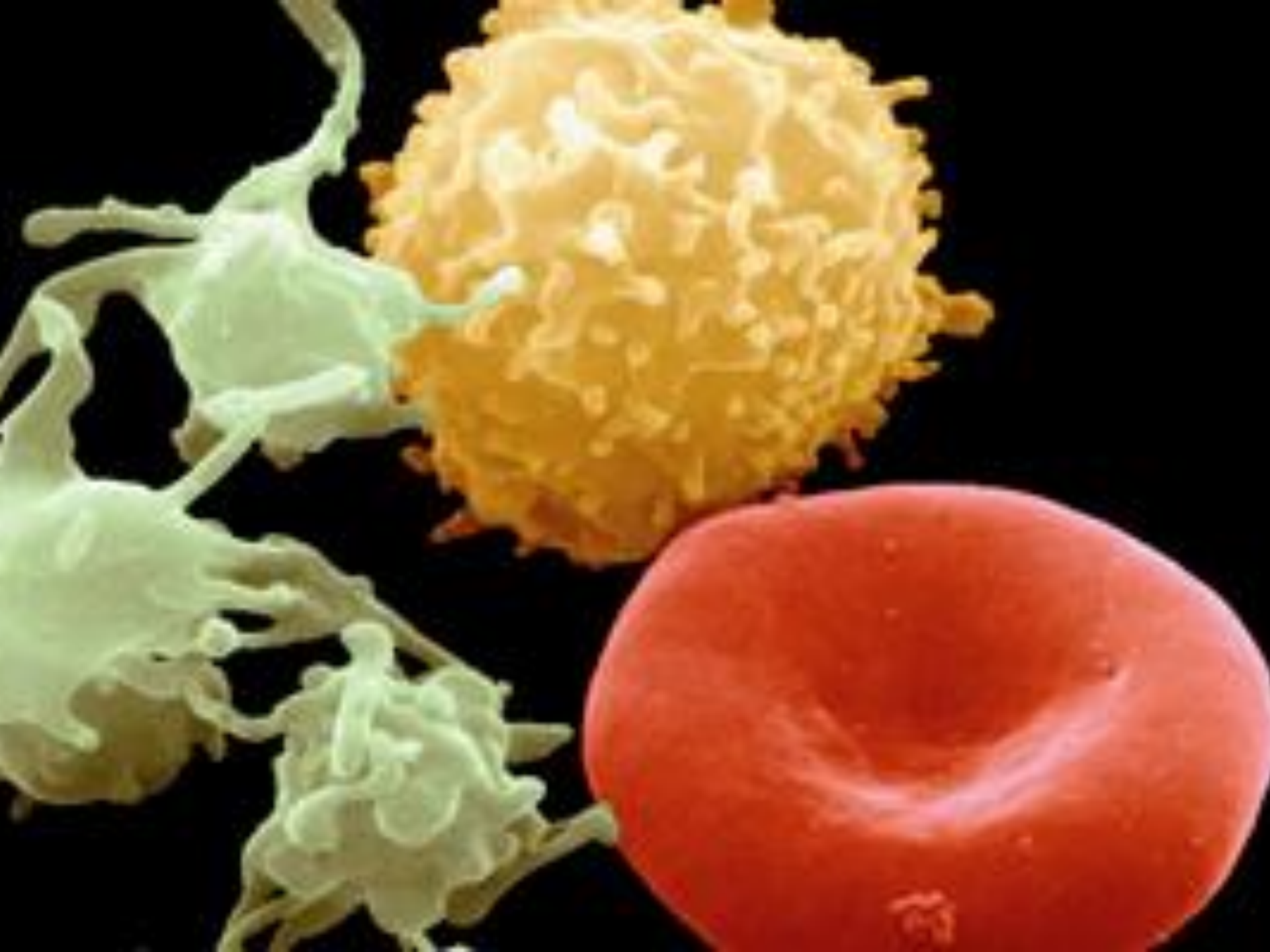


Sickle cell anemia -

7th November 2009

Anne Grete Bechensteen

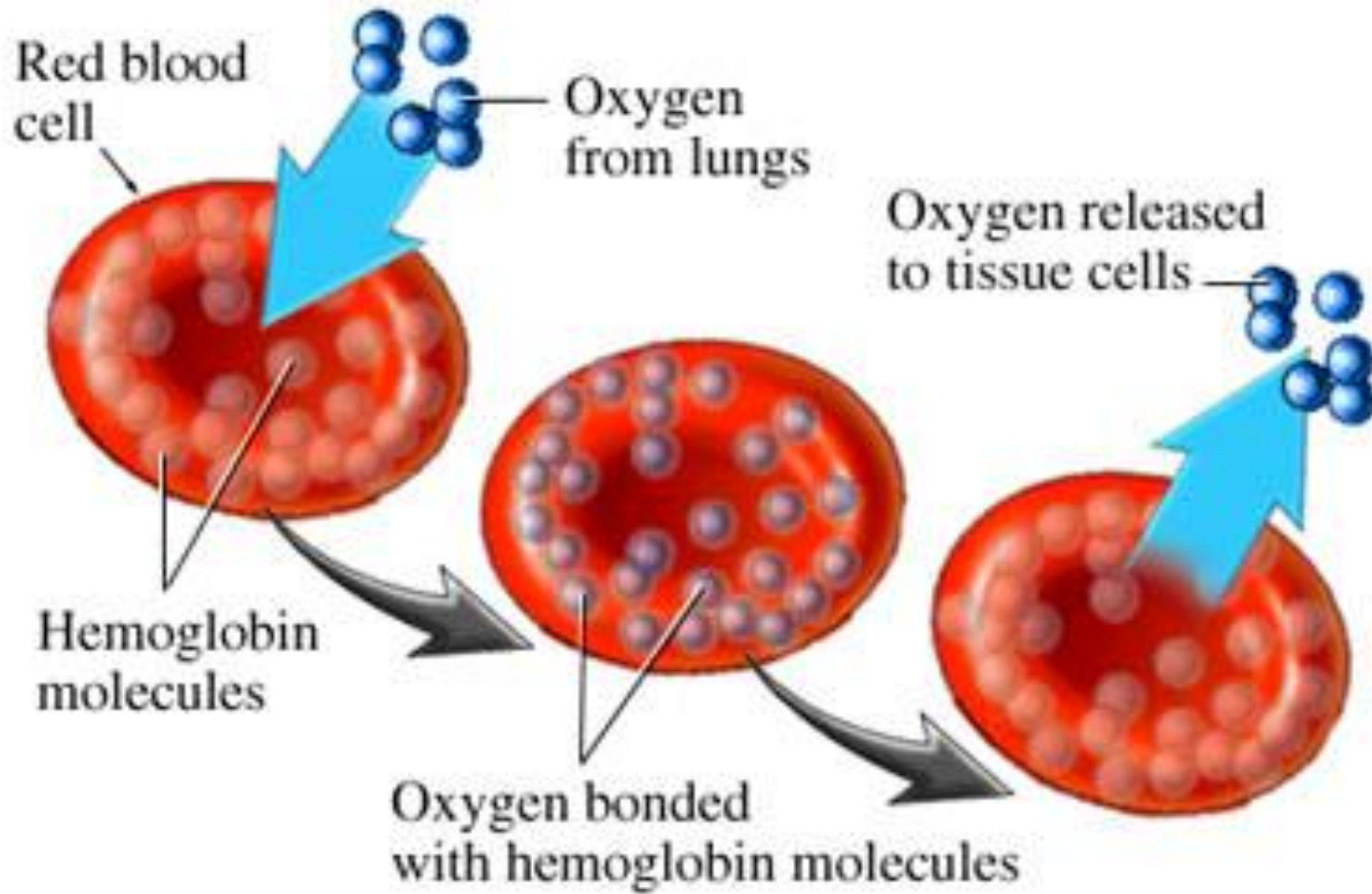




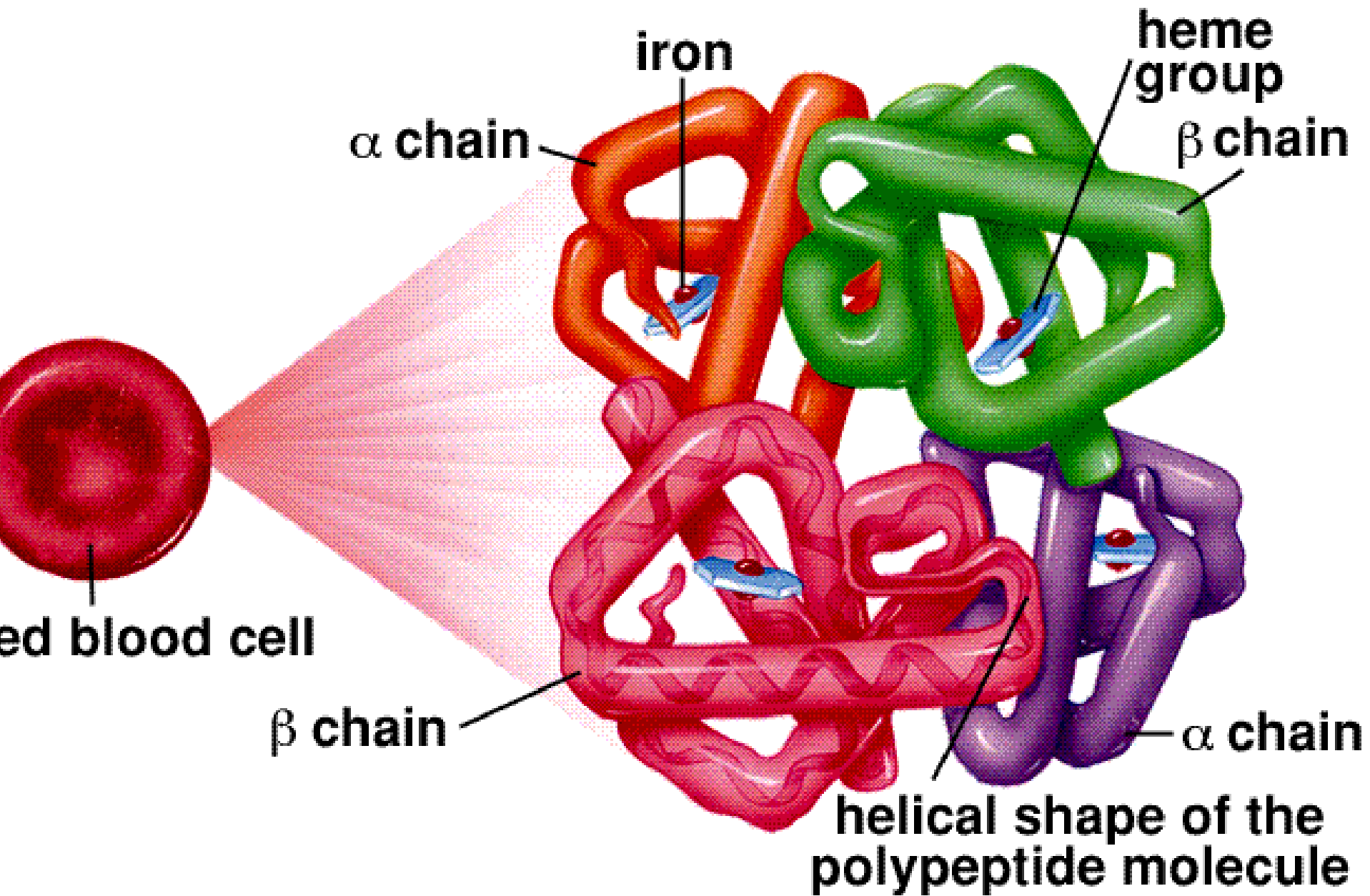


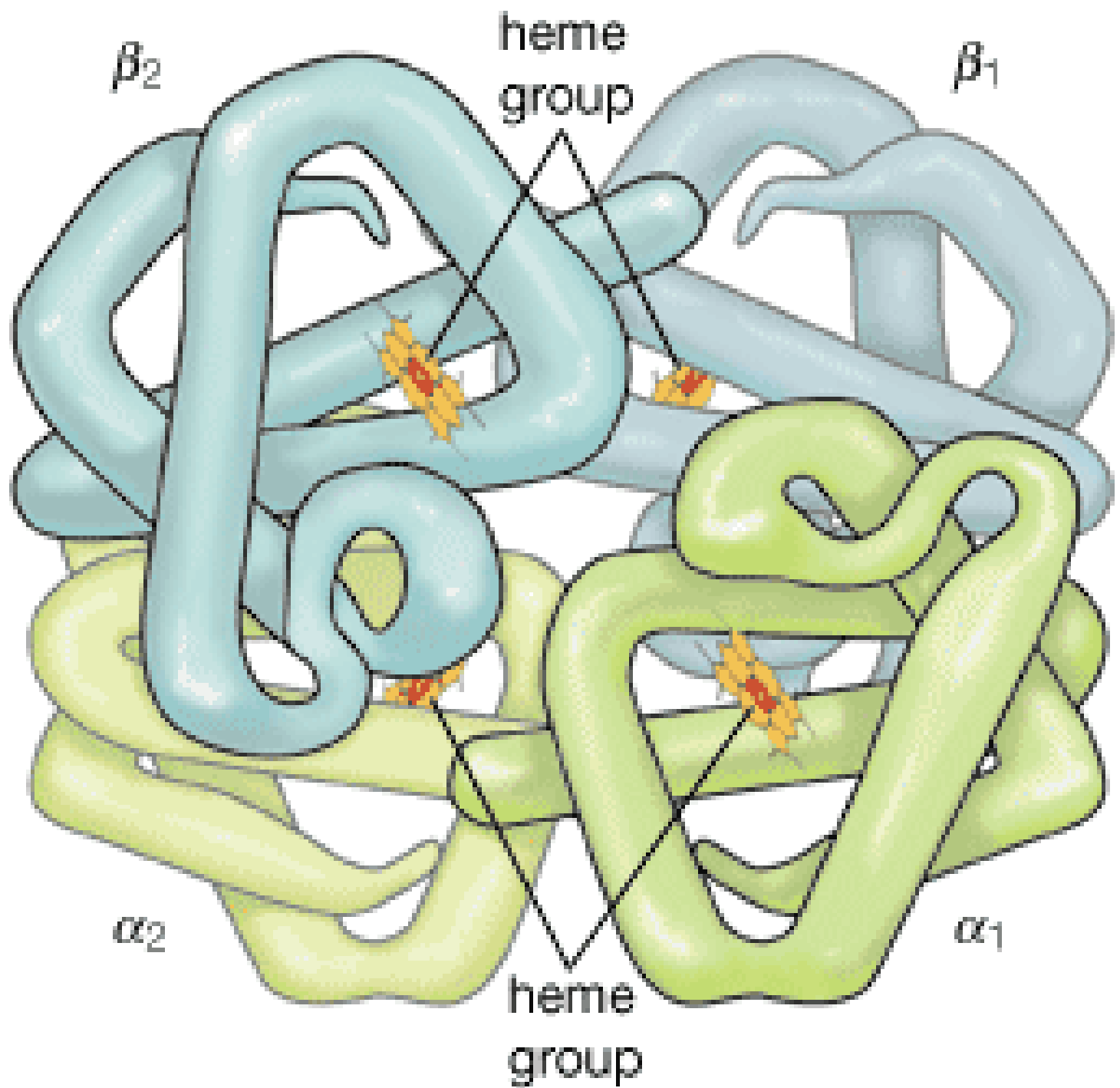


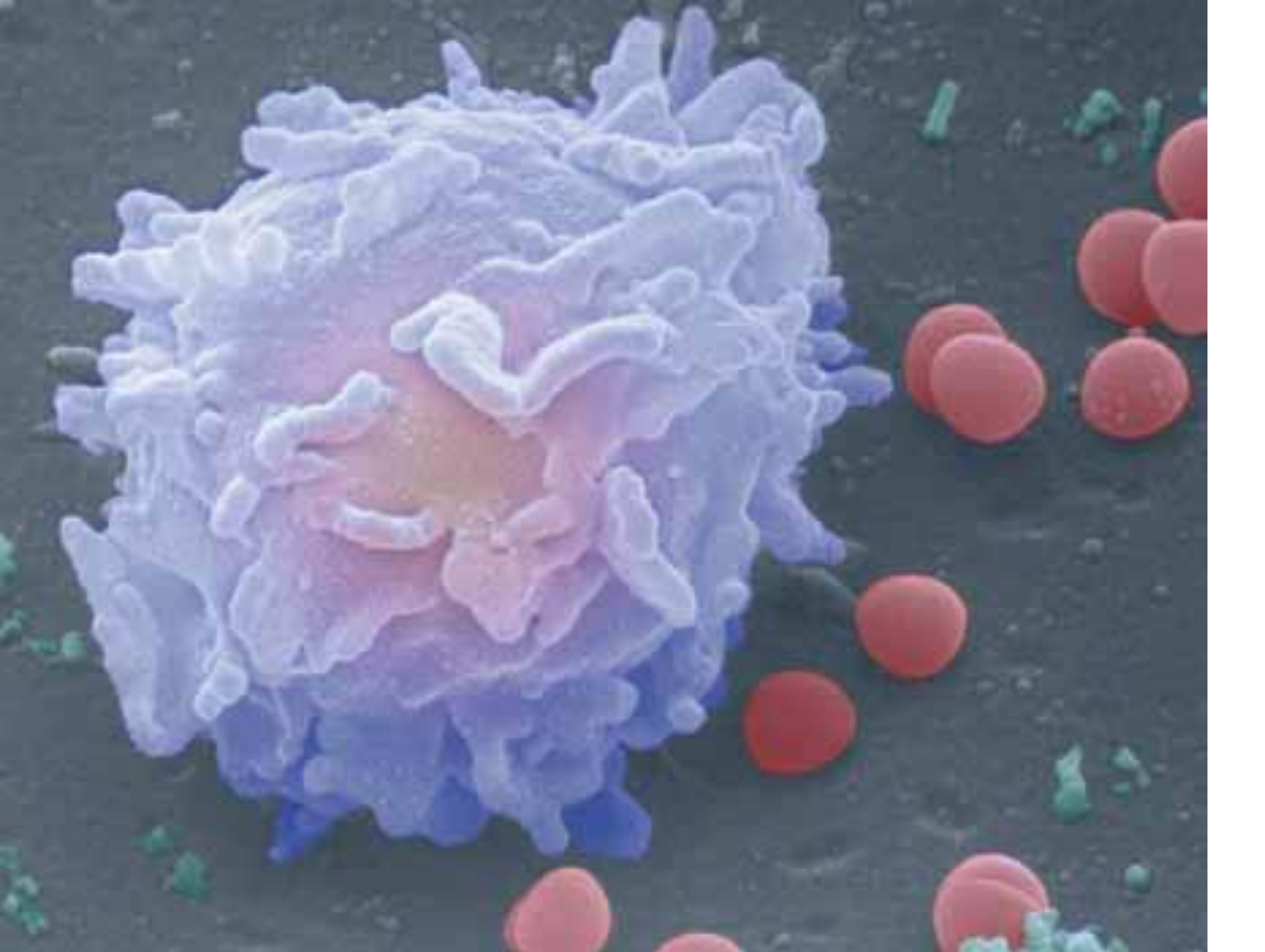
**Air with
oxygen is
breathed - it
goes into the
