Haematology I

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Haematology

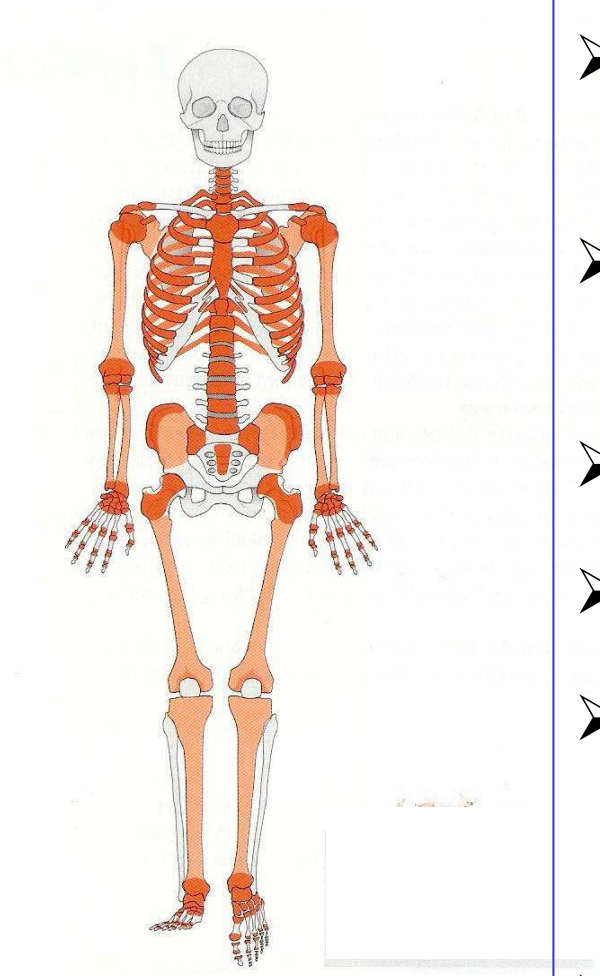
- Haematopoiesis – normal

- Diagnosis of blood diseases

  - Red blood cells

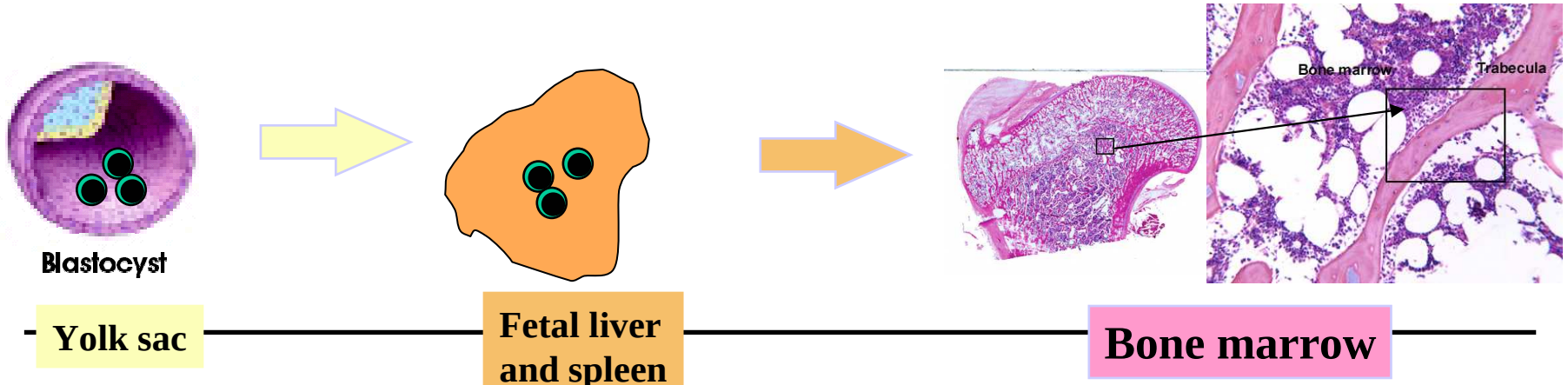
  - White blood cells

Haematopoiesis



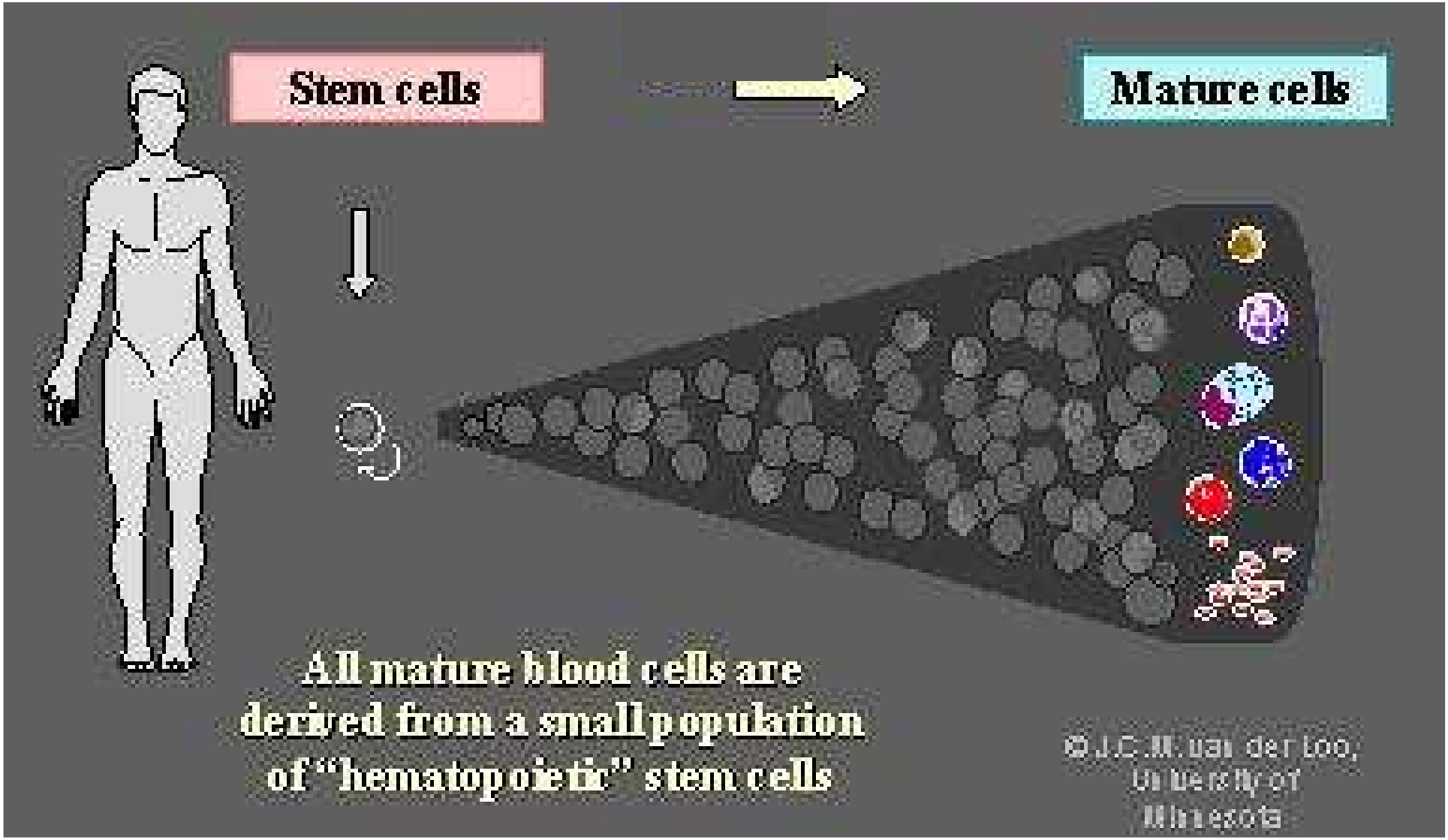
- **The production of blood cells is called haematopoiesis (haemopoiesis)**
- **Haematopoiesis starts 17 days after fertilisation**
- **Haematopoiesis continues throughout life**
- **Haematopoiesis is regulated**
- **Haematopoietic tissues can respond rapidly to increase cell production (blood loss, infection)**
- **Where does haematopoiesis occur?**

Sites of haematopoiesis during embryogenesis

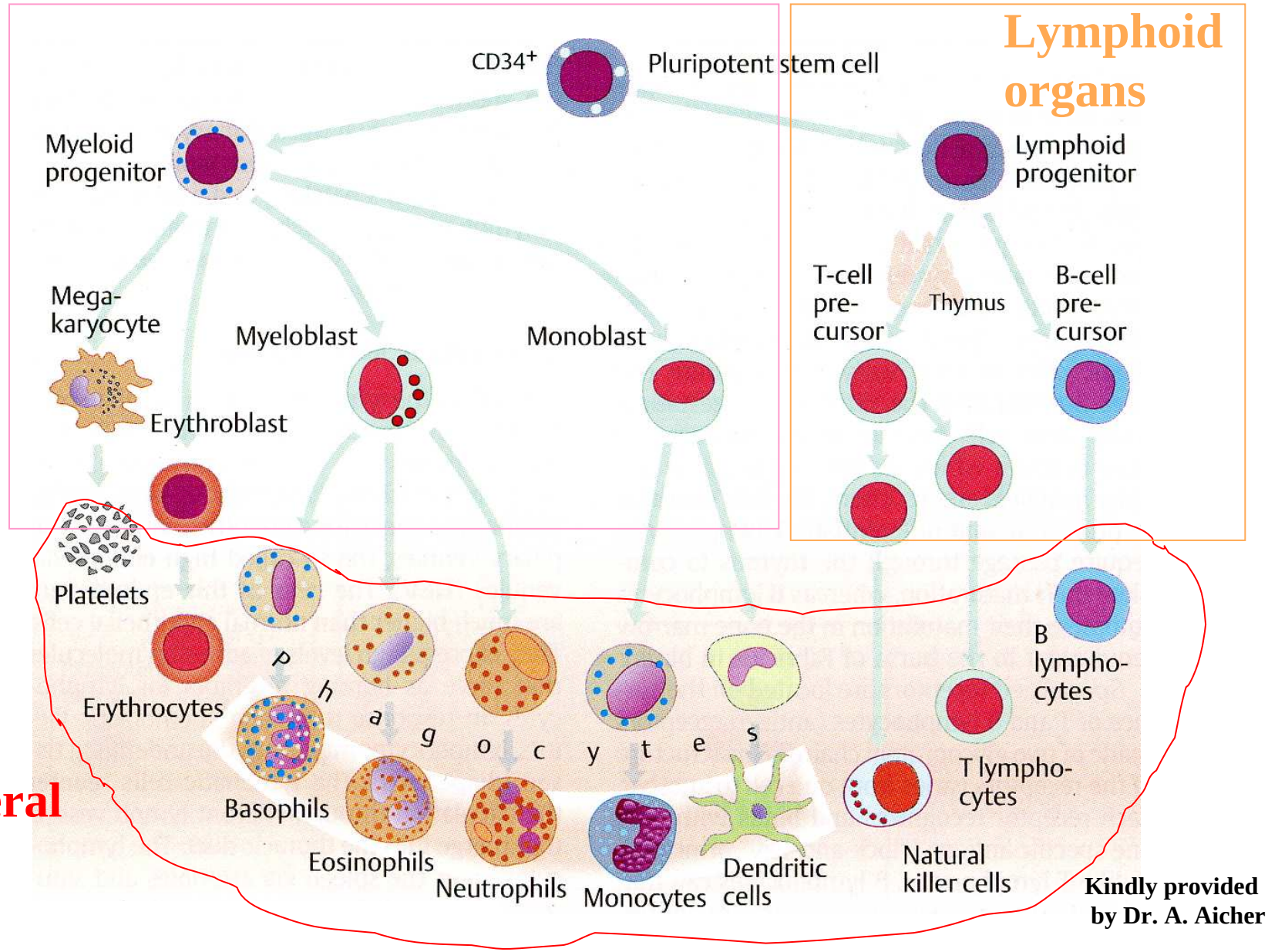


➢ 17 days	Yolk sac	red cells and platelets
➢ 6 weeks	Liver	red cells, platelets, leukocytes
➢ 12 weeks	Liver and spleen	red cells, platelets, leukocytes
➢ 20 weeks	Bone marrow	red cells, platelets, leukocytes

