MEDICAL UNIVESITY- PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF PROPEDEUTICS OF INTERNAL DISEASES

Lecture: The blood- white cells. Common diseases

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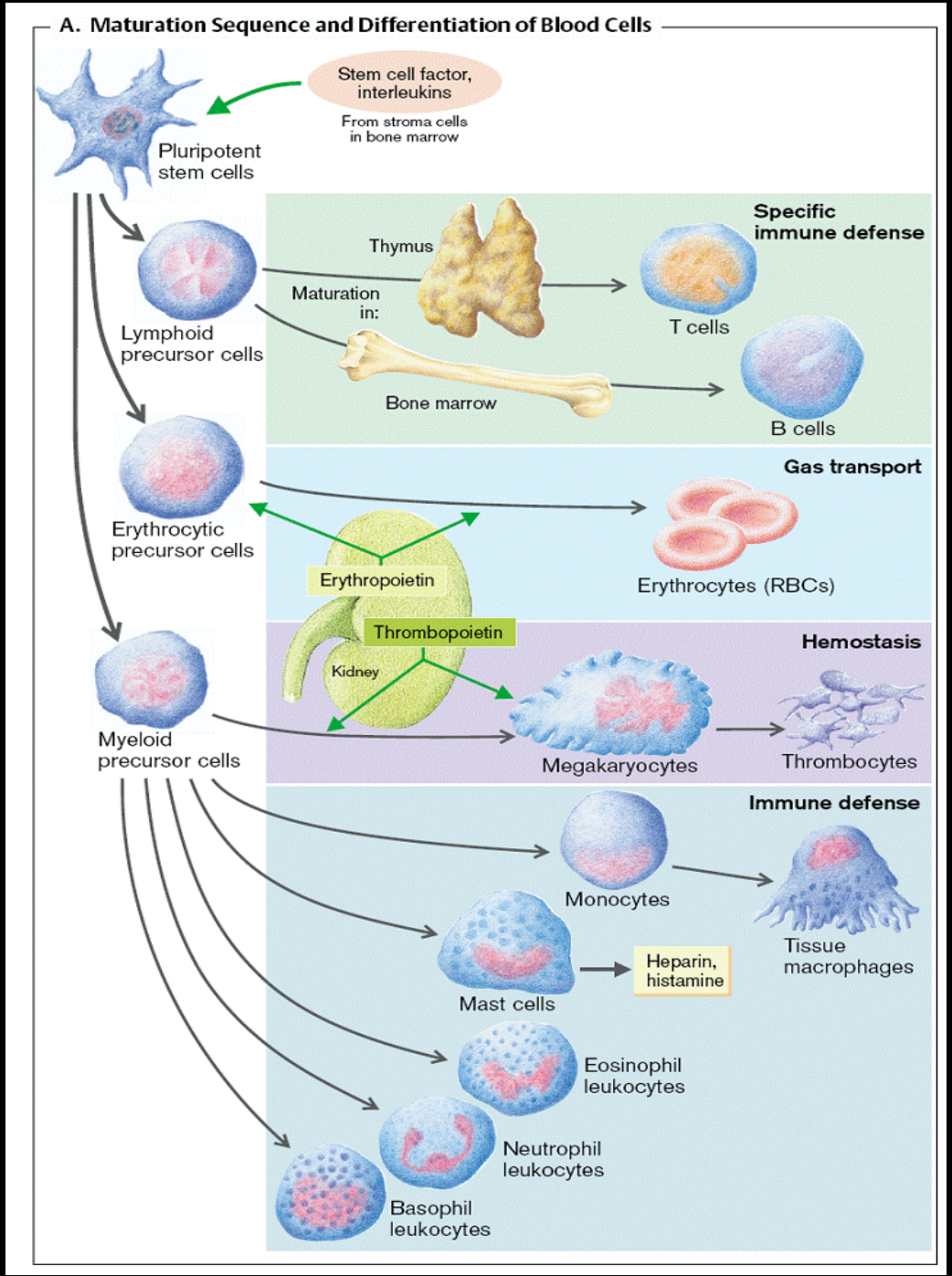
Maturation and differentiation of blood cells