lungs and
oxygen goes
from the air
to the blood
where it binds
to the red
cells**



Hemoglobin Molecule







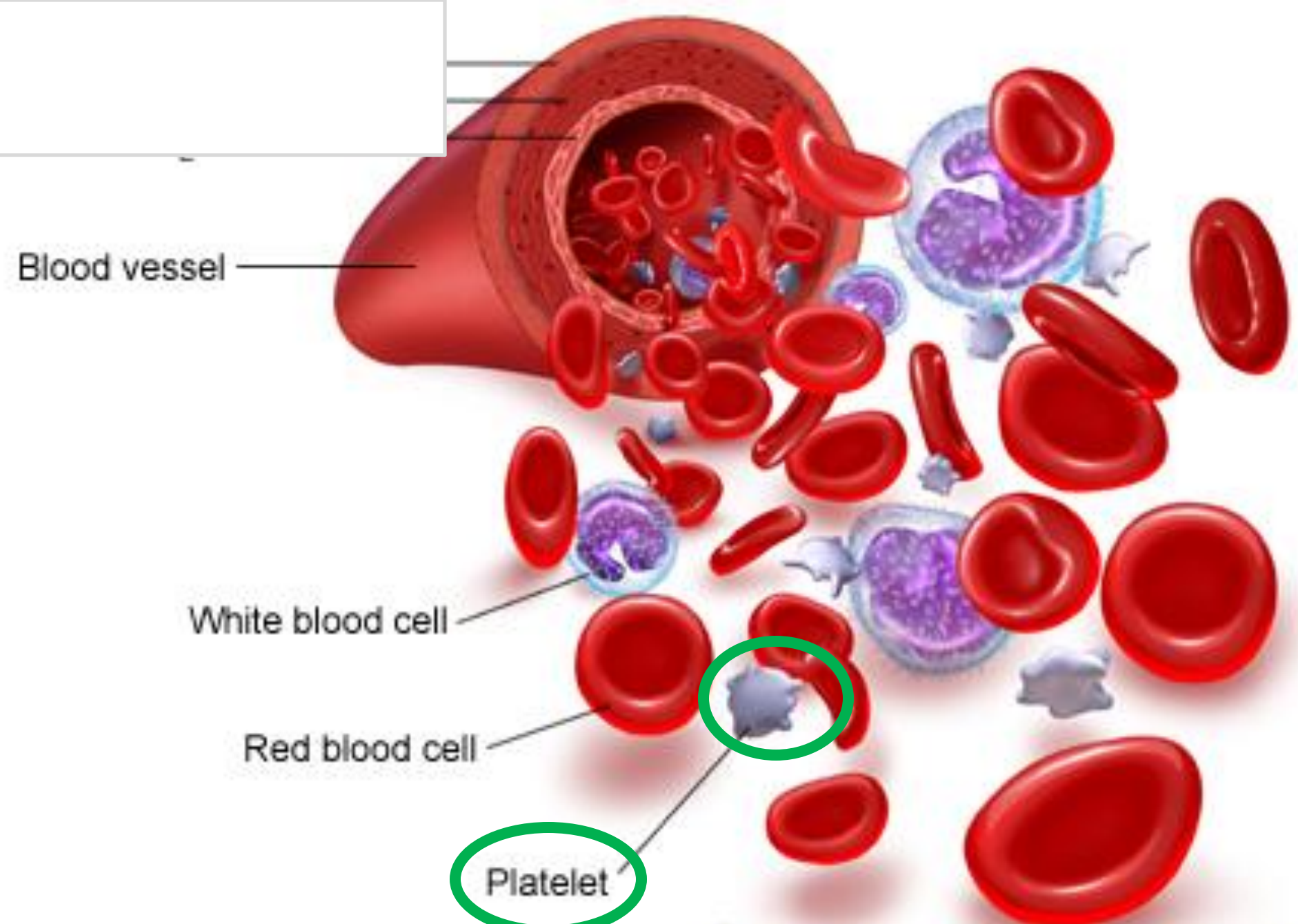
White blood
cells
fighting
intruders





Infections

- **Viral**
 - Cold
 - Influenza
 - Gastroenteritis
 - Chicken pox
- **Bacterial**
 - Pneumonia
 - Meningitis
- **Fungi - rare**