Haematopoietic stem cells

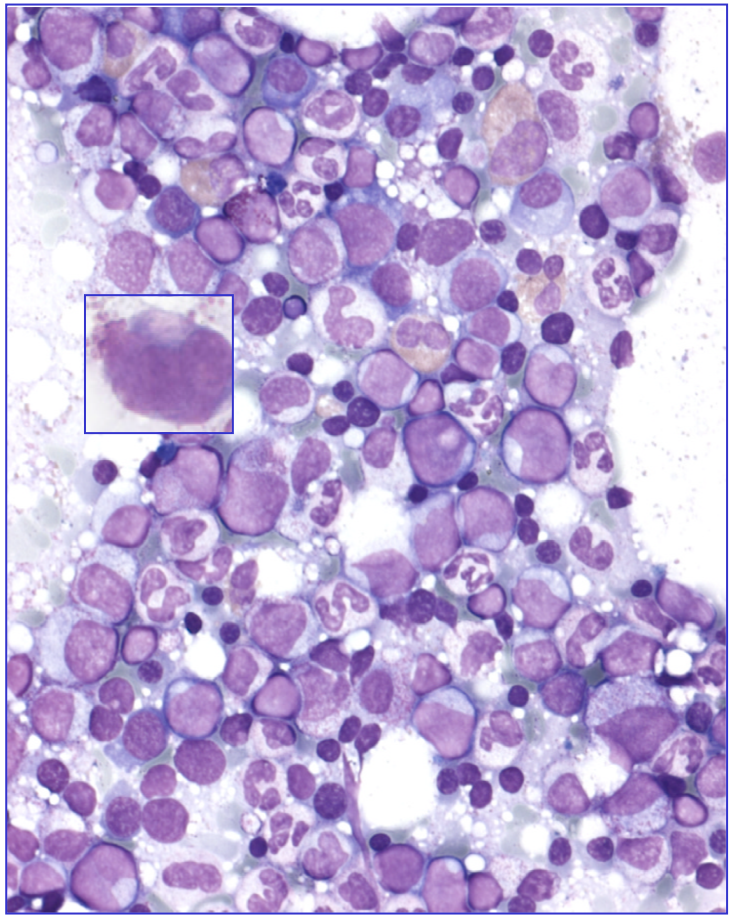


Model of haematopoiesis



Kindly provided by Dr. A. Aicher

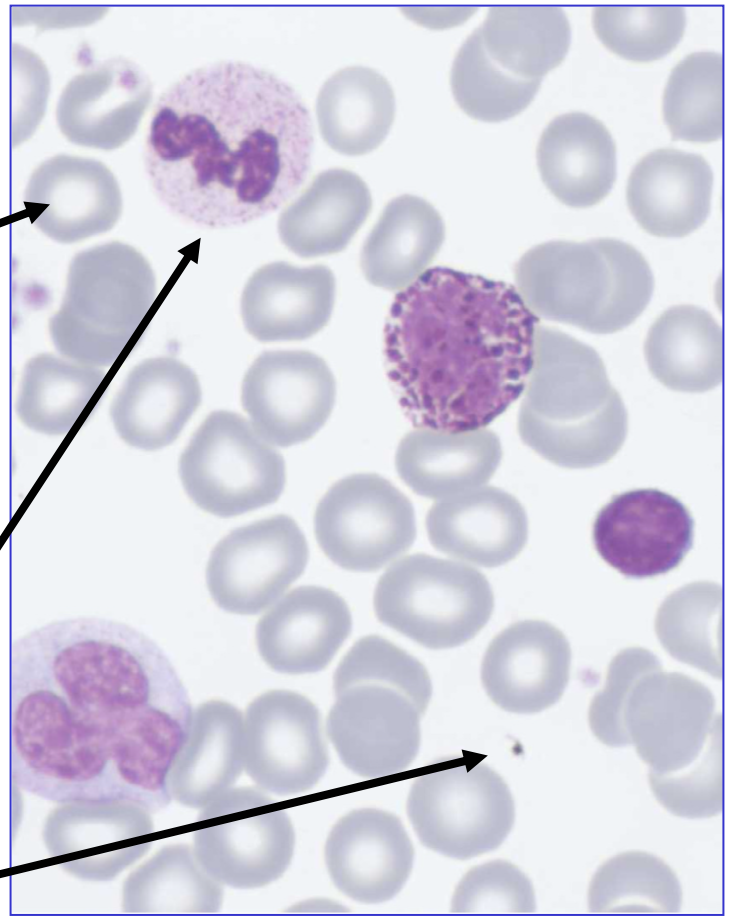
Production of each cell type per day



2×10^{11}
erythrocytes

1.2×10^{11}
granulocytes

1.5×10^{11}
platelets



Bone marrow → **Peripheral blood**

Content of blood

Blood volume

- ~ 8% of the body weight → 80 ml/kg
- Adults: ~ 5 liter
- New borns: ~ 300 ml

Blood contains

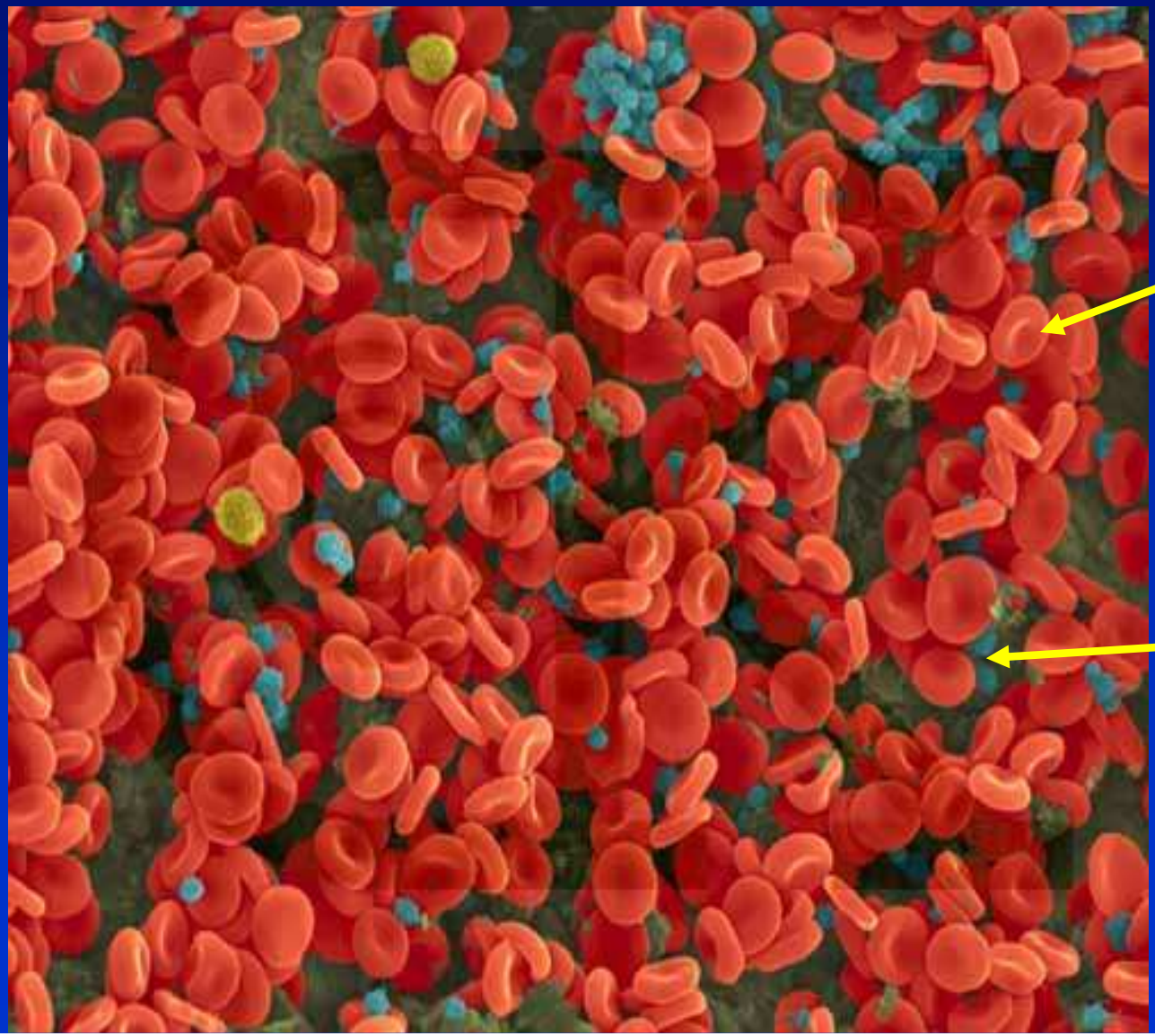
- ~ 45% cellular components
- ~ 55% plasma (water, proteins, clotting factors, elektrolytes…)

serum = plasma without factors for coagulation

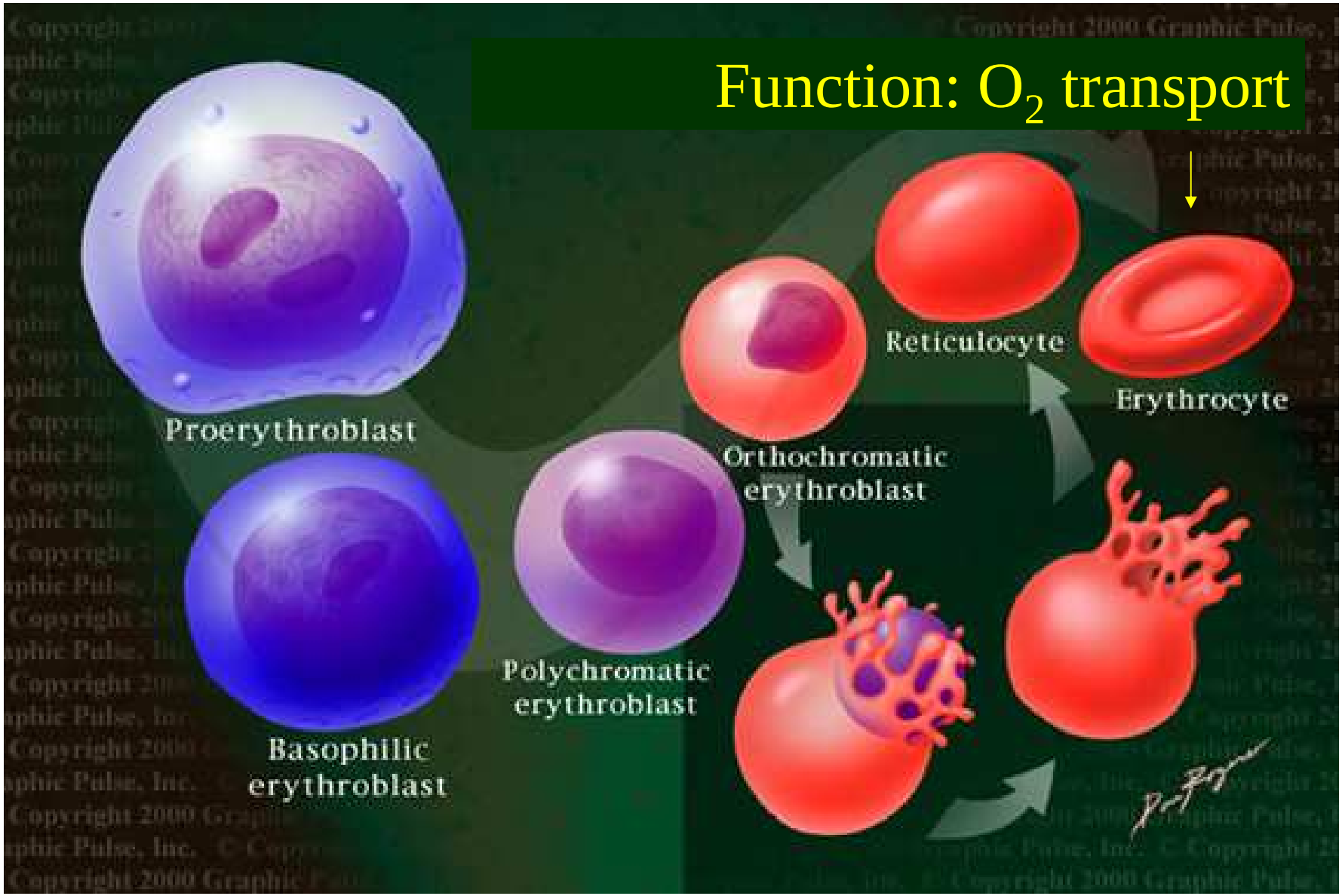
Cellular components of the blood

Cells	Concentration	Duration of living	„juvenile form“	
Erythrocytes	4 800 000/µl	100-120 days	Retikulozytes **1(**-3) days	
Platelets	200 000/µl	7-12 days		
Granulocytes	4 500/µl	2-3 days	„Stabkerniger“	
Lymphozytes	3000/µl	up to many years		

Blood cells



Erythropoiesis



Haematology

- Haematopoiesis – normal

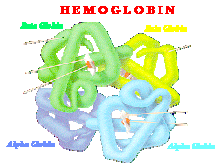
- Diagnosis of blood diseases

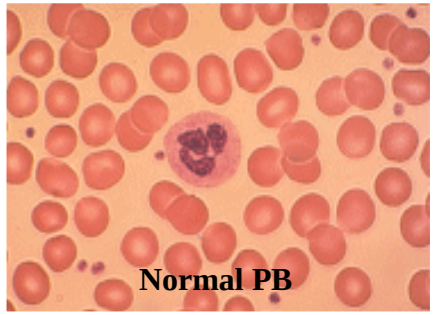
  - Red blood cells
  - Thrombocytes

  - White blood cells

Red blood cells

- **Erythrocytes**: 4 – 5.5/pl (4 - 5.5 Mio/µl)





- **Haemoglobin (Hb):** 12-17 g/dl

  Hb increased → „Polyglobulia“
  Hb decreased → „Anaemia“
  Clinical symptoms: paleness, tired, exhausted

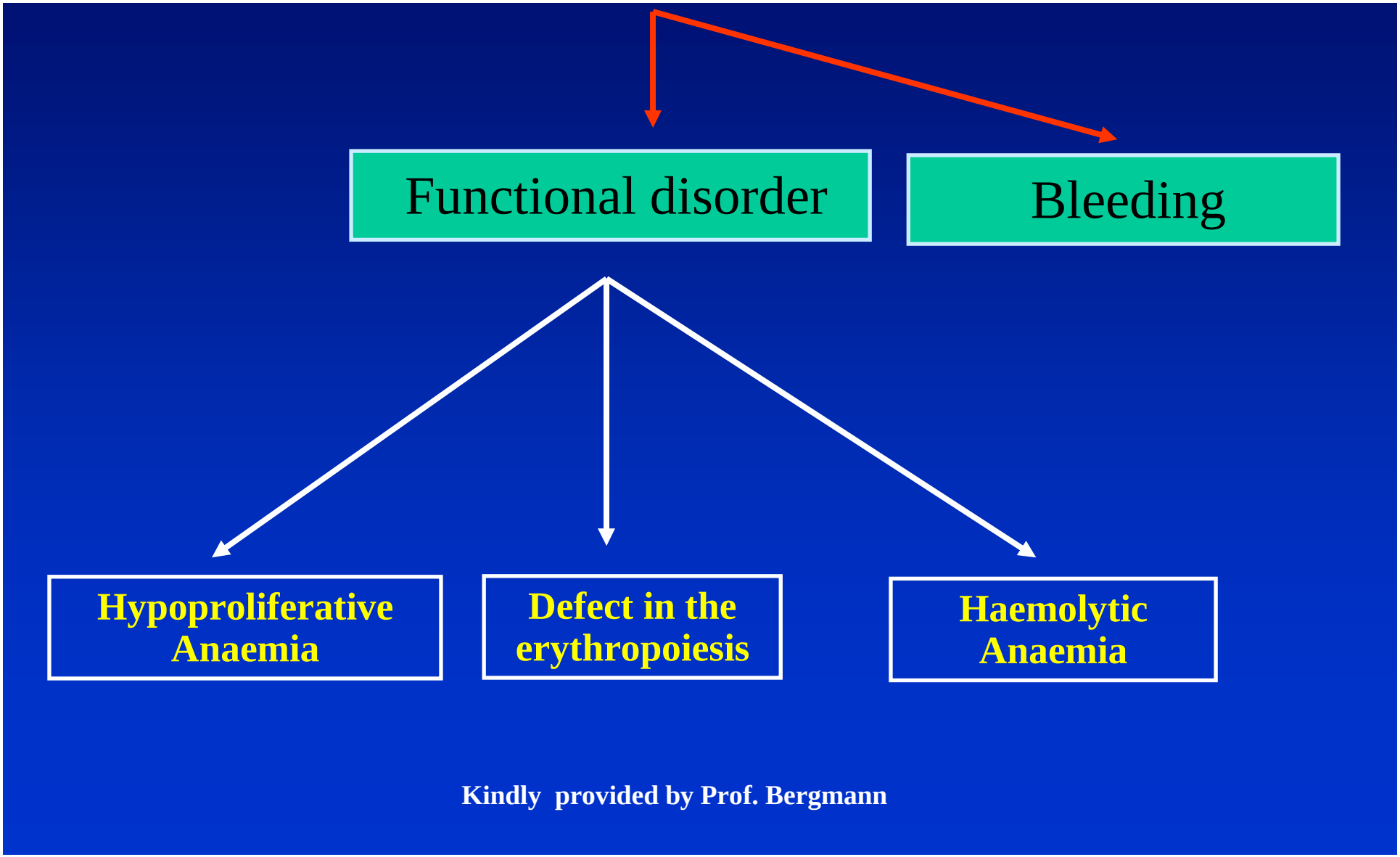
- **Mean corpuscular volume of erythrocytes (MCV):** 80-100fl