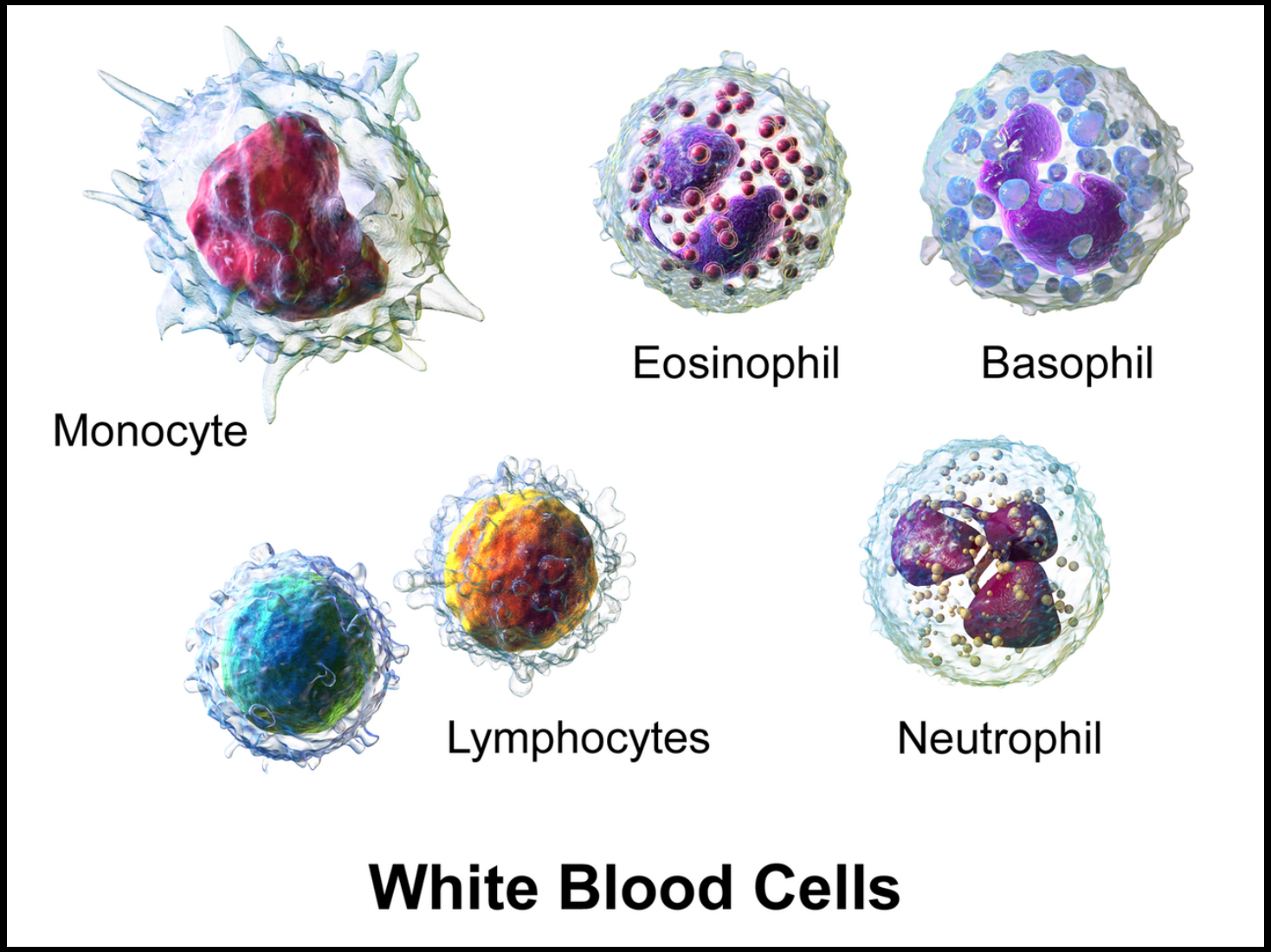
- All white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells. Leukocytes are found throughout the body, including the blood and lymphatic system.