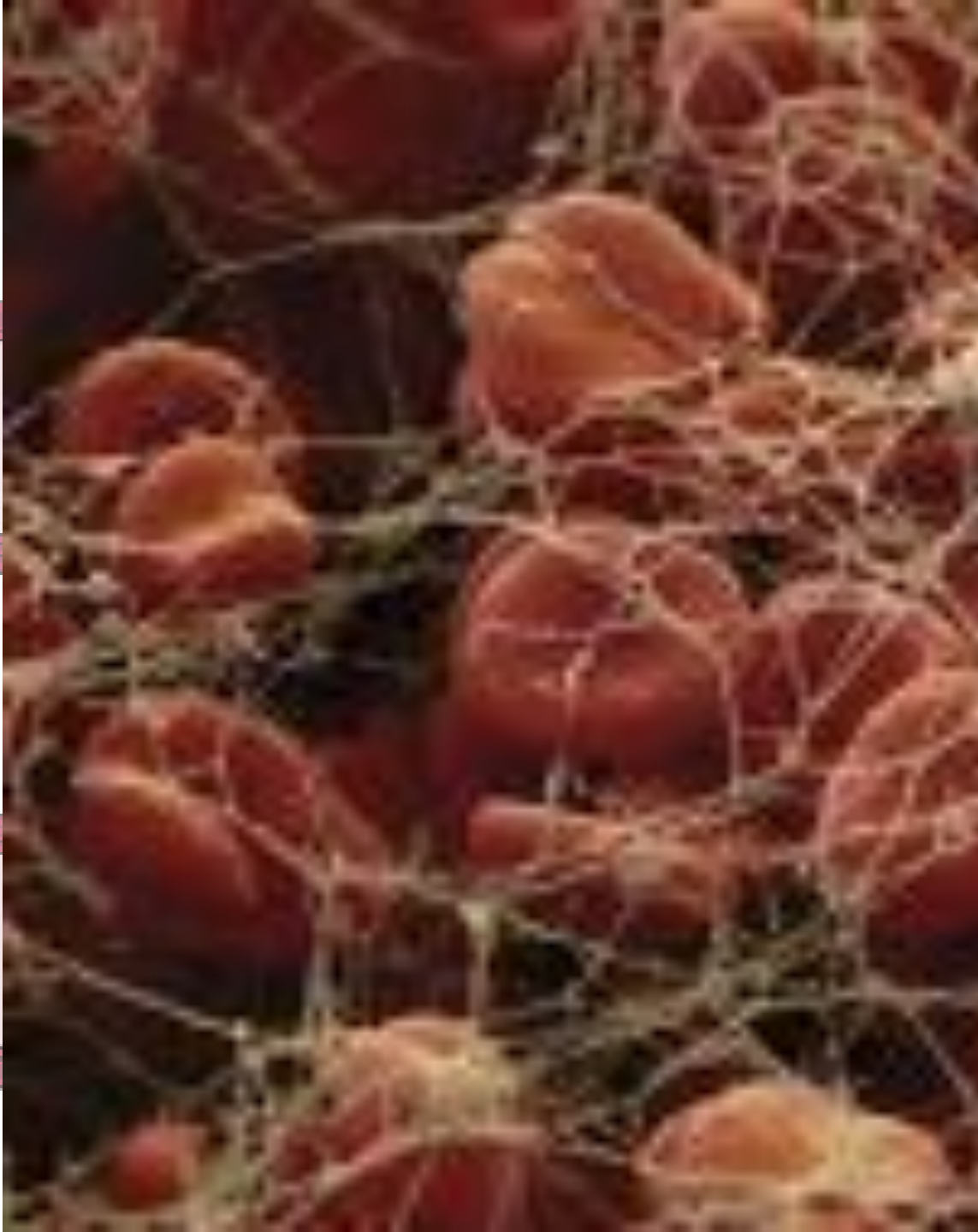
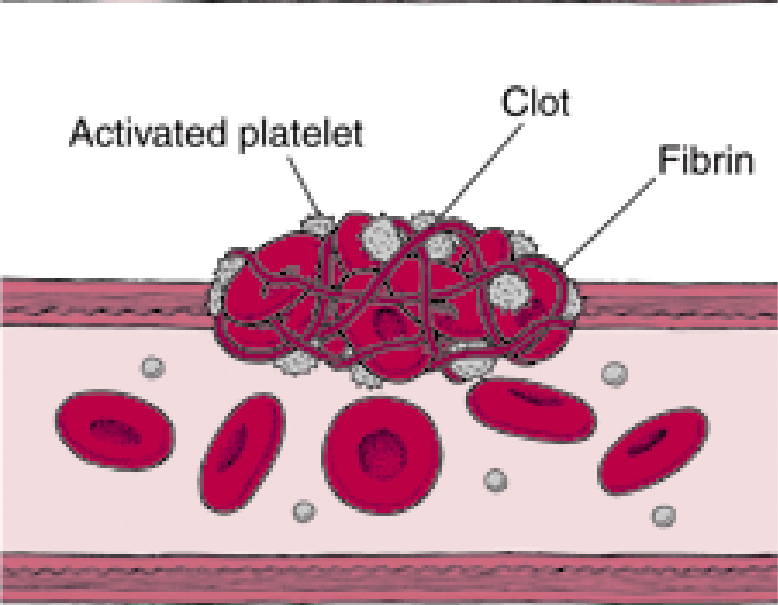
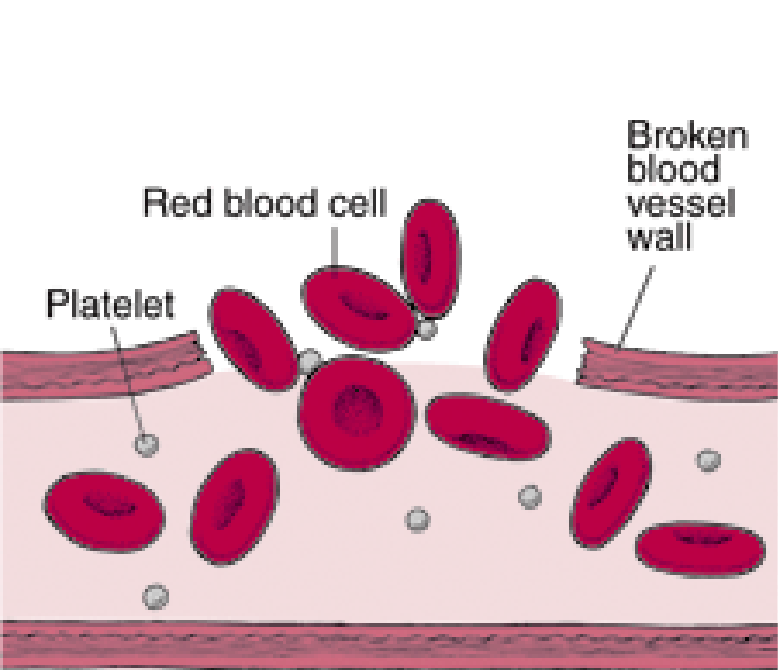


Blood vessel

White blood cell

Red blood cell

Platelet



Introduction -anemias

- **Anemia** = low hemoglobin (Hb) or "blodprosent"
- **Hemoglobin** is the color in the red blood cells, making the bllood red
- Hemoglobin binds oxygen from the air and transports it to all parts of the body.
- When you are anemic, you are pale, and little oxygen is transported to the tissue, and you feel weak.



Causes of anemia

1. **Bloodloss**, nosebleed, surgery, injury
2. Increased destruction of red cells av røde blodlegemer - **hemolysis**, gives **hemolytic anemia**
3. **Decreased production** in bone marrow

Hemolytic anemia

- Inborn diseases or aquired:



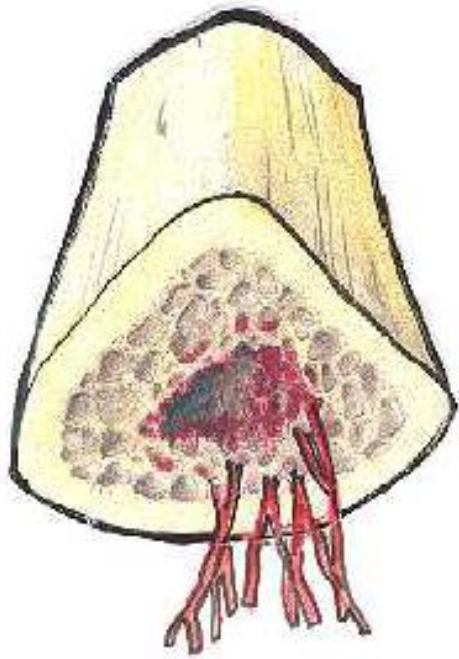
- **Causes:**

- Something wrong in the red blood cells, and the body recognizes the sick cells, and the spleen gets rid of them.
- Antibodies in the blood attacking the red cells
- Large spleen- eating the red cells - even though the cells are normal

Reduced production in the bone marrow

Congenital or occurring later
in life

- **Mechanisms:**
 - **Reduced production** of red
cells in BM



Reduced production in the bone marrow

Causes:

- Lack of building substrates (vitamines, iron, protein).
Treatment is to give building substrates.
- No ability to produce
 - Enough RBC
 - Normal RBC

Constitutional anemia

- Born with it.
- Not necessarily discovered at birth

Constitutional anemia

- Inborn or occurring later in life
- Inherited or accidentally
- Mild, moderate, severe