  MCV increased → „macrocytosis“„
  MCV decreased → „microcytosis“

- **Reticulocytes**: 0.5-1.5%

  Reticulocytes decreased → „hypo- or aplastic“
  Reticulocytes increased → exhausted use

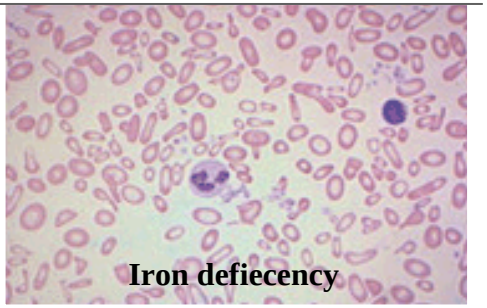
Reason for Anaemia



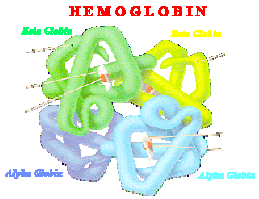
Anaemia

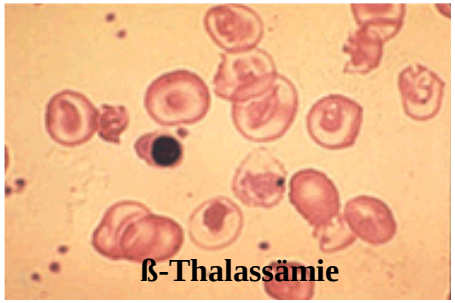
Mikrocytic:

- Iron decreased → Ferritin (marker for iron load) important during pregnancy


Iron defiecency

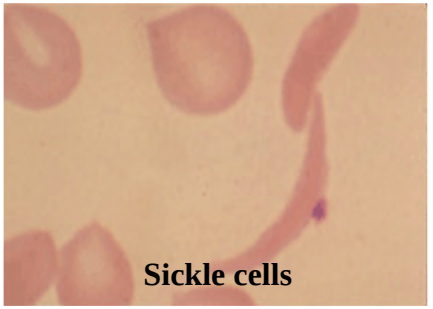
- Thalassaemia → LDH small increased, Reticulocytes very high; functional defect in the Haemoglobin synthesis ($\alpha_2ß_2$)




ß-Thalassämie

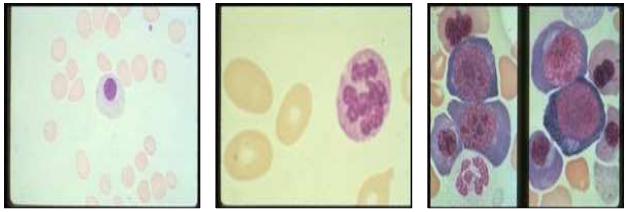
Normocytic:

- Bleeding, renal, aplastic
- Haemolytic → LDH increased, p.e. Haemolytic Uraemic Syndrom, Sickle Cell Disease

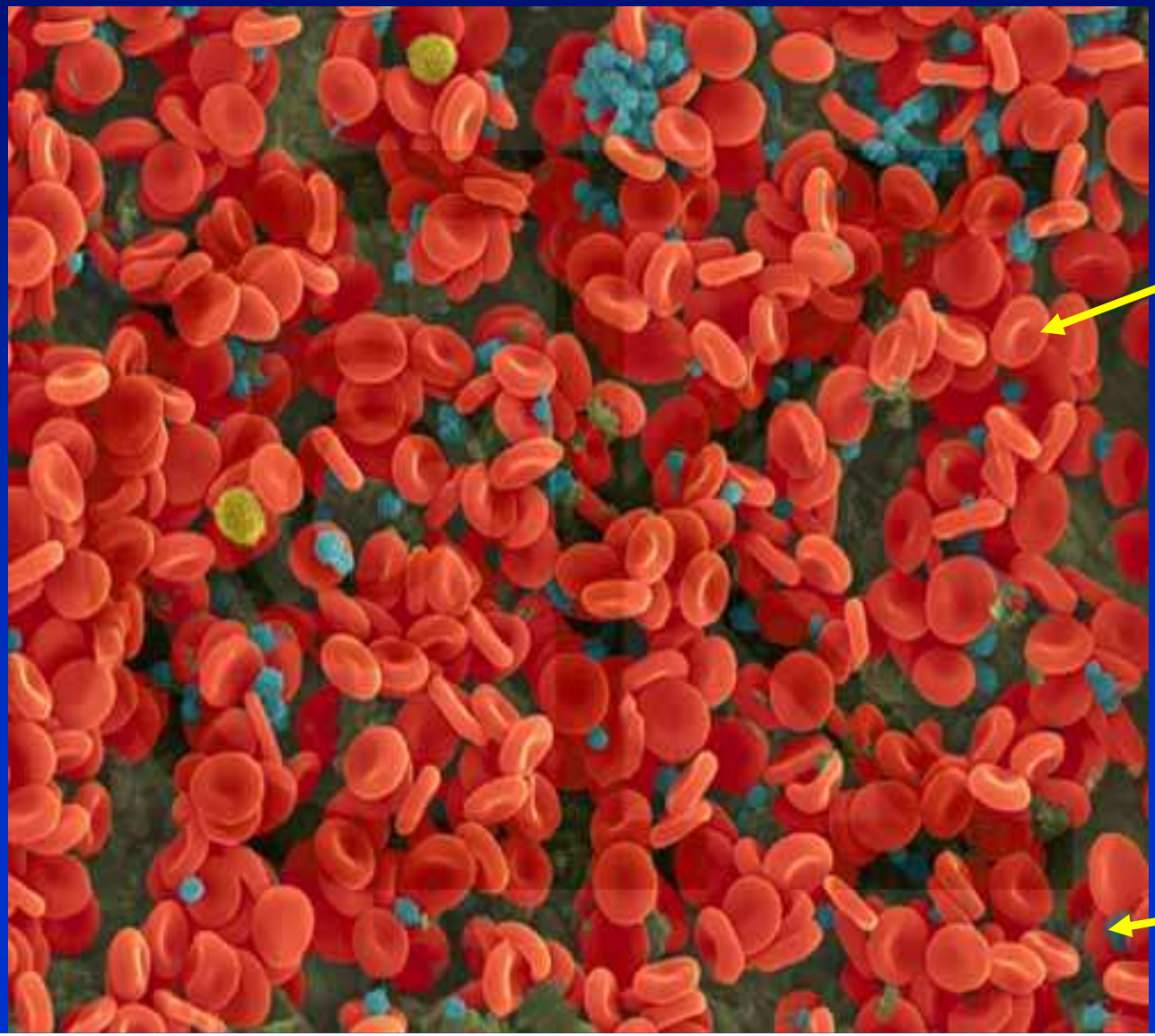

Sickle cells

Makrocytic

- B12 or folic acid deficiency



Blood cells



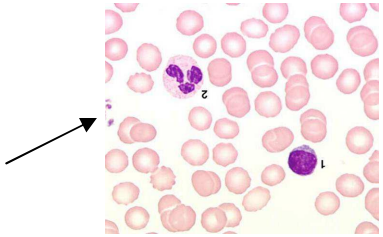
Red blood cells

Platelets where ?

White blood cells

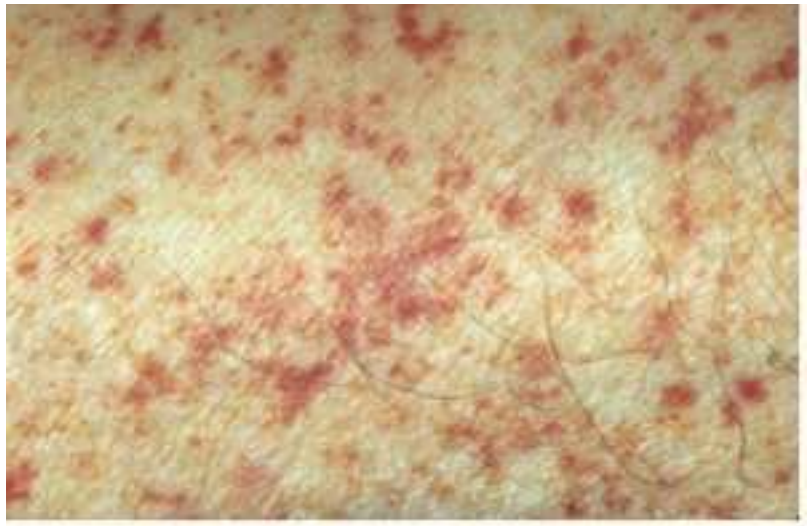
Platelets

Platelets: 150 - 400/nl (150 000 – 400 000/µl)



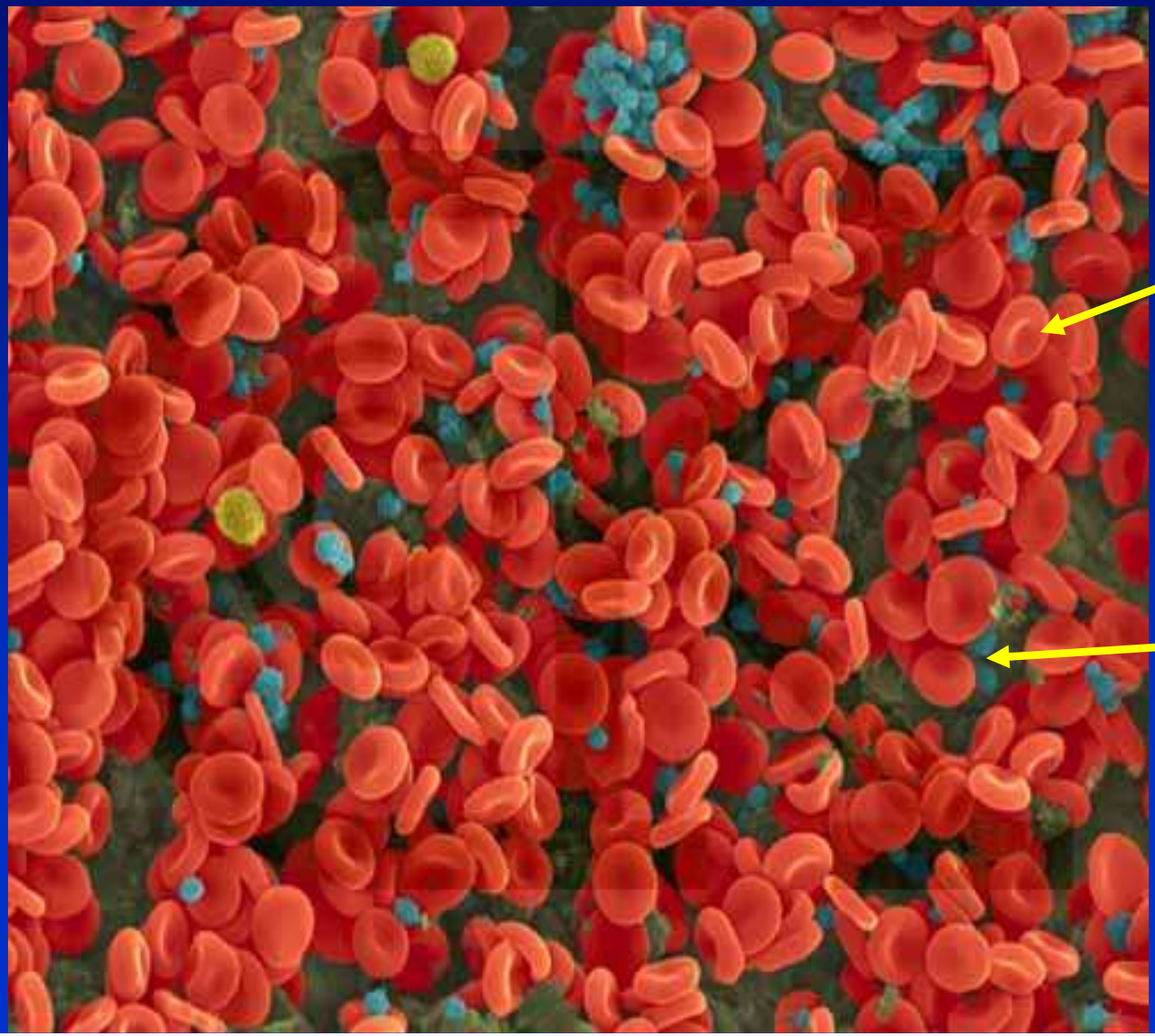
- Less Platelets: Thrombopenia, bleeding may start below 50 000/µl

Petechien



- Increased Platelets: Thrombozytosis, increased risk for thrombosis > 800 000/µl