White blood cells types

Cell type	Function	Count (% of leukocytes)
Neutrophilic band granulocytes (band neutrophil)	Precursors of segmented cells that provide antibacterial immune response	0–4%
Neutrophilic segmented granulocyte (segmented neutrophil)	Phagocytosis of bacteria; migrate into tissue for this purpose	50–70%
Lymphocytes (B- and T-lymphocytes, morphologically indistinguishable)	B-lymphocytes (20% of lymphocytes) mature and form plasma cells → antibody production. T-lymphocytes (70%): cytotoxic defense against viruses, foreign antigens, and tumors.	20–50%
Monocytes	Phagocytosis of bacteria, protozoa, fungi, foreign bodies. Transformation in target tissue	2–8%
Eosinophilic granulocytes	Immune defense against parasites, immune regulation	1–4%
Basophilic granulocytes	Regulation of the response to local inflammatory processes	0–1%

Leucocytes

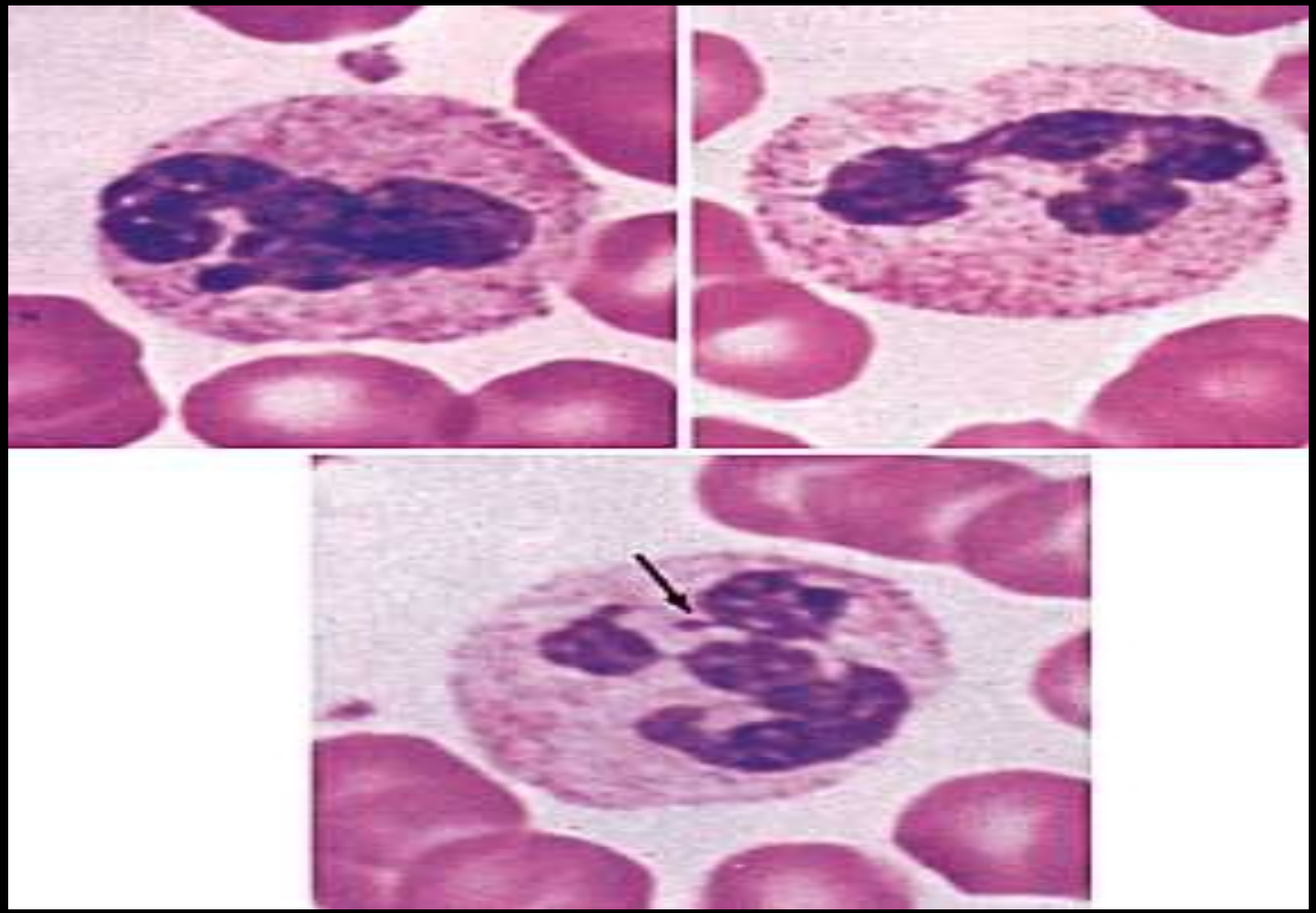

Monocyte
Eosinophil
Basophil
Lymphocytes
Neutrophil
White Blood Cells

Neutrophils

- Neutrophils are the most changeable group of leucocytes. Their num-ber increases in many infections, intoxication, and tissue decomposition. Normal neutrophil count includes 1-6% stab (band) and 45-70% segmented neutronphils. Neutrophilia (neutrophilosis) is characterized not only by the increased total number of neutrophils but also by the appearance in the blood of imma-ture forms: the quantity of stab neutrophils increases; juvenile neutrophils (absent in norm) and even myelocytes appear. This rejuvenation of the neu-trophil composition is called the blood shift to the left, because the figures grow on the left side of the laboratory blank where leucocyte counts are nor-mally recorded. Regenerative and degenerative shifts are distinguished. In the regenerative shift to the left the mentioned changes are observed, while in the degenerative shift to the left, the number of stab neutrophils only increas-es along with the degenerative changes in neutrophils in the absence of leu-cocytosis (vacuolization of cytoplasm, nuclear pyknosis, etc.). The regenera-tive shift indicates active protective response of the body, while the degenera-tive one indicates the absence of this response.
- The protective role of neutro-phils consists in phagocytosis, bactericidal action, and production of proteo-lytic enzymes promoting resolution of necrotized tissue and healing of wounds. The regenerative shift to the left occurs most frequently in the pres-ence of an inflammatory or necrotic focus. An especially marked shift to the left (to promyelocytes and even myeloblasts in the presence of significant leucocytosis) is called leucemoid reaction