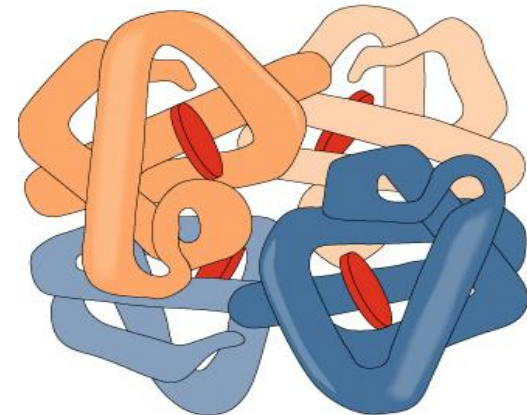
Constitutional anemia

- Different types
 - **Sickle cell anemia** - inherited, various degree of severeness
 - **Thalassemia** - inherited, various degree of severeness
 - **Blackfan-Diamond-anemi**
 - **Dyserythropoietisk anemi** -inherited , different clinical picture
 - **G6PD** -inherited occurs in attacks
 - **Sfærocytosis** - inherited, different clinical picture

Hemoglobin disorder

Thalassemias

Structural hemoglobin disorders
("hemoglobinopathies")



Unaffected
carrier
father



Unaffected
carrier
mother



LEGEND



RECESSIVE
GENE



DOMINANT
GENE



Unaffected child



Unaffected
carrier child



Unaffected
carrier child



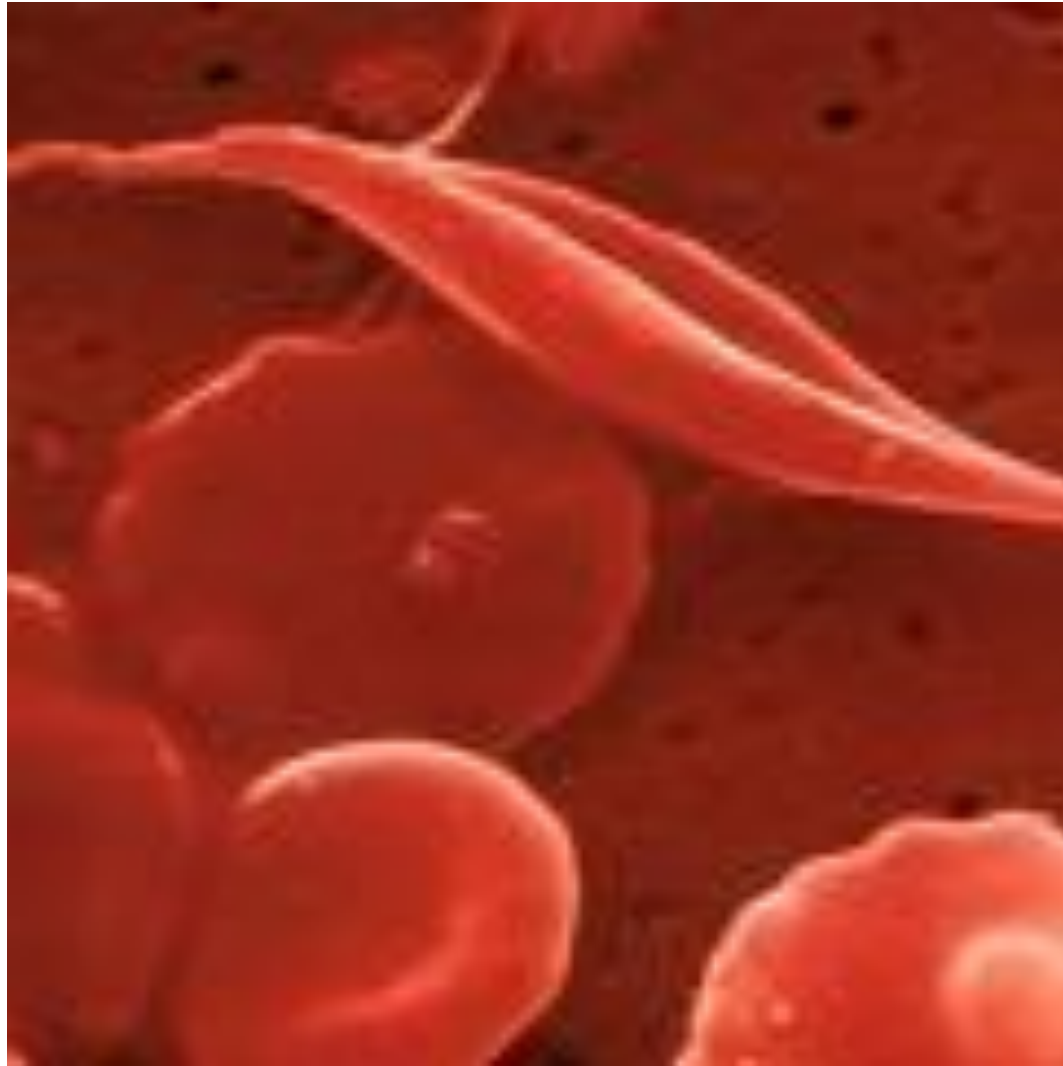
Affected child

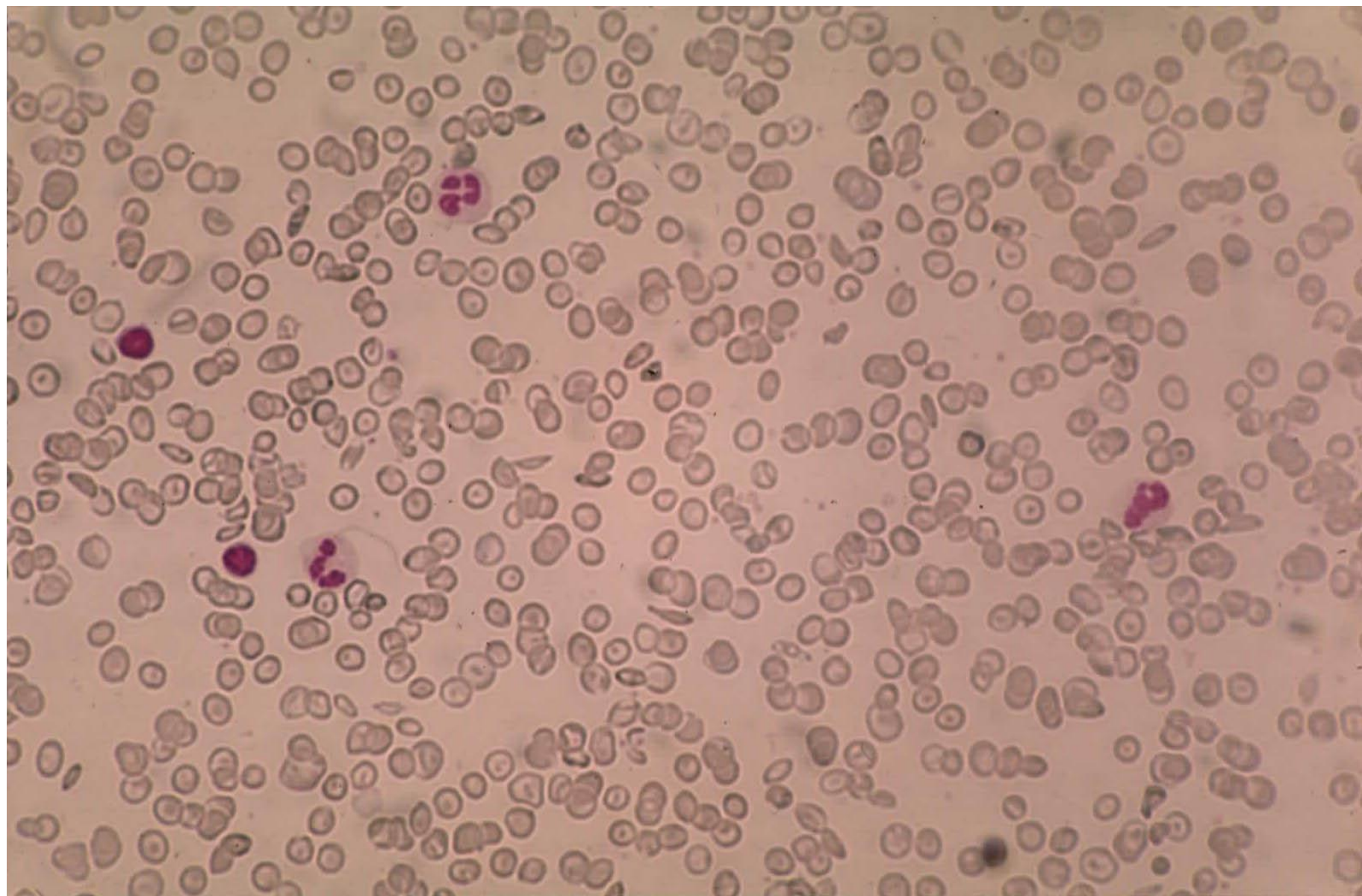
Red Blood Cells