Blood cells



Red blood cells

White blood cells

Haematology

- Haematopoiesis – normal

- Diagnosis of blood diseases

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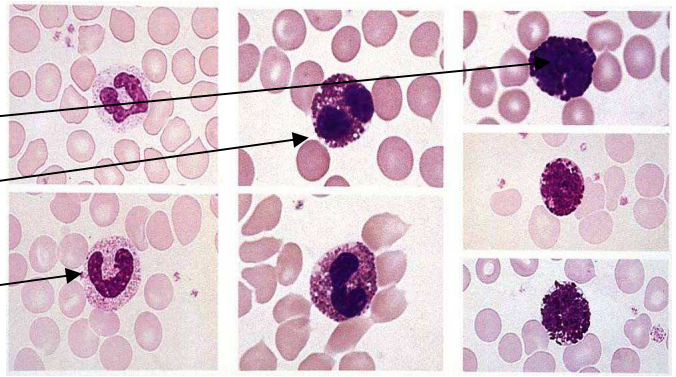
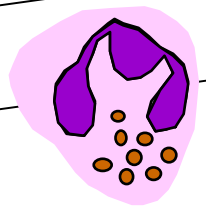
  - White blood cells

    normal versus illness

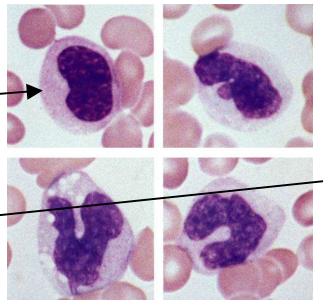
White blood cells

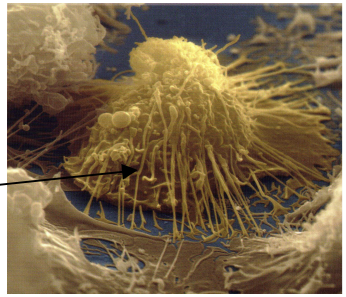
- Basophil Granulocytes
- Eosinophil Granulocytes
- Neutrophil Granulocytes



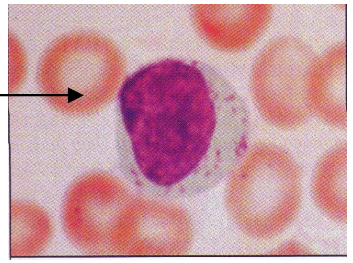


- Monocytes Macrophages
- Langerhans / Dendritic cell family





- Natural killer cells



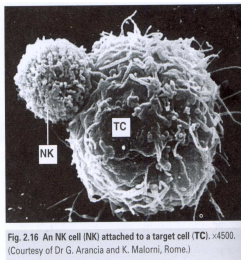
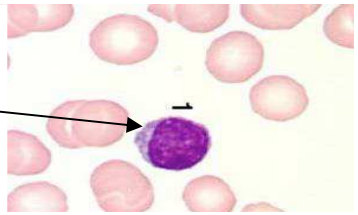


Fig. 2.16 An NK cell (NK) attached to a target cell (TC). ×4500. (Courtesy of Dr G. Arancia and K. Malorni, Rome.)

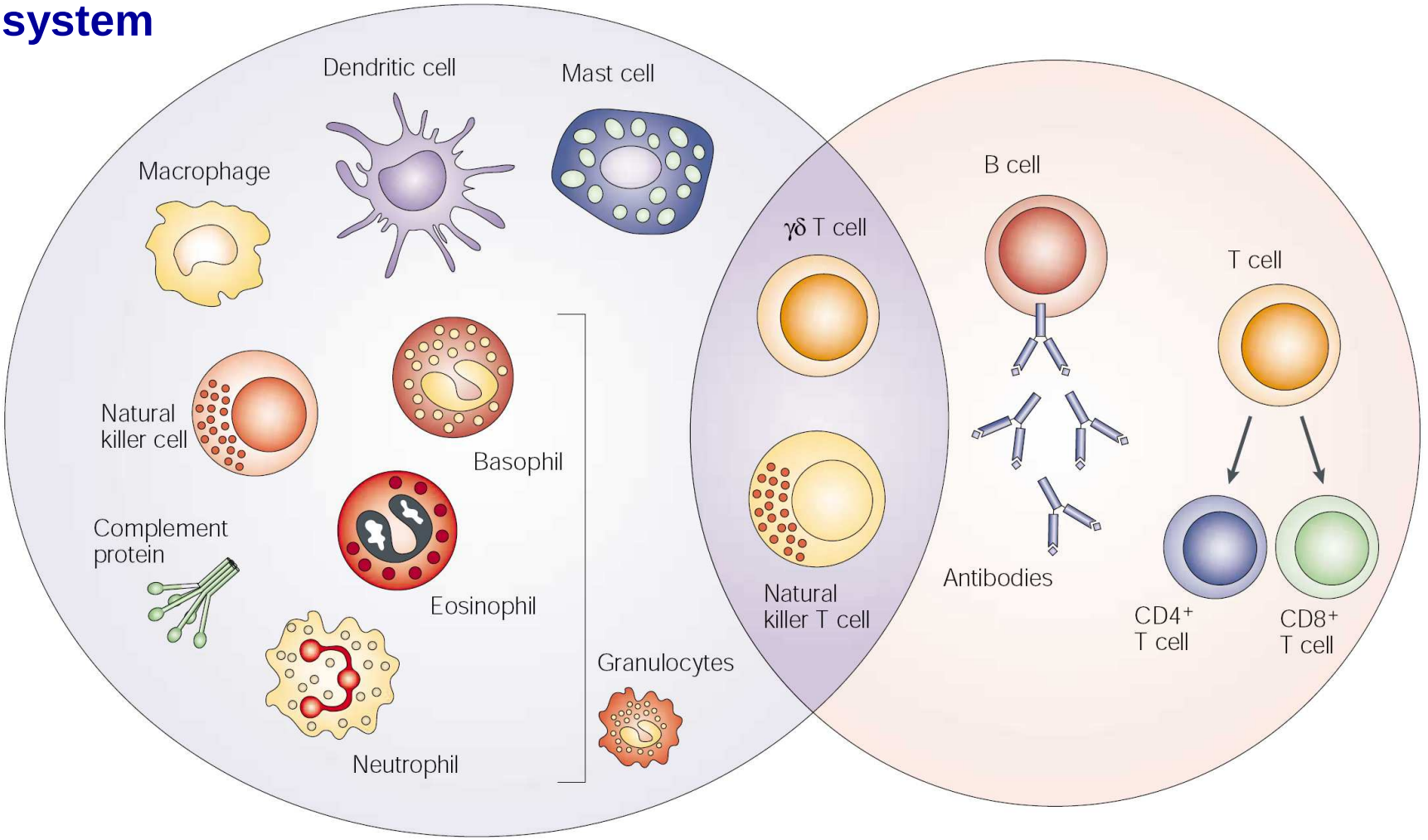
- B lymphocytes
- T lymphocytes



„Key players“ of the immune system

Innate immune system

Adaptive immune system



Dranoff D et al. ***Nat Rev 2004***

Innate Immune system

- Is the first line of defence
  after the skin/epithelial/
  mucosal barrier is breached

- Comprises of a cellular arm (cells)
  and
  a humoral arm (soluble factors)

- At best: Can eradicate infection

- At worst: Slows down/delays infection until adaptive immune response is generated

Cells of the innate immune system

What Do They All Do?

Neutrophils – kill rapidly dividing bacteria

Eosinophils - kill parasites (worms)

NK cells - kill virus-infected cells

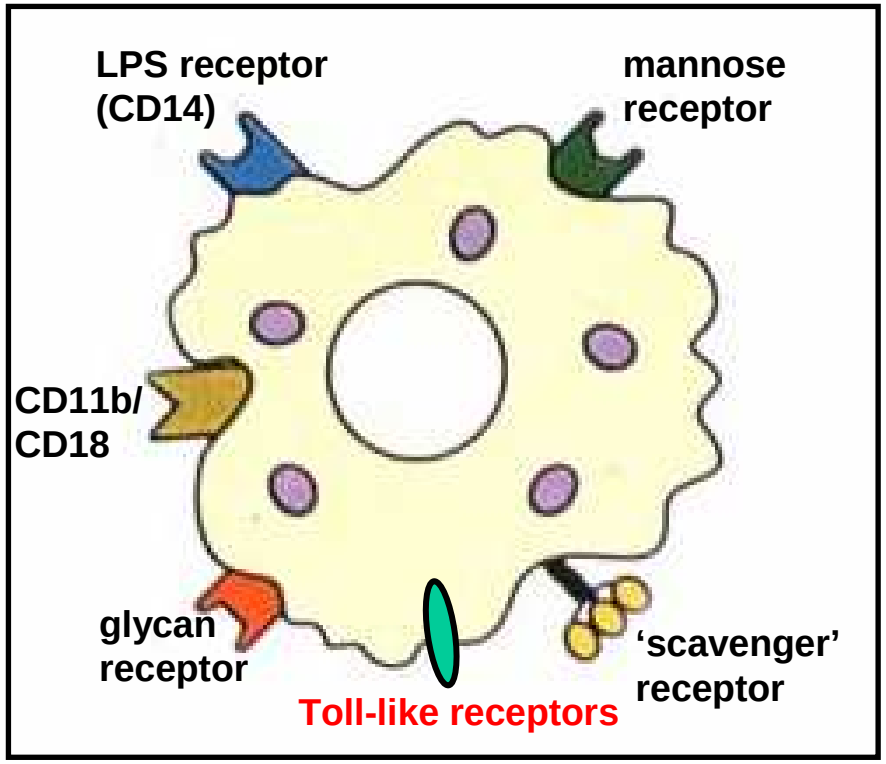
Macrophages – kill intracellular pathogens

(also sentinel cells raise the alarm following infection)

Dendritic cells - activate adaptive immune response

Mast cells – trigger inflammatory response

Effector cells of the innate immune system



Neutrophils/Monocytes/ Macrophages/Dendritic cells/Eosinophils

recognise pathogens as:

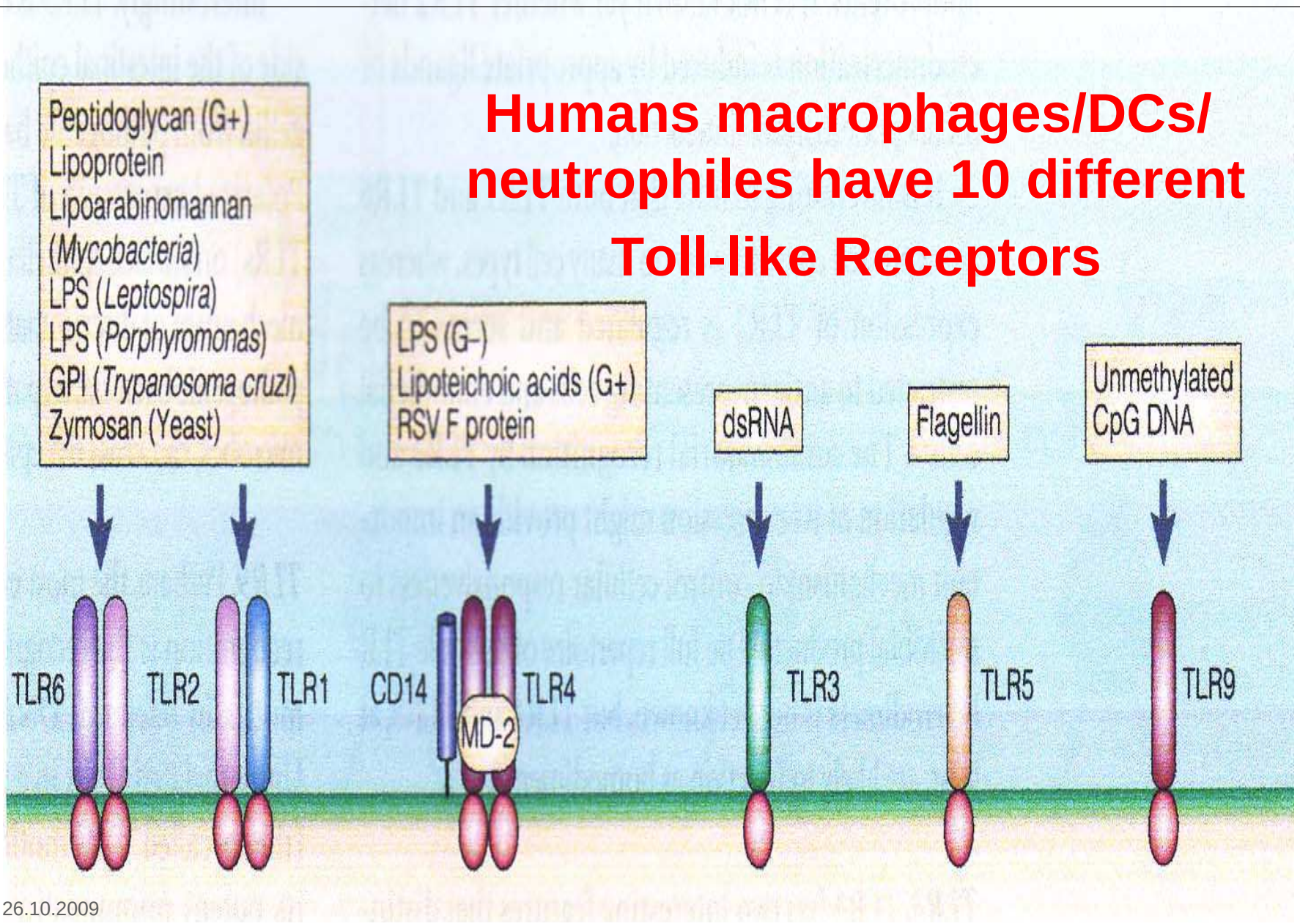
"dangerous non-self"

via

Pattern Recognition Receptors (PRR's)

(approx 20 or so)

TLRs recognise different pathogen structures



Humans macrophages/DCs/ neutrophiles have 10 different Toll-like Receptors

Patients with systemic meningococcal disease associated with a TLR4 gene polymorphism

The adaptive immune system

- **The adaptive immune response allows recognition of a wide range of varying pathogens**
- **A memory population of cells is created that can respond more rapidly and efficiently to subsequent infections**
- **The response to a primary infection is relatively slow (days)**
- **Only upon re-exposure is the adaptive response rapid and efficient**
- **Cellular arm and a humoral arm (antibodies)**

Cells of the adaptive immune system
B and T cells

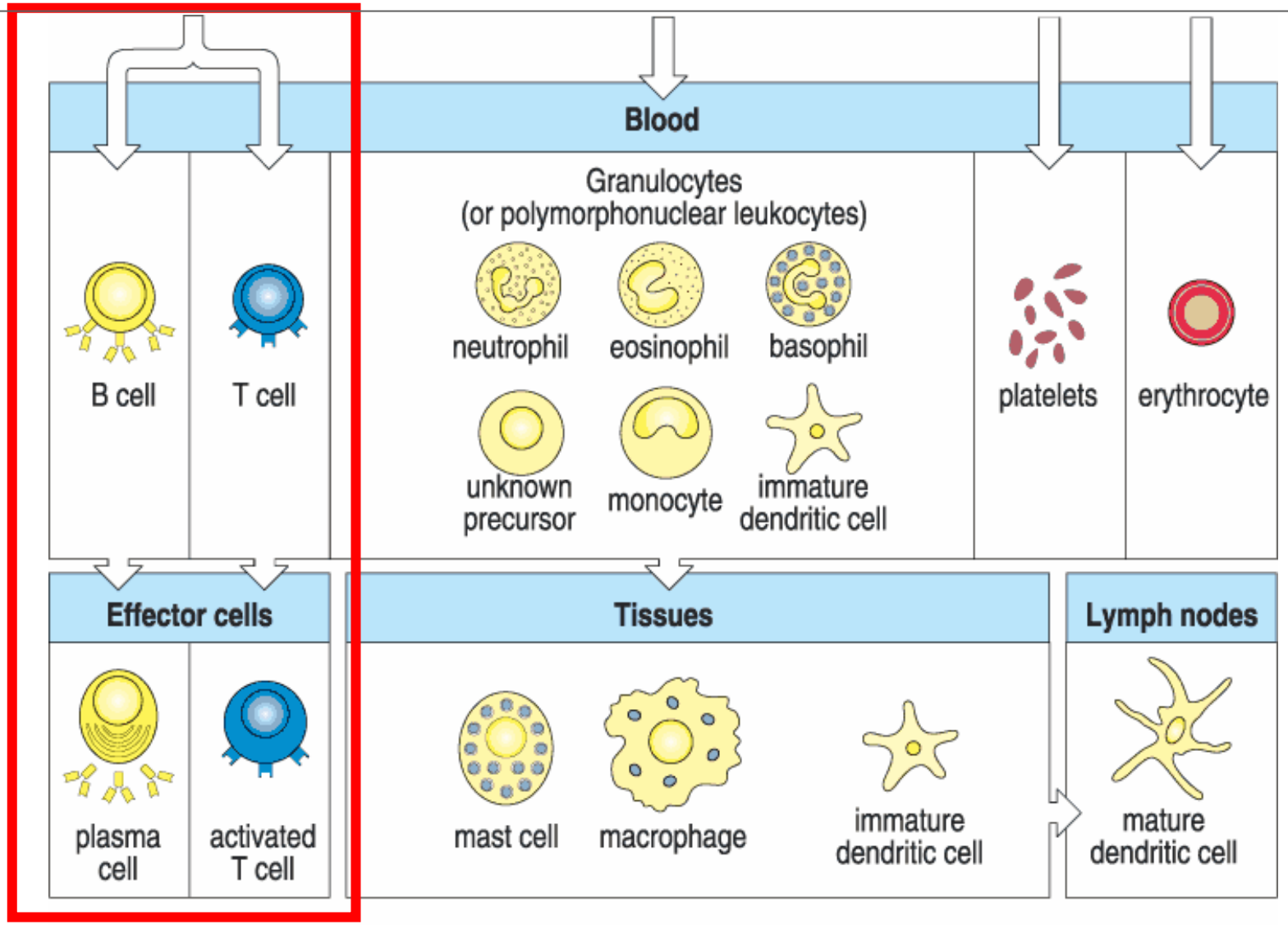
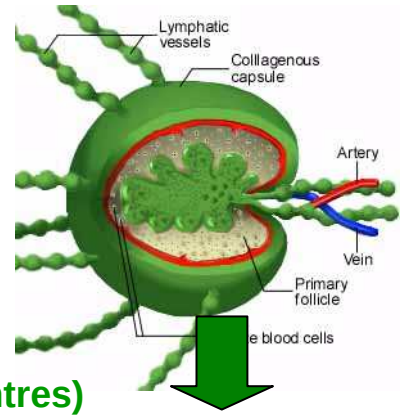


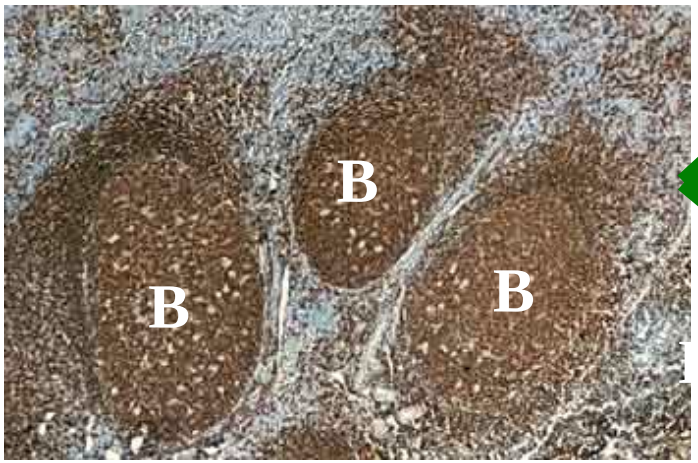
Fig 1.3 part 2 of 2

Where B cells do their thing

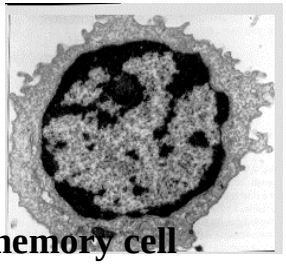
lymph node



follicles (germinal centres)

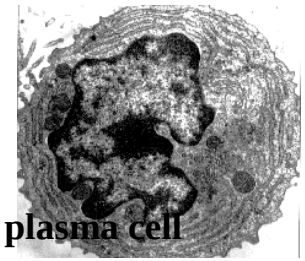


periphery



memory cell

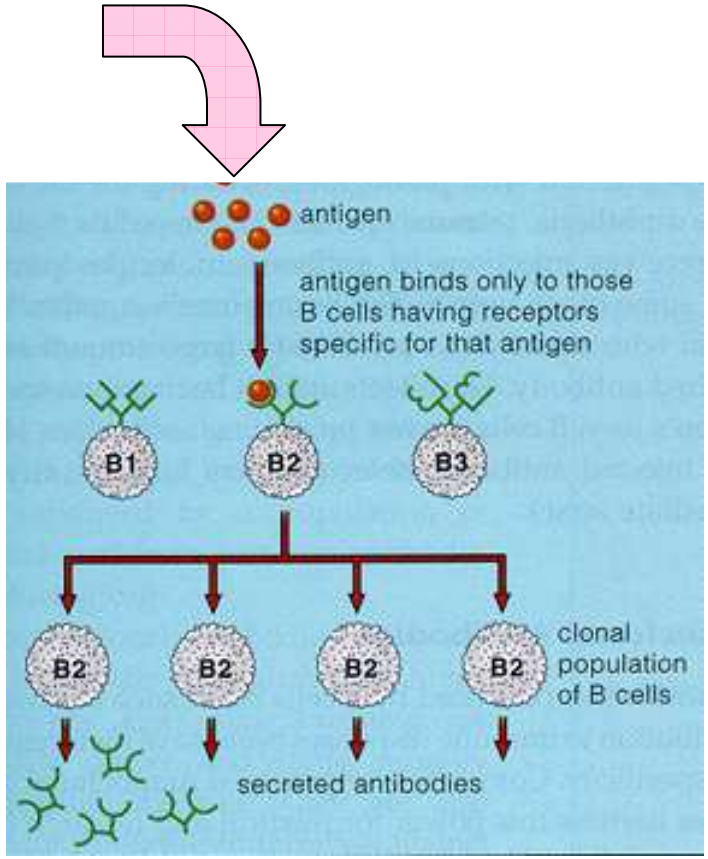
bone marrow



plasma cell

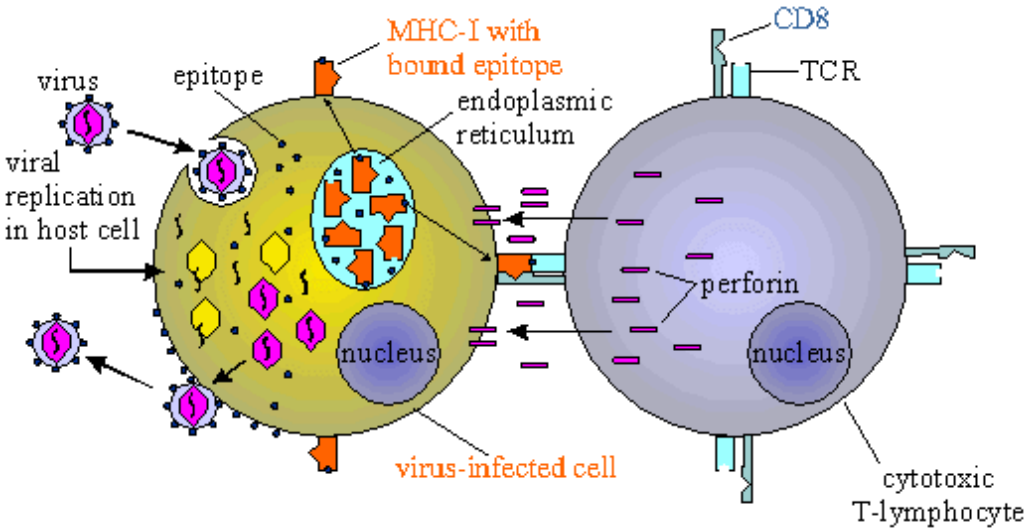
Clonal selection of B cells

- Each individual B cell makes only one set of variable regions with a highly restricted specificity for antigen
- An antigen entering the body "selects" only those very few (from the billions available) to activate to do their thing
- The end result is the the production of plasma cells – "antibody factories" – that make antibodies of the "right fit"

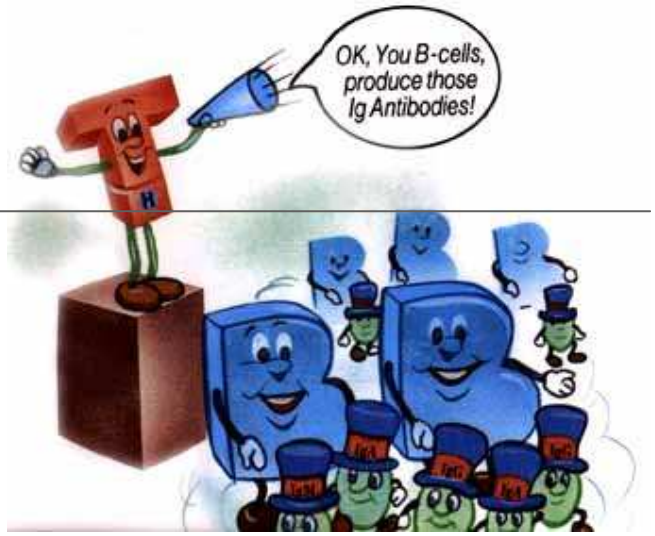


Cytotoxic T-Cells

- Extremely important in eliminating virally-infected cells and leukemic cells
- Almost all nucleated cells (the targets of viral infection) express MHC Class I
- Recognition of peptide/ MHC Class I via TCR is stabilised by CD8

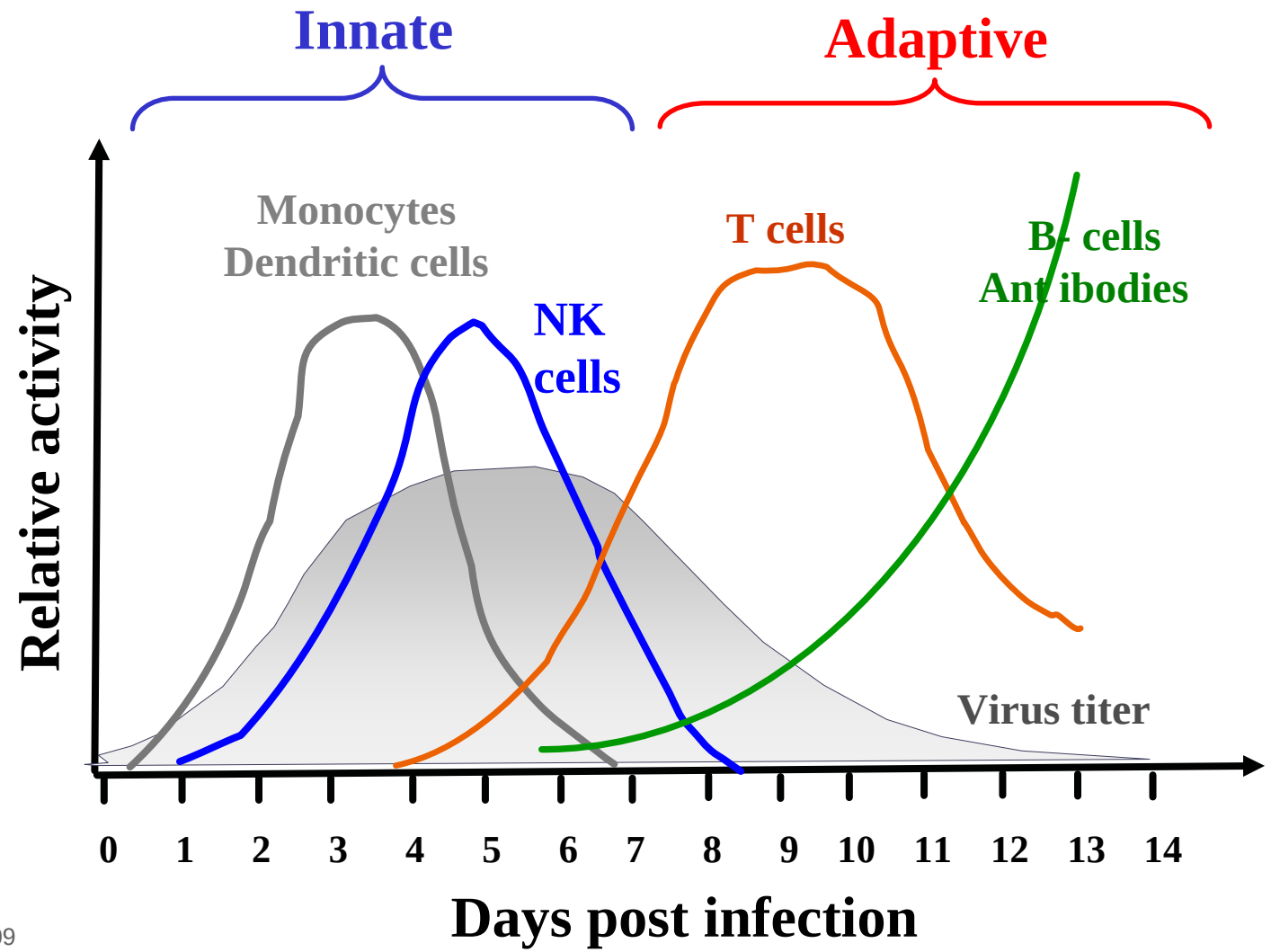


Helper T-Cells



- Orchestrators of an immune response
- Drive and direct inflammatory and antibody responses
- See foreign peptides via MHC Class II; TCR recognition stabilised via CD4
  [CD4 is the major receptor for HIV]
- Only "antigen presenting cells" express MHC Class II (e.g. macrophages, DC, B cells)