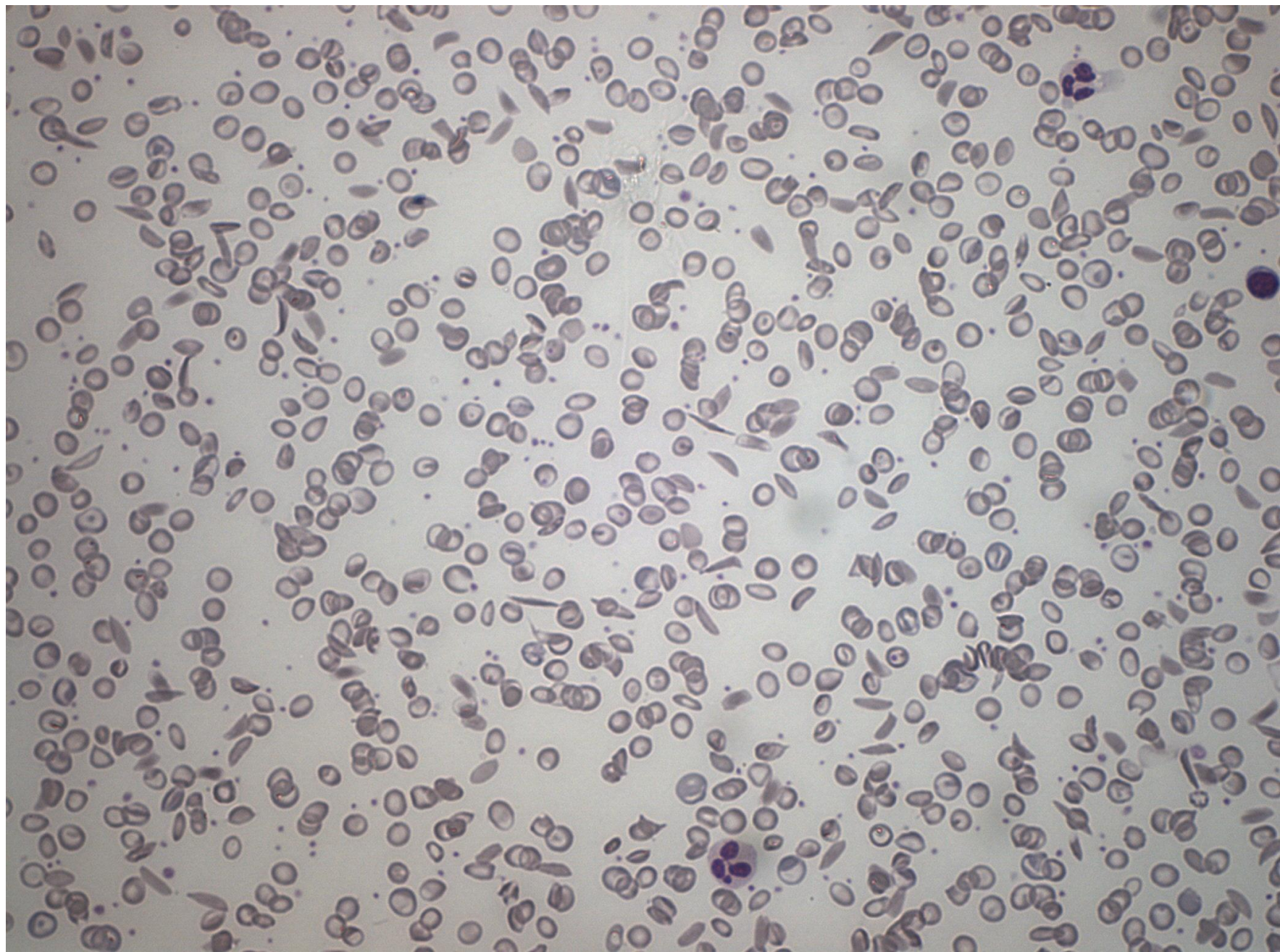


Sickle cell

Normal red
blood cell







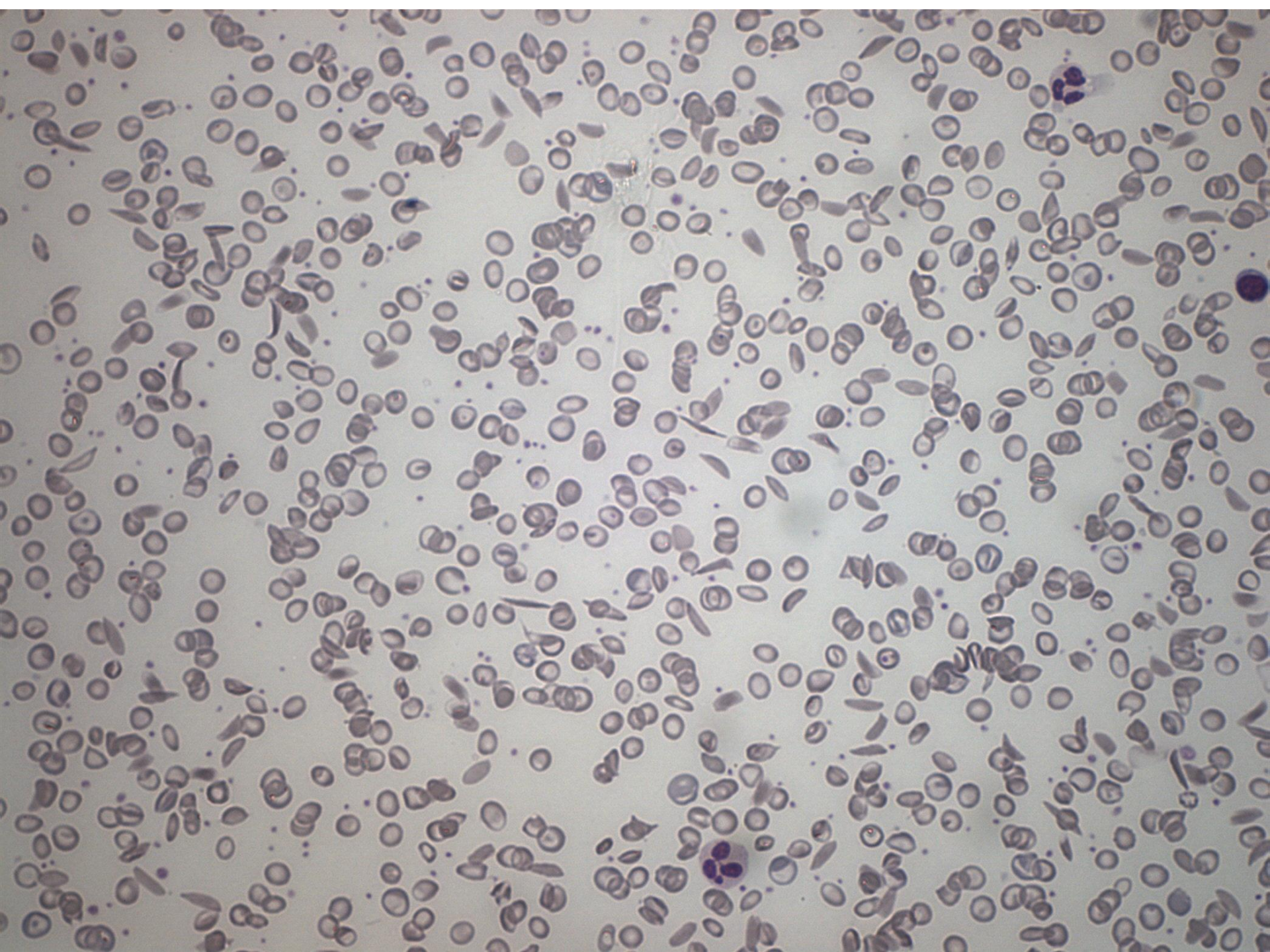


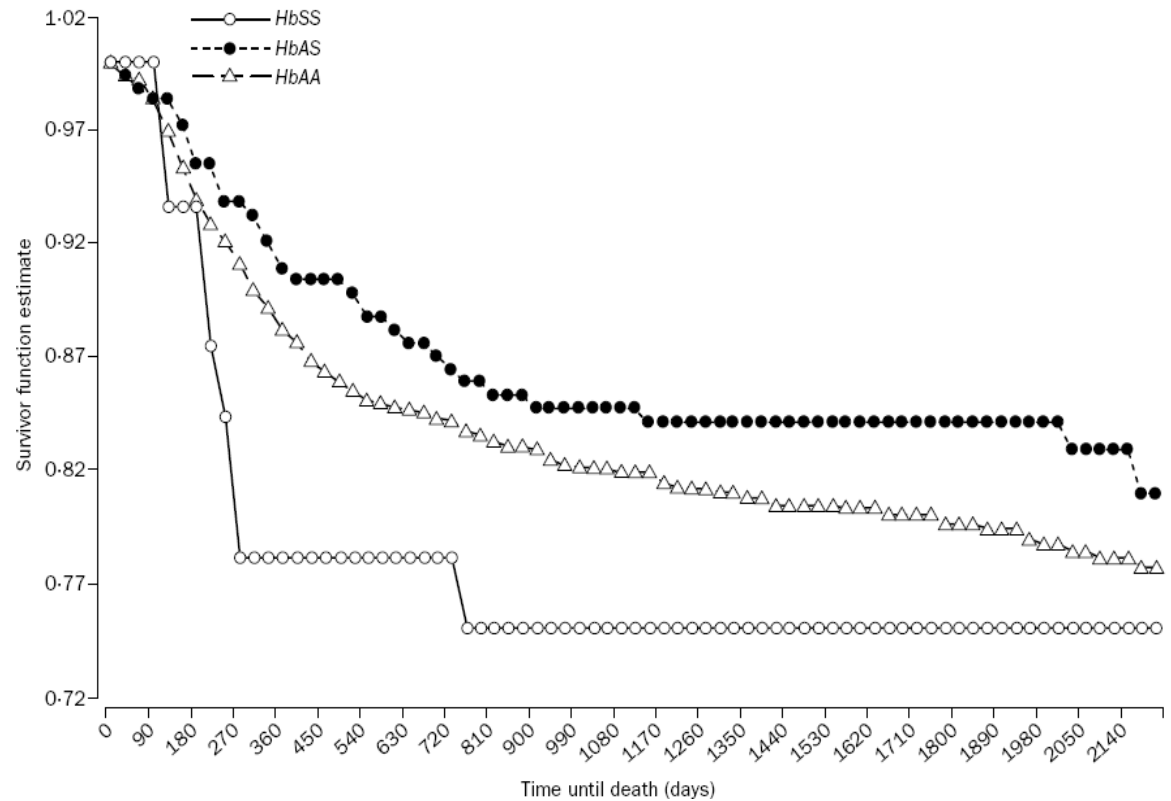
Fig. 2. Global distribution of haemoglobins S and E



Fra: Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: An increasing global health problem. Bull WHO 2001; 79: 704-712

Sickle cell anemia

- Heterozygote carriers have better outcome when it comes to malaria



Strukturelle Hb-varianter

- **HbE** - most common in South East-Asia,
- **HbS** -mostly in Africa
 - Most important structural Hb variant
 - Heterozygot (x) - healthy carrier
 - Homozygot (xx) or HbS combined with β^0 -thalassemia or HbC gives sickle cell disease
- **HbC** - innocent by itself, but can give sickle cell disease in combination with HbS