The Innate Immune Response Slows Down A Pathogenic Viral Infection But The Adaptive Response Clears It



Press Release Sept 2003

Boy Leaves Bubble After Gene Therapy Fixes Adaptive Immune System

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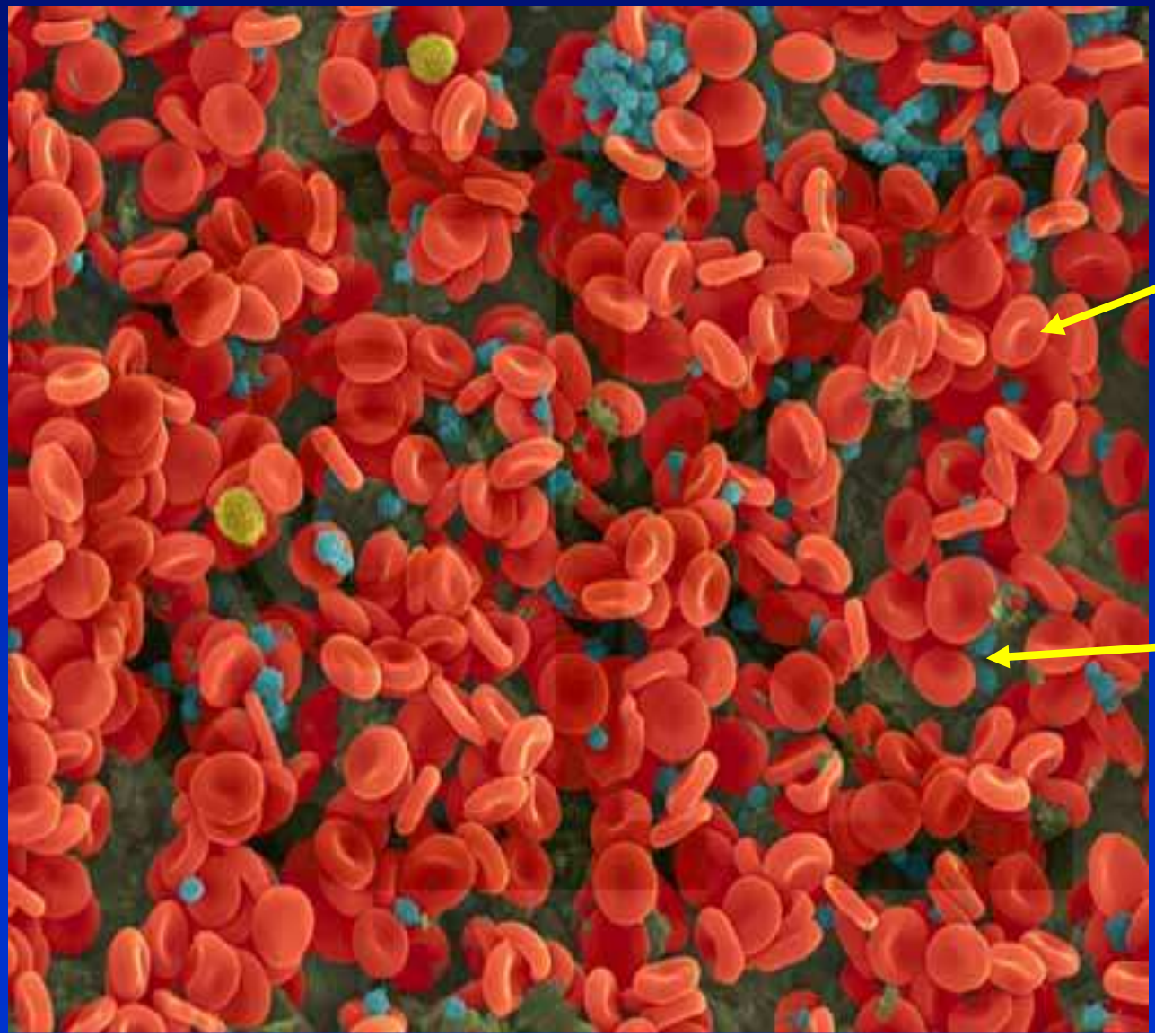
Wilco Conradi, a 2-year-old "bubble boy" from the Netherlands, who recently underwent gene therapy that has apparently cured his disease and allowed him to leave his plastic bubble.

He suffers from Severe Combined Immunodeficiency (SCID) an inherited disease that occurs in 1 in 75,000 births.

The illness renders the immune system ineffective against microbes ordinarily harmless to people with normal resistance.

Such Children Have No Adaptive Immune System
No T cells or B cells

Blood cells



Red blood cells

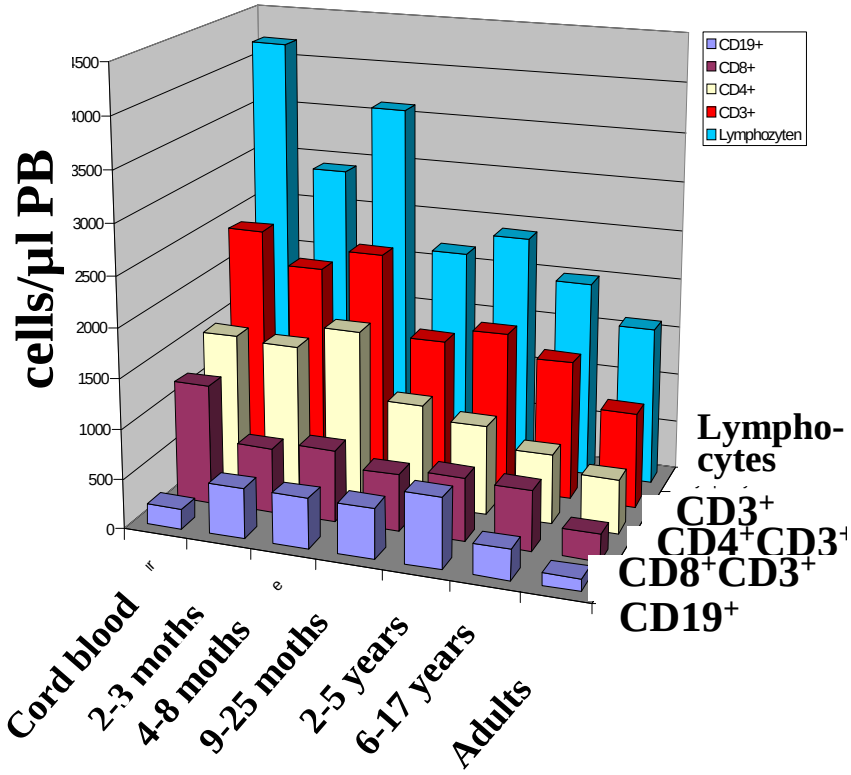
White blood cells

Lymphocytes

Lymphocytes: 2-5/nl 2000 – 5000/µl

- Less: Lymphopenia, p. e. HIV
- More: Lymphozytosis, p. e. various viral infections, Leukemia

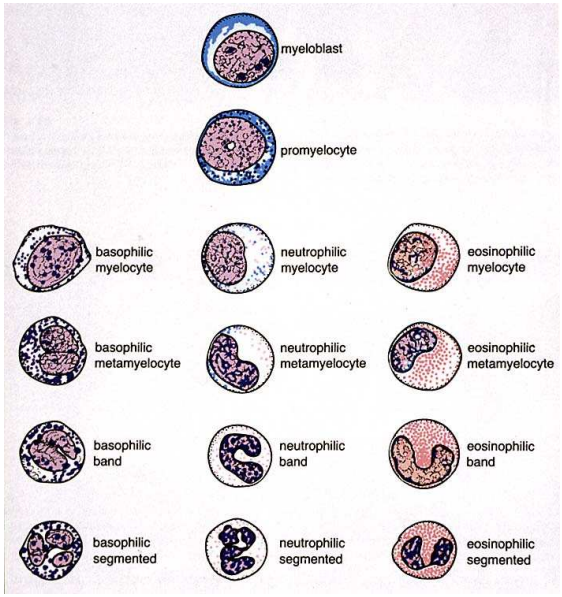
5. percentile of lymphocyte subsets



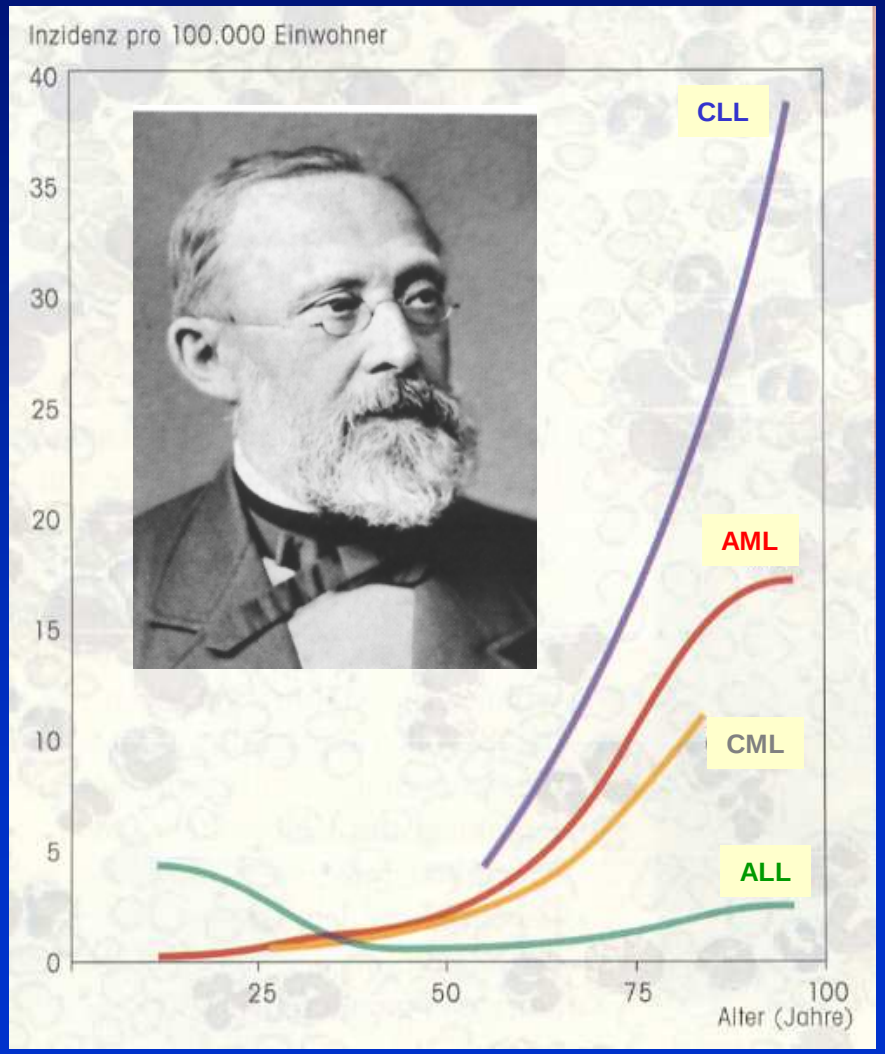
Neutrophil granulocytes

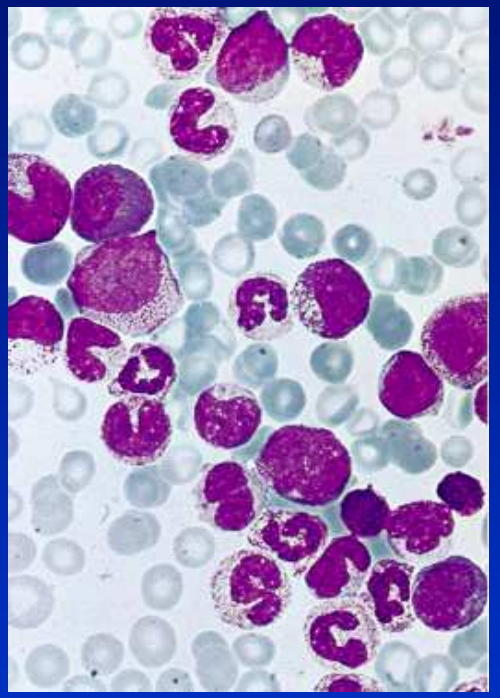
Neutrophils: 2-6/nl 2000 – 6000/µl

- Less: Neutropenia, Agranulozytosis, p.e. Bone marrow aplasia, Leukaemia, Chemotherapy, post-infection after viral diseases, Typhus
- More: Granulozytosis, p. e. acute (germs) Infection, Appendicitis, Leukaemia



Leukaemia





Leukaemia is a clonal disorder

Kindly provided by PD Dr. H. Martin

Leukaemia, the current hypothesis

- Defect in maturation of white blood cells
- May involve a block in differentiation and/or a block in apoptosis
- Acquired genetic defect
- Initiating events unclear
- Transformation events involve acquired genetic changes
- Chromosomal translocation implicated in many forms of leukaemia
- Unspecific clinical signals like paleness, tired, exhausted,
- Sometimes typical changes in the blood and bone marrow

Leukaemia

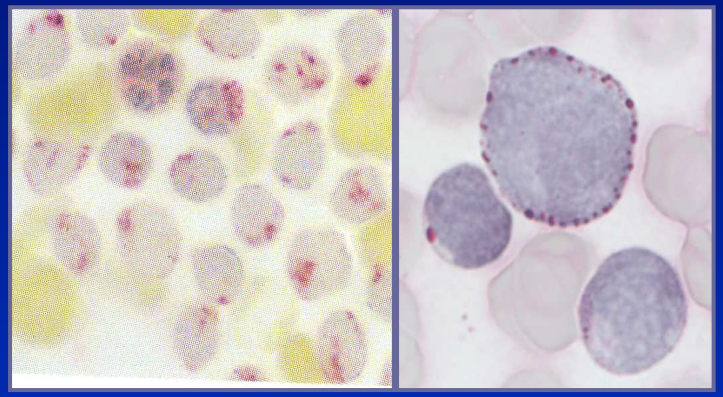
- **Akute Leukaemia**
  - Akute Lymphoblastic Leukaemia (ALL)
  - Akute Myeloid Leukaemia (AML)