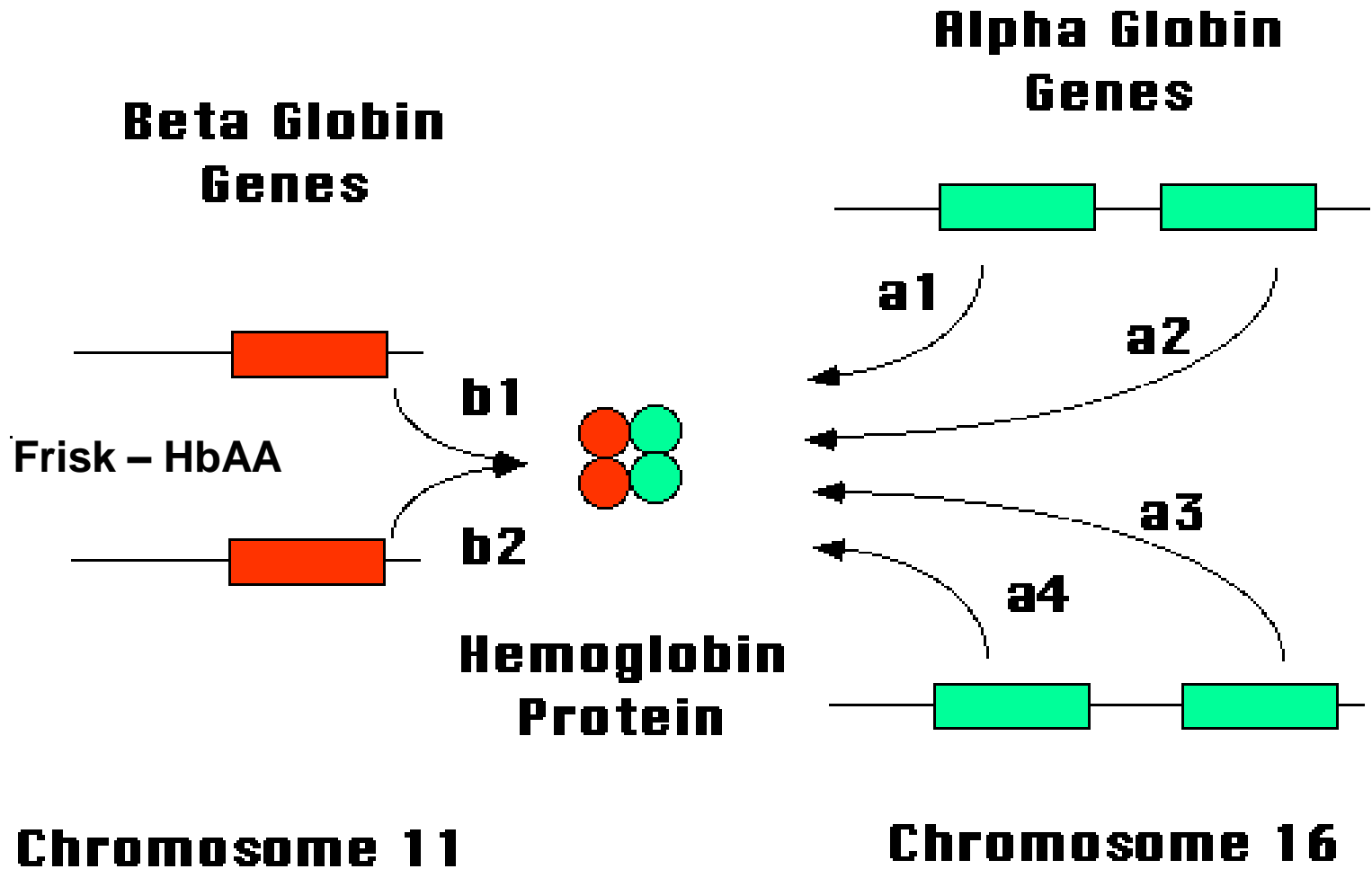
Sigdcelleanemi / sigdcellesykdom

(eng. sickle cell anaemia/sickle cell disease)

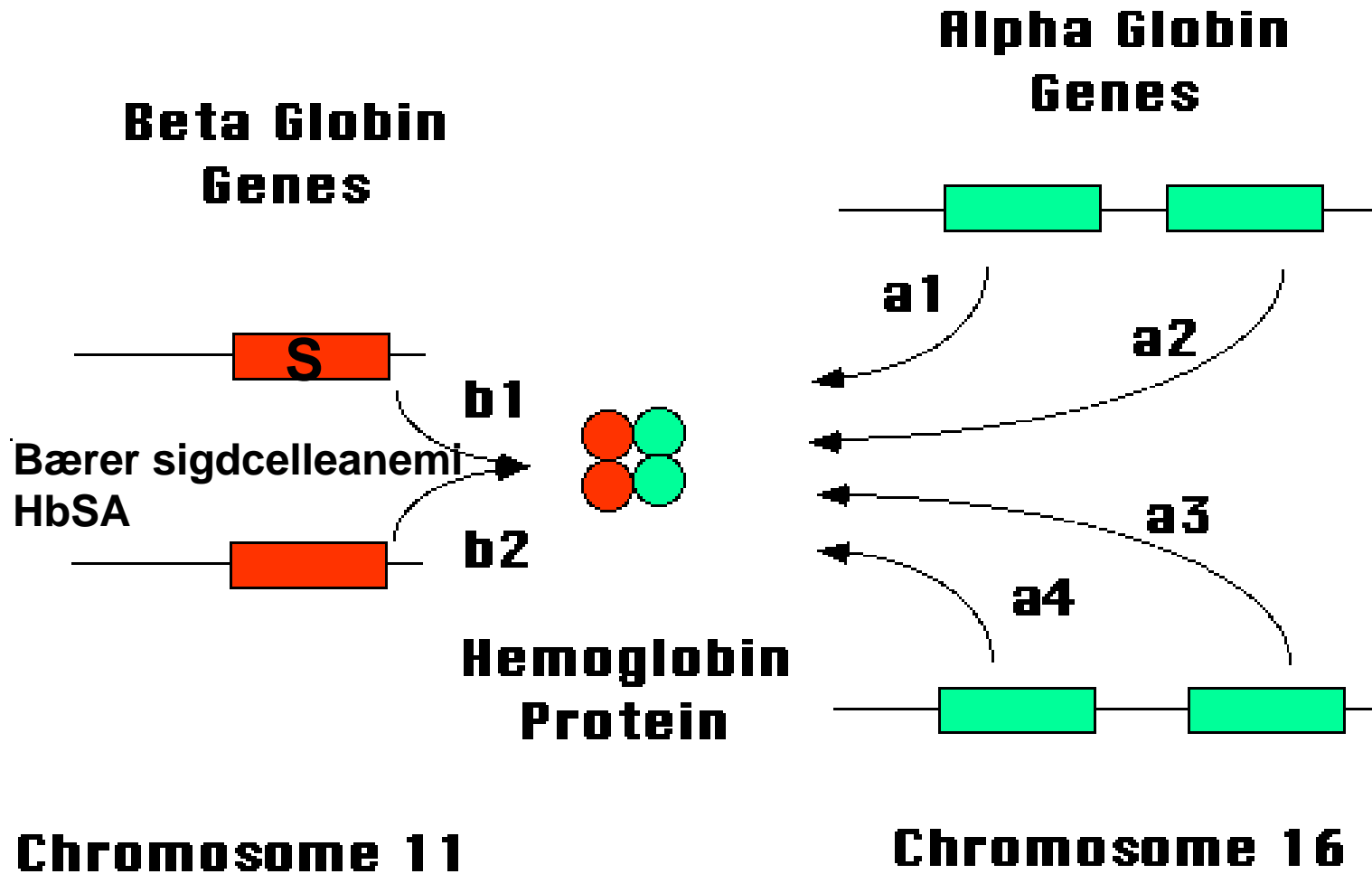
Viktigste typer:

- HbSS - sigdcelleanemi - SCA
 - HbS β^0
 - HbS β^+
 - HbSC
- } Sigdcelle disease - SCD