- **Chronic Leukaemia**
  - Chronic Lymphoblastic Leukaemia (CLL)
  - Chronic Myeloid Leukaemia (CML)

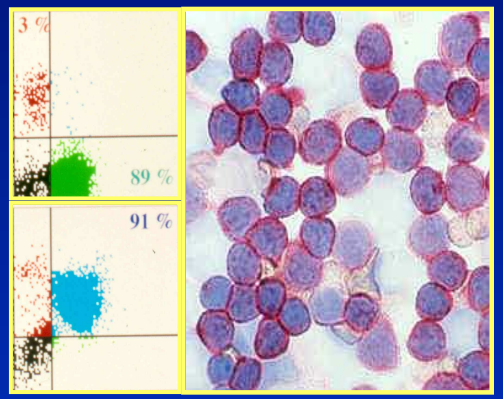
Diagnosis of Leukaemia

Morphology

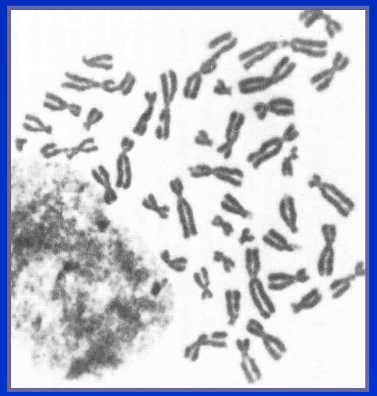
Cytochemistry

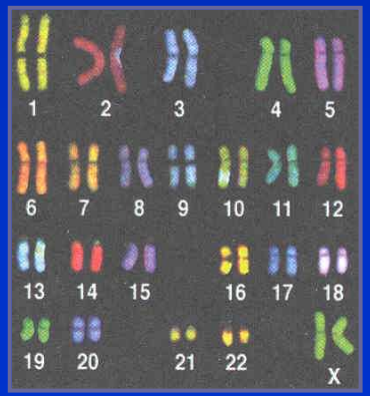


Immunology

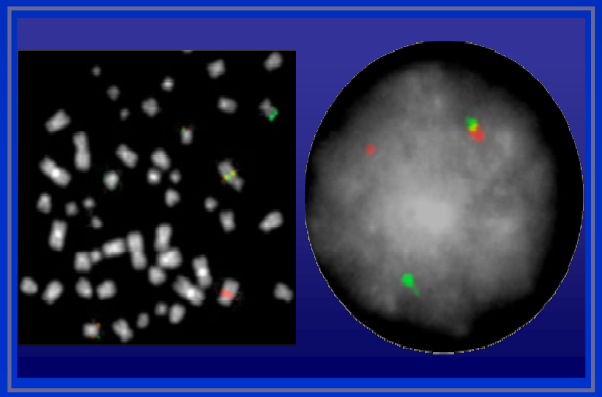


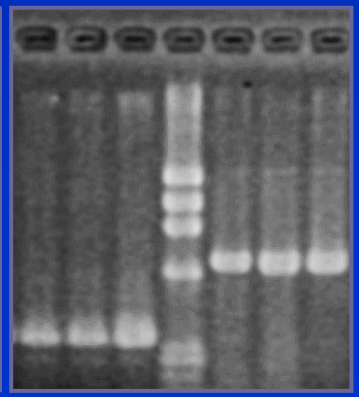
Chromosome analysis



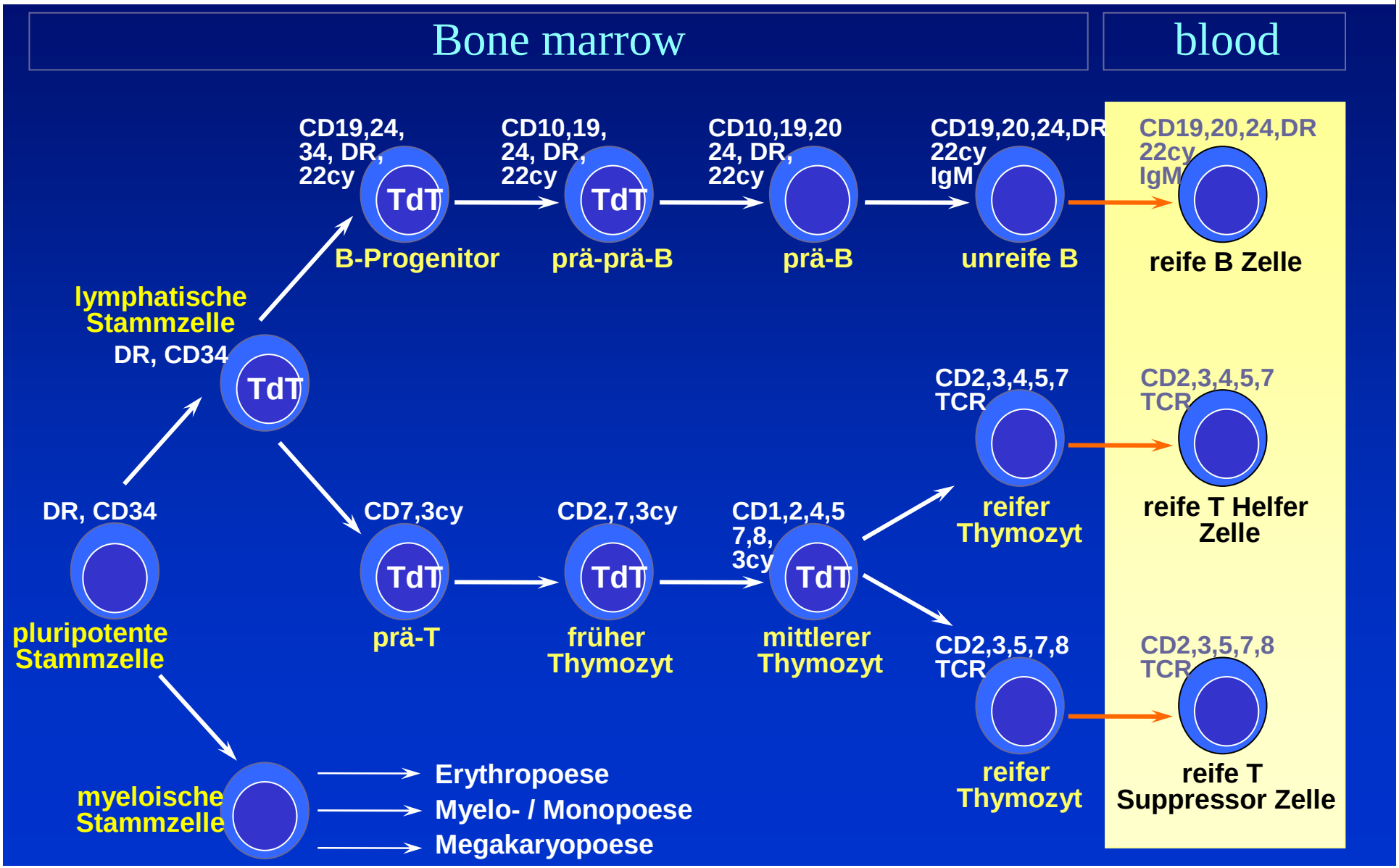


Cyto- / Molecular genetics

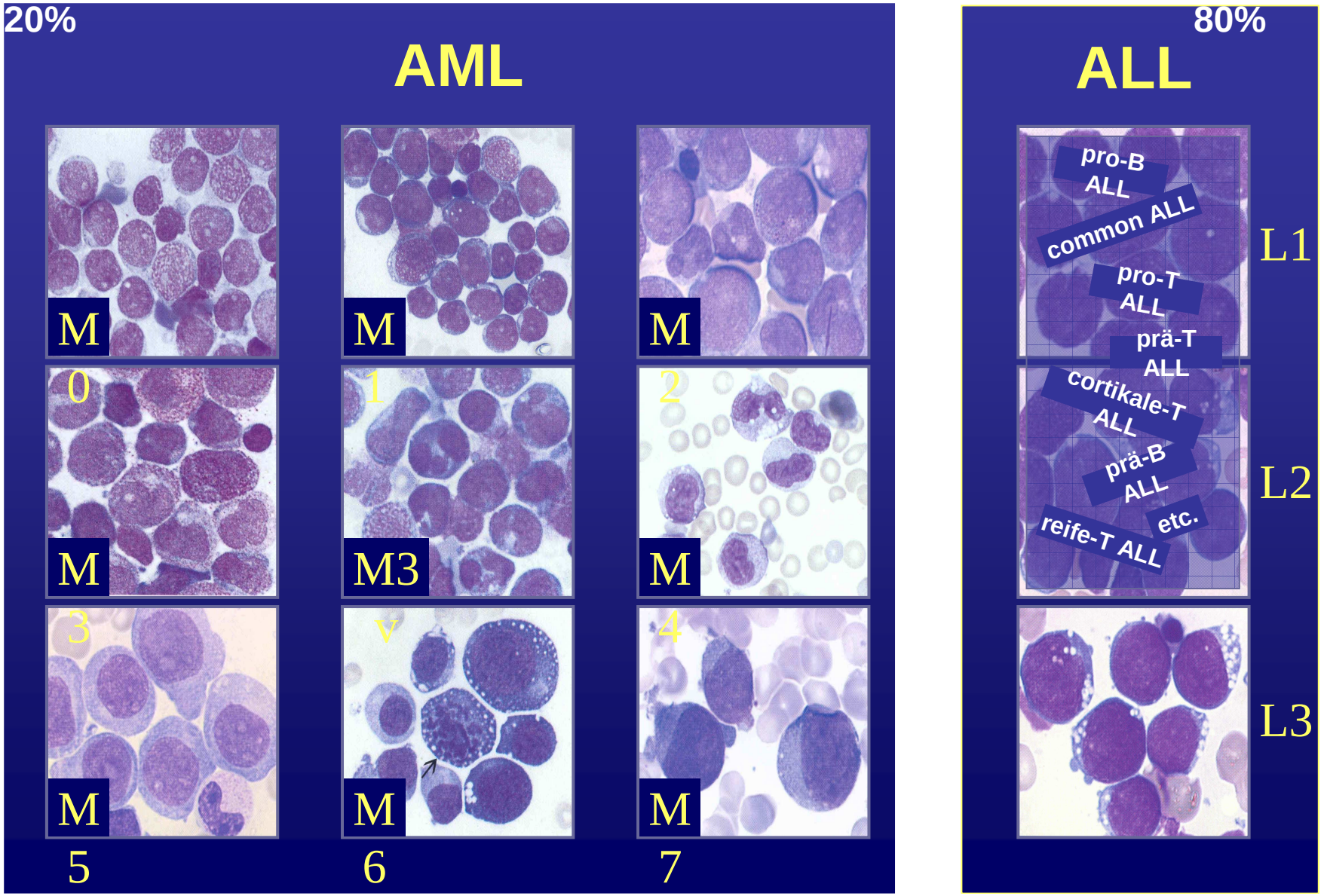




Possibility for clonal disorder of leukaemia



Acute Lymphatic and Myeloid Leukaemia in Children



Immunophenotyping in AML

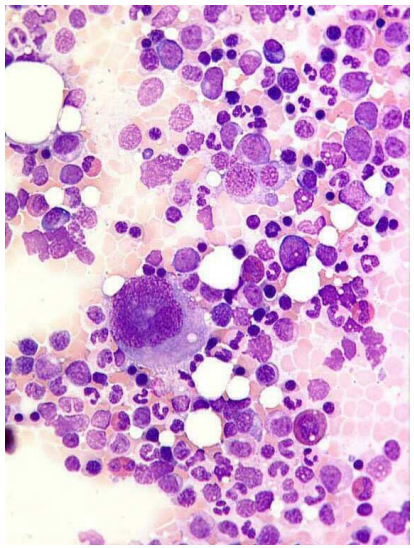
	FAB-Subtypen (AML)							
	M0	M1	M2	M3	M4	M5	M6	M7
HLA-DR	+	+	+/-	-	+	+	+/-	+/-
CD34	+	+	+/-	-	+/-	+/-	+/-	+/-
CD13	+/-	+	+	+/-	+	+/-	+/-	+/-
CD33	+/-	+	+	+	+	+	+	+/-
CD65	+/-	+	+	+/-	+	+	+/-	+/-
CD14	-	-	-	-	+	+/-	-	-
CD15	-	-	+	-	+	+/-	+/-	-
CD235a	-	-	-	-	-	-	+	-
CD41	-	-	-	-	-	-	-	+
CD61	-	-	-	-	-	-	-	+

Labor f. Stammzelltransplantation und Immuntherapie / Dr. U. Köhl / S. Wehner

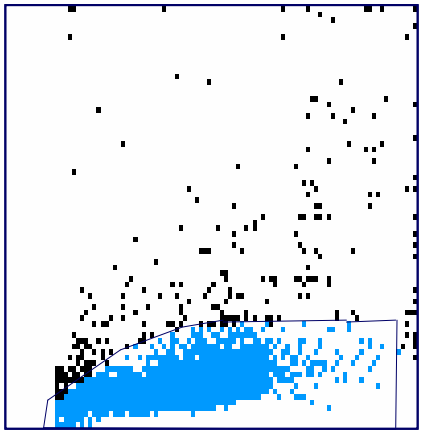
Stand 09/2004

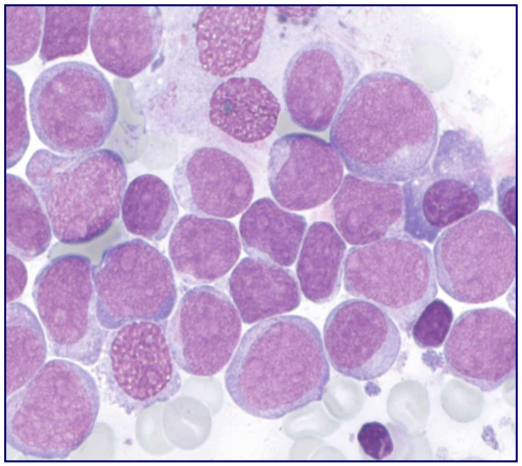
Akute Myelogenous Leukaemia

(FAB-AML-M1)