Syntesis of hemoglobins

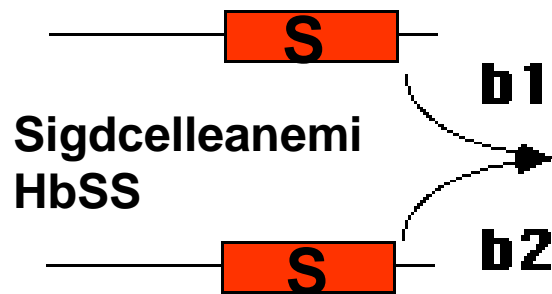


Syntesis of hemoglobins



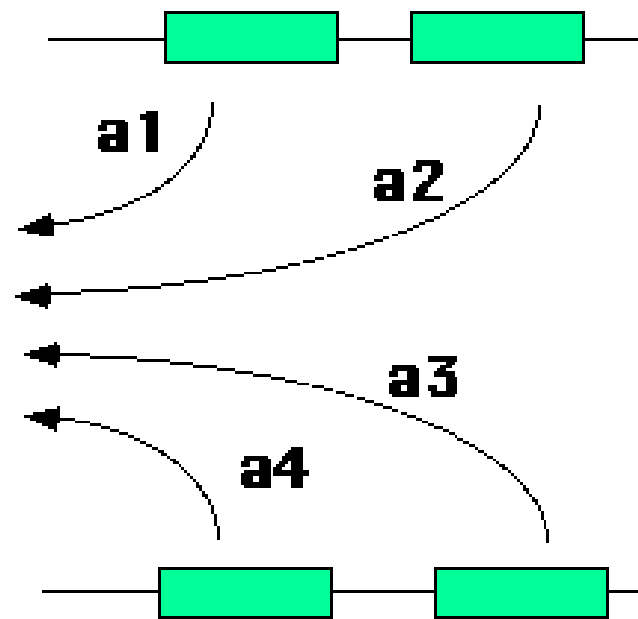
Syntesis of hemoglobins

Beta Globin Genes



Chromosome 11

Alpha Globin Genes

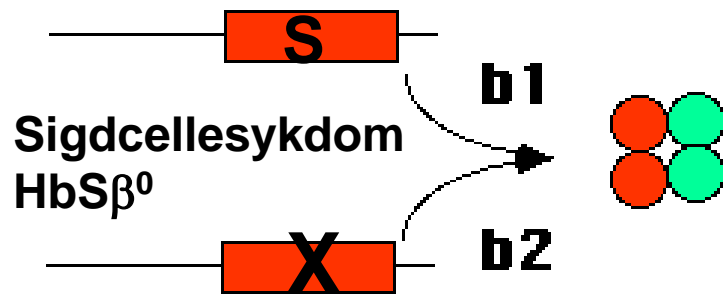


Chromosome 16

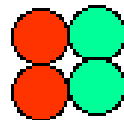
Hemoglobin Protein

Syntesis of hemoglobins

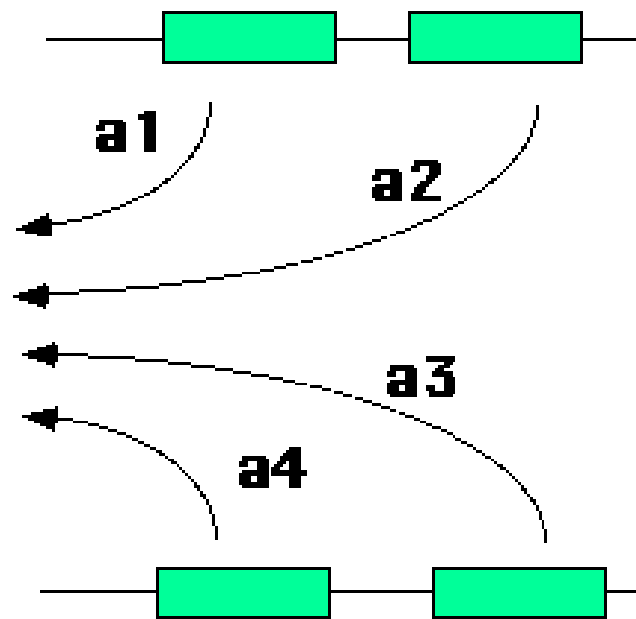
Beta Globin Genes



Hemoglobin Protein



Alpha Globin Genes

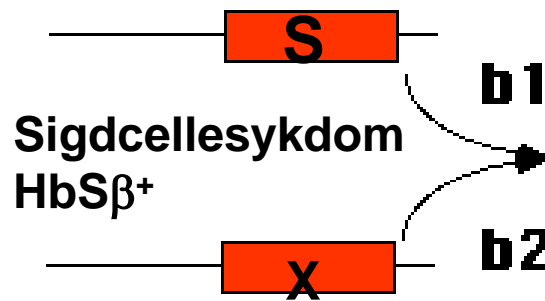


Chromosome 11

Chromosome 16

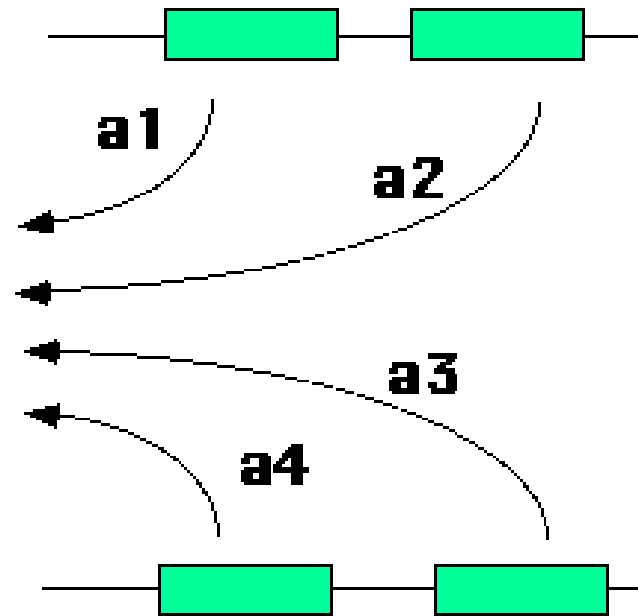
Syntesis of hemoglobins

Beta Globin Genes



Chromosome 11

Alpha Globin Genes

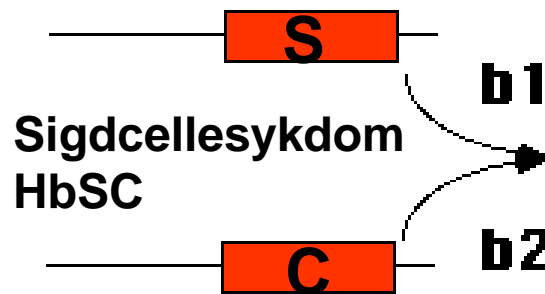


Chromosome 16

Hemoglobin Protein

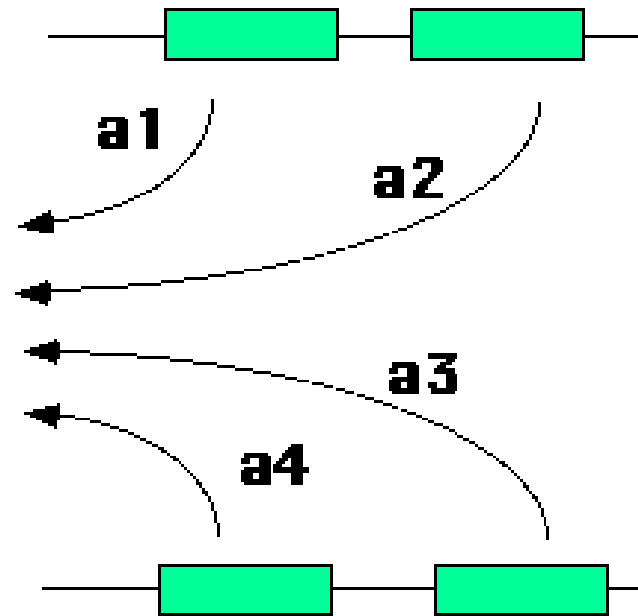
Syntesis of hemoglobins

Beta Globin Genes



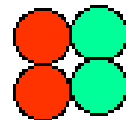
Chromosome 11

Alpha Globin Genes



Chromosome 16

Hemoglobin Protein



Sickle cell anemia

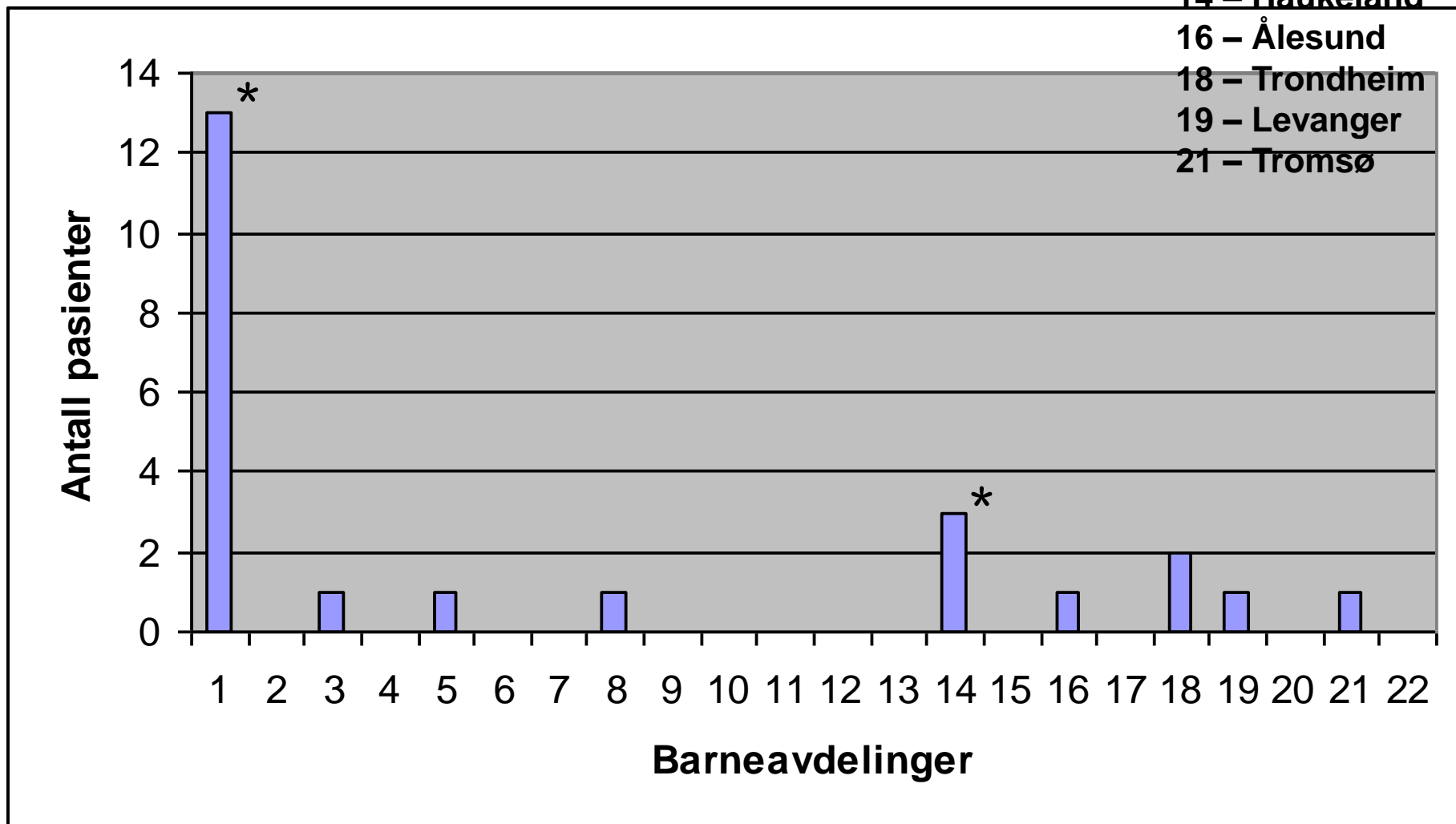
- Glutamate is substituted with valine in β -chain in Hb-molecule
- Gives tendency of rbc to stick/clump together when they are not oxygenated

Clinical picture:

- Chronic hemolytic anemia
- Tendency towards vasoocclusive /painful crises
- Increased tendency to infections
- Organ damage
- High vessel pressure in the lungs

Number of patients with Sca At dep of pediatrics (nov. 2006)

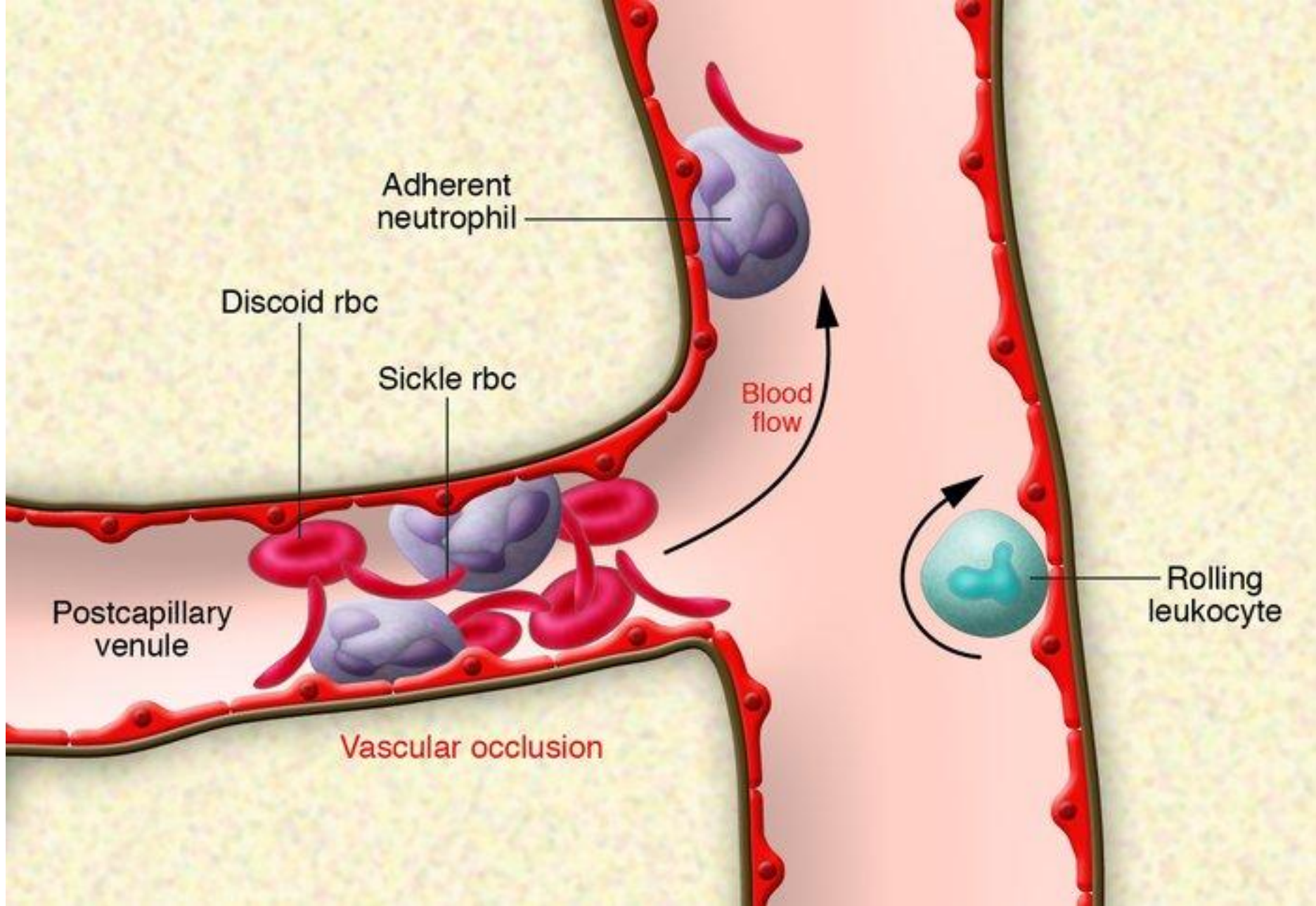
- 1 – UUS
- 3 – Åhus
- 5 – Lillehammer
- 8 – Tønsberg
- 14 – Haukeland
- 16 – Ålesund
- 18 – Trondheim
- 19 – Levanger
- 21 – Tromsø