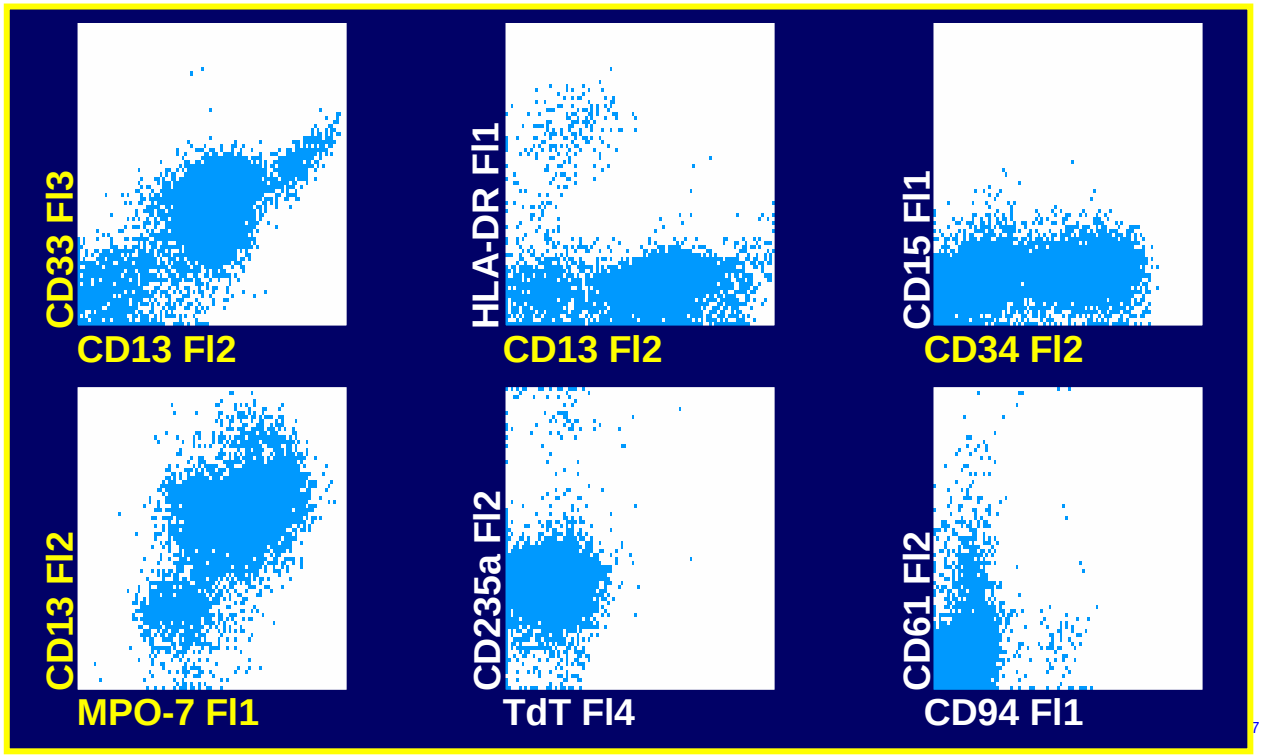


Normal bone marrow





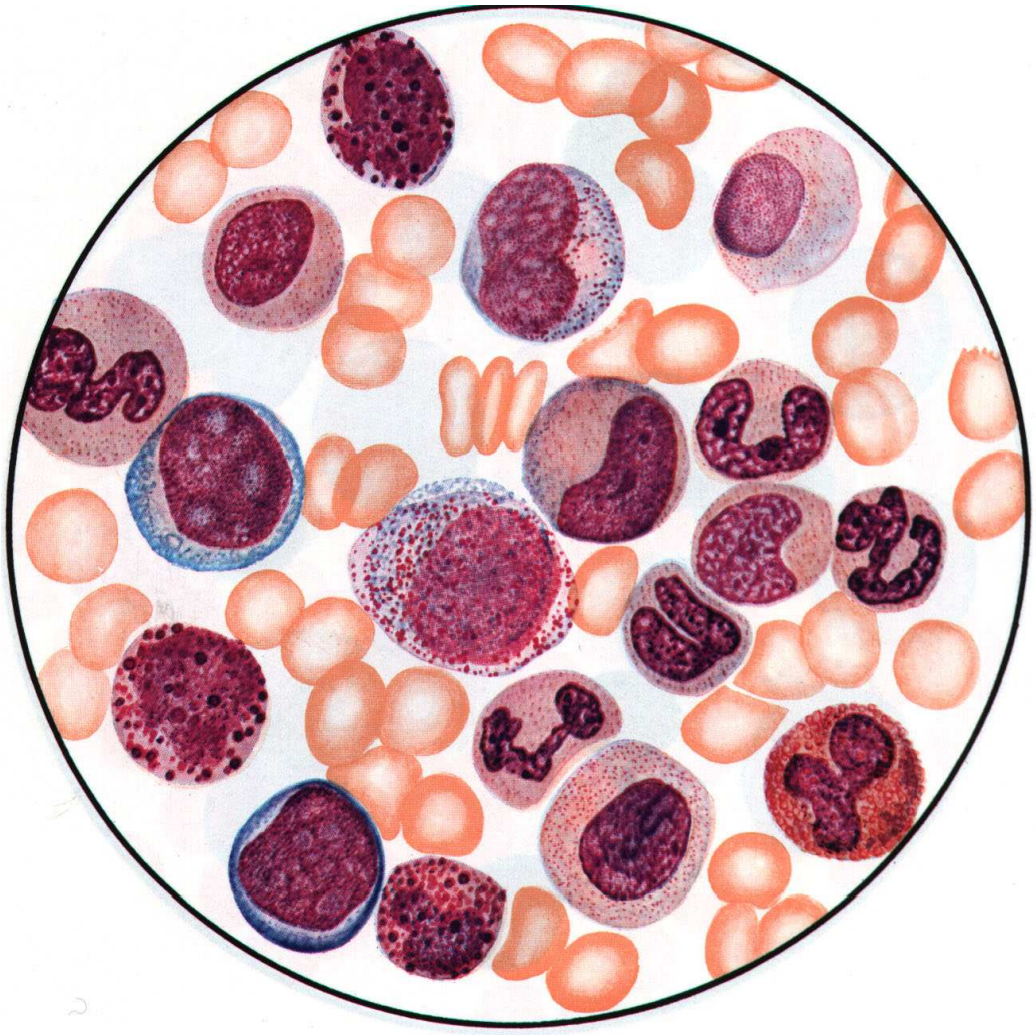
AML



Chronic Myeloid Leukaemia

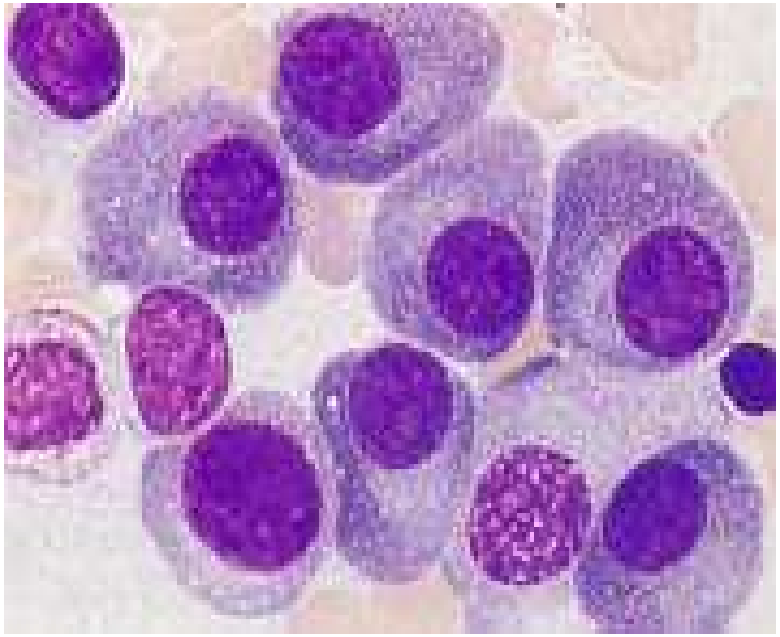
- Malignancy of the haemopoietic system
- Transformation of the pluripotent stem cell
- 9;22 translocation giving rise to the Philadelphia (Ph') chromosome
- Creation of a leukaemia specific mRNA (BCR-ABL)
- Resistance to apoptosis, abnormal signalling and adhesion

Chronic Myeloid Leukaemia



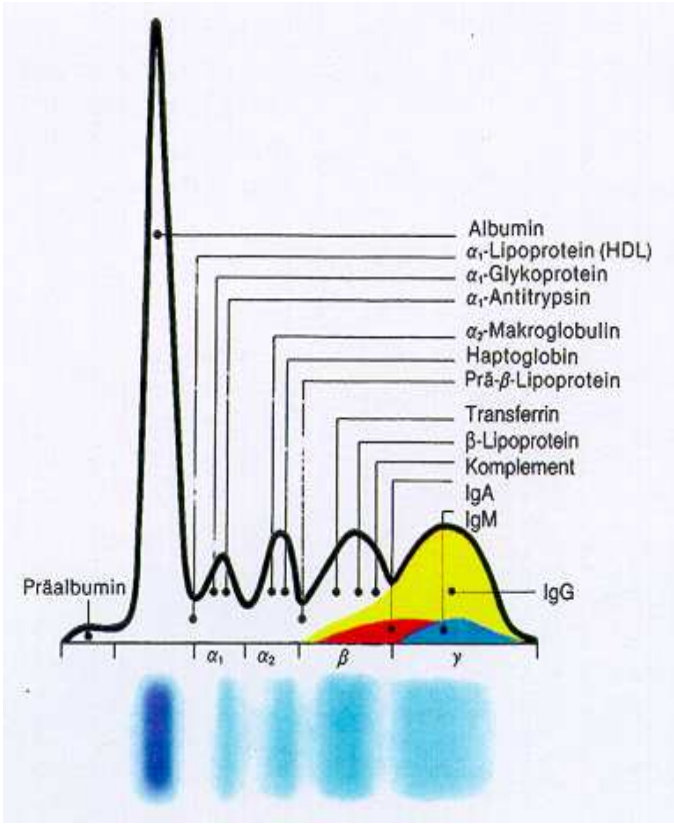
Multiple Myeloma

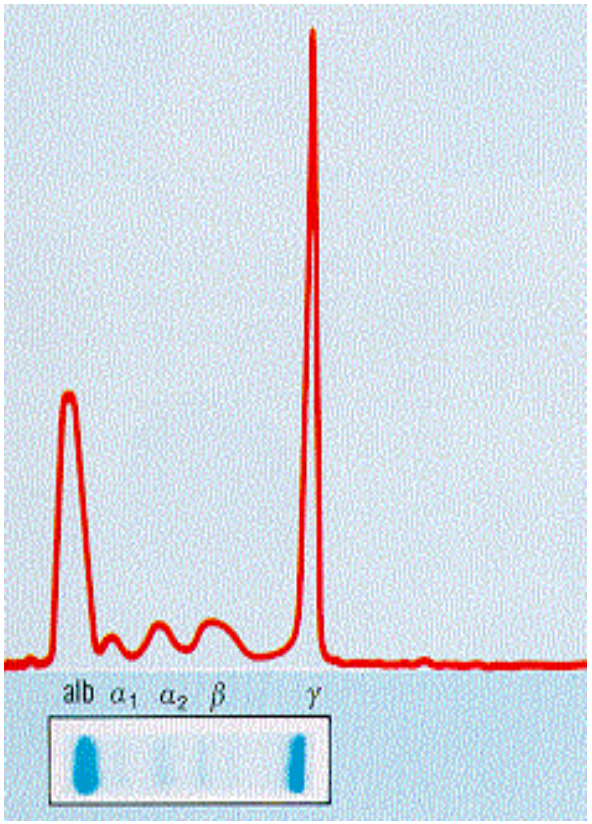
- **Maligne haematological disease**
- **Monoklonal proliferation of plasma cells**



Multiple Myeloma

Serum elektrophoresis





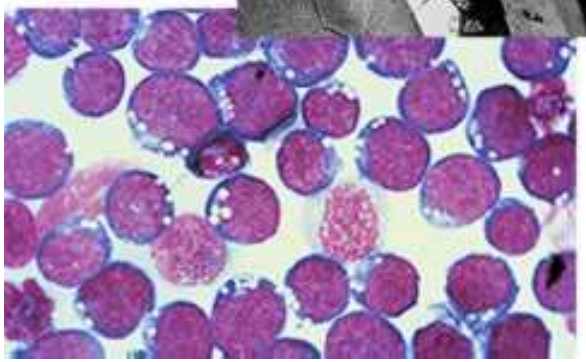
normal

M protein

Kindly provided by PD Dr. H. Martin

Burkitt's lymphoma: A highly malignant B cell tumour

Dennis Burkitt



BL cells in suspension

Can double in size by 24 hours

6 days treatment

Blood cells

Hb: 13 g/dl

MCV: 90 fl

Thombo: 250 000/µl

Leuko: 8 000/µl

Granulo: 3 000/µl

Lympho: 4 000/µl

?

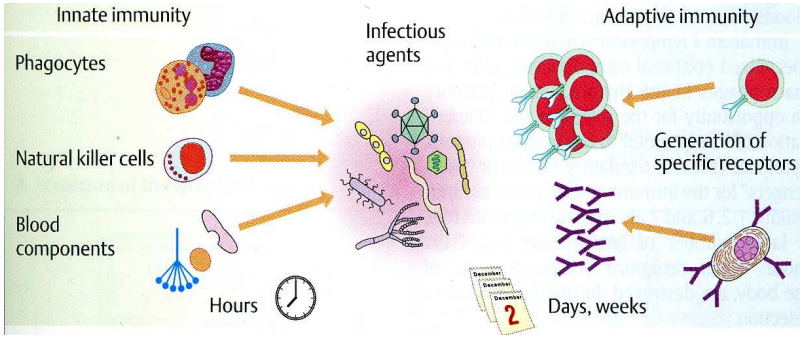
Normal

Cellular components of the blood

Cells	Concentration	Duration of living	„juvenile form“	
Erythrocytes	4 800 000/µl	100-120 days	Retikulozytes **1(**-3) days	
Platelets	200 000/µl	7-12 days		
Granulocytes	4 500/µl	2-3 days	„Stabkerniger“	
Lymphozytes	3000/µl	up to many years		

Take home message

- The production of cellular blood cells is called haematopoiesis (haemopoiesis)
- Differentiation of granulocytes in the bone marrow, of T- and B-cells in the lymohoid organs
- Innate immune system and adaptive immune system



- Living duration of blood cells: 100-120 days (Ery), 7-12 days (Thrombo), 2-3 days (Granulo) and years (Lymph)
- Haematopietic diseases can be related to the various cells types and lineage commitment