* En pasient har HbS/ β^0

Klinisk bilde

- Various degree of chronic hemolytic anemia ("lav blodprosent")
- Otherwise very varying- some very little symptoms while others very frequent painful crises and lifethreatening complications
- Some patients have persistent elevated HbF(foster-Hb) protecting against painful vasoocclusions



Different types of crises

- **Vaso-occlusive crises**
 - Pain
 - "Chest syndrome"
 - Stroke
- **Sequestration**
- **Aplastic crises**

Vaso-occlusive/painful crises

- The pain is often localised to the skeleton
 - Hands, feet- may be the first symptoms in small children(dactylitis)
 - Back, arms, legs
 - Little oxygen to tissue
- NB - dd.**
- Osteomyelitis

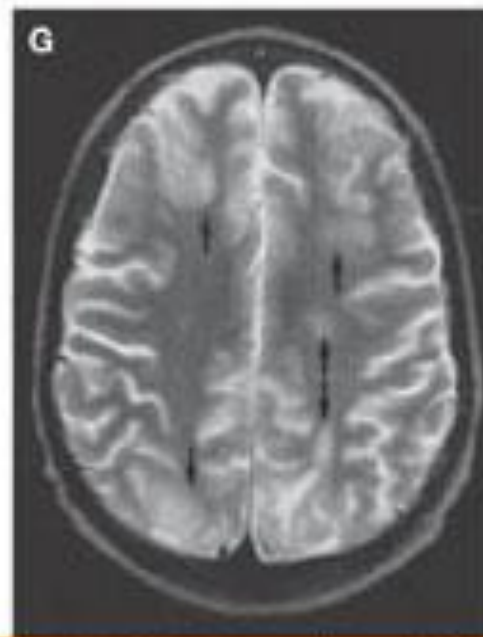
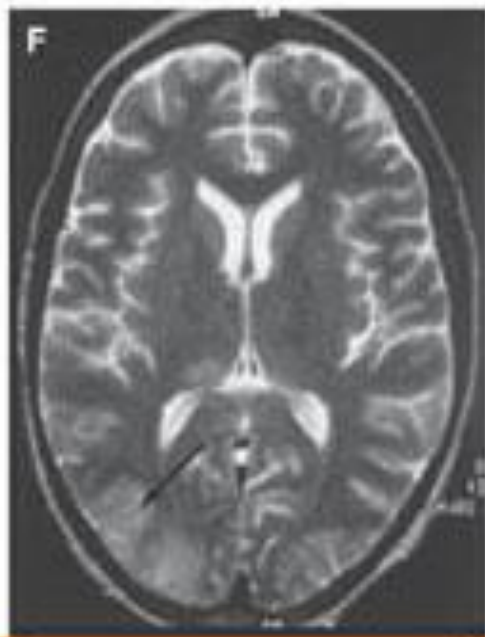
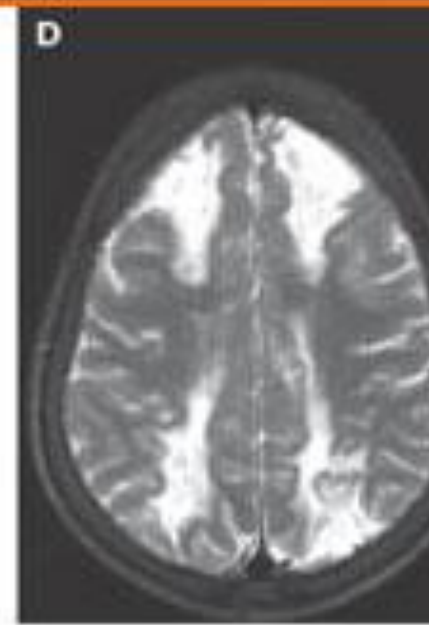
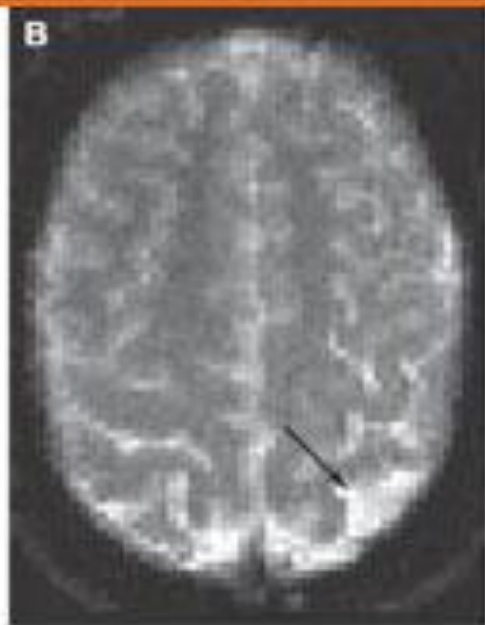


Akutt "chest syndrome"

- Acute chest pain, fever, breathing difficulties, and chest x-ray changes.
- In ca. 30% of patients - once or several times
- Due to infections, vaso-occlusion or a combination
- Lifethreatening situation

Acute stroke

- In ca. 7-10% of patients with SCA
- Age 5-10
- Due to acute "sickling" in a vessel, and this vessel has been -due to chronic stress- been damaged due to the sickle cells
- If it first happens, very large risk of a new stroke (70%)



Acute sequestration

- Most frequently the spleen
- Sudden, rapid and huge enlargement of the spleen, due to increased blood volume in the spleen. Severe < 2 years, cause of death
- Can reoccur

parents need to learn to
palpate the abdomen.

Aplastic crisis

- Transient arrest of red cell production due to an infection with BM affection.
- Nearly always due to *Parvovirus B19*
- Normalises within some days, but might need a transfusion

Infections

- Increased risk for serious bacterial infections (septicimia/meningitis)
 - Pneumococci
 - Haemophilus influenzae
 - Salmonella
- Due to spleen dysfunction

Profylaxis against pneumococci infections

- Penicillin V (Apocillin, Weifapenin el. tilsvarende) 125 mg x 2 / 250 mg x 2 from diagnosis to age 5
- Pneumococci immunisation
 - < age 2-years:
conjugatimmunisation(Prevenar) - er nå i det vanlige vaksinasjonsprogrammet
 - > age 2-years: : polysaccharid (Pneumovax)
 - Pneumovax to be repeated about every 5th year.

Aseptic/avascular necrosis

- Upper part of femur or humerus is destroyed due to a chronic insufficient blood supply
- Teenagers
- Pain and lumping
- Treatment : symptomatic, not to use
- surgery: protese

Treatment of patients with SCA

General

- Early diagnosis -penicillin-profylaxis ASAP
- Good information to parents
 - Deal with milder crises at home
 - When to go to hospital
- Immunisations
- Frequent to the policlinic
- Open access to nearest dep of pediatrics in case of crises

Treatment of patients with SCA

Smertebehandling/krisebehandling

- Plentyful Fluid- basal + 25-50 %
- Painkillers to no pain



- Antibiotics
- Monitor respiration

Treatment of patients with SCA

Hydroxyurea

- The only drug that may change the course of the disease
- Increases the production of HbF
produksjonen av HbF (foster-Hb)
- HbF a normal Hb in patients with SCAP
- Reduces many of the complications of the disease

Treatment of patients with SCA

Hydroxyurea

- Chemotherapy that has been used for years to treat various blood diseases
- HbF ↑
- Reduced hemolysis because the F cells stay longer in the circulation
- Reduces the amount of some of the white cells that patients with SCA have too much of
- Reduces the number of platelets that play a role in connection with thrombi formation

Treatment of patients with SCA

Hydroxyurea

- From about 1984 in SCA
- Reduces painful crises
- Reduces number of chest syndrome
- Reduces number of spleen sequestration
- Reduces the risk for stroke- ?
- Lasts effect more than 5 years
- Some have been treated in about 25 år

Treatment of patients with SCA Hydroxyurea

To whom??

- Many stays in hospitals due to painful crises
- Patients with repeated chest syndrome

Hydroxyurea

To children??

- Tested to infants
- Does not reduce growth and development
- Effect as in adults
- Prevent organ damage?

Hydroxyurea

Side effects

- White blood cells and platelets
 - Nausea
 - Hair loss
 - Skin and nail changes
- } rare
- Thick skin with increase pigmentation
 - Dark nails
 - Legulcer- ?

Treatment of patients with SCA

Hydroxyurea

Cancer?

- No proven increase in cancer - neither children nor adults

Hydroxyurea

Fertility?

- HU may damage the fetus in rat studies in large doses
- Not seen in human beings but:
 - Recoment to stop HU if planning pregnancy (Both men and women)
 - Contraception

Treatment with hydroxyurea

- **Dosing: 20-30 (-40) mg/kg /day**
 - **Europ: Same dosing 20-30 mg/kg**
 - **USA: dose increase to max tolerated dose (white cells)**

Treatment of patients with SCA

Stemcelletransplantation

- Cures the disease
- Many complications - some die of the procedure
- Many have so milde course of the disease that they do not need it
- After HU, many do get a better QOL with less diease activity, so they do not need it

Pain killing

1. Paracetamol
2. NSAIDs
3. Opioider
 - oral
 - parenteralt

Target/Goal: No pain

Transfusions

Generel:

Be restrictive

- Sekvestreringskriser (påfyll)
- CNS-infarkt (utskiftning)
- Chest syndrome med hypoxi (påfyll el. utskiftning)
- Aplastiske kriser (påfyll)
- Preoperativt (påfyll el. utskiftning)

Transfusions

- **Practical:**
 - Fall in Hb with about 2 g/dL from steady state

Gir behandling med hydroxyurea ved sigdcelleanemi økt risiko for malignitetsutvikling?

- ***Voksne:*** Behandlet inntil 9 år med HU uten opptreden av sekundær leukemi (n=233)
- ***Barn:*** Beskrevet 1 tilfelle av ALL og 1 tilfelle av Hodgkin
 - ALL: 1 tilfelle diagnostisert 7 uker etter oppstart av HU
 - Hodgkin: 1 tilfelle diagnostisert 6 måneder etter start av HU
- For kort eksponeringstid til at disse tilfellene kan oppfattes som sekundære

TEST EARLY FOR
SICKLE CELL



USA
37

2004



Diagram over utviklingen av hemoglobinsyntesen