- The number of neutrophils decreases (absolute neutropenia) in the presence of the inhibiting action of toxins of some microbes (e.g. causative agents of typhoud fever or sepsis) and viruses, ionizing radiation, and some medicinal preparations. In grave toxicosis, granularity of neutrophils becomes even more pronounced, the granules become larger and coloured; this granulation is called toxicogenic.

Neutrophils



Lymphocytes

- Lymphocyte count is 18-40% in norm. The absolute number of lymphocytes increases less frequently. Lymphocytosis occurs dur-ing recovery in acute infectious diseases, infectious mononucleosis, infectious lymphocytosis, lymphoid leucosis, rubella, brucellosis, and thyrotoxico-sis. More frequently lymphocytosis is only relative, associated with a de-creased number of neutrophils (like relative lymphopenia in the presence of increased number of neutrophils). Absolute lymphopenia occurs in radiation sickness and systemic affections of the lymphatic system: lymphogranuloma-tosis and lymphosarcoma. Indistinct spots are sometimes revealed in blood smears; they are stained like the nuclear substance of leucocytes. These are Botkin-Gumprecht shadows, the remains of nuclear chromatin characterizing brittleness of leu-cocytes due to which they decompose (leucocytolysis).

Lymphocytes- types

Lymphocytes are much more common in the lymphatic system than in blood. Lymphocytes are distinguished by having a deeply staining nucleus that may be eccentric in location, and a relatively small amount of cytoplasm. Lymphocytes include:

- **B cells make antibodies that can bind to pathogens, block pathogen invasion, activate the complement system, and enhance pathogen destruction.**
- **T cells:**

-CD4+ helper T cells: T cells displaying co-receptor CD4 are known as CD4+ T cells. These cells have T-cell receptors and CD4 molecules that, in combination, bind antigenic peptides presented on major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. Helper T cells make cytokines and perform other functions that help coordinate the immune response. In HIV infection, these T cells are the main index to identify the individual's immune system integrity.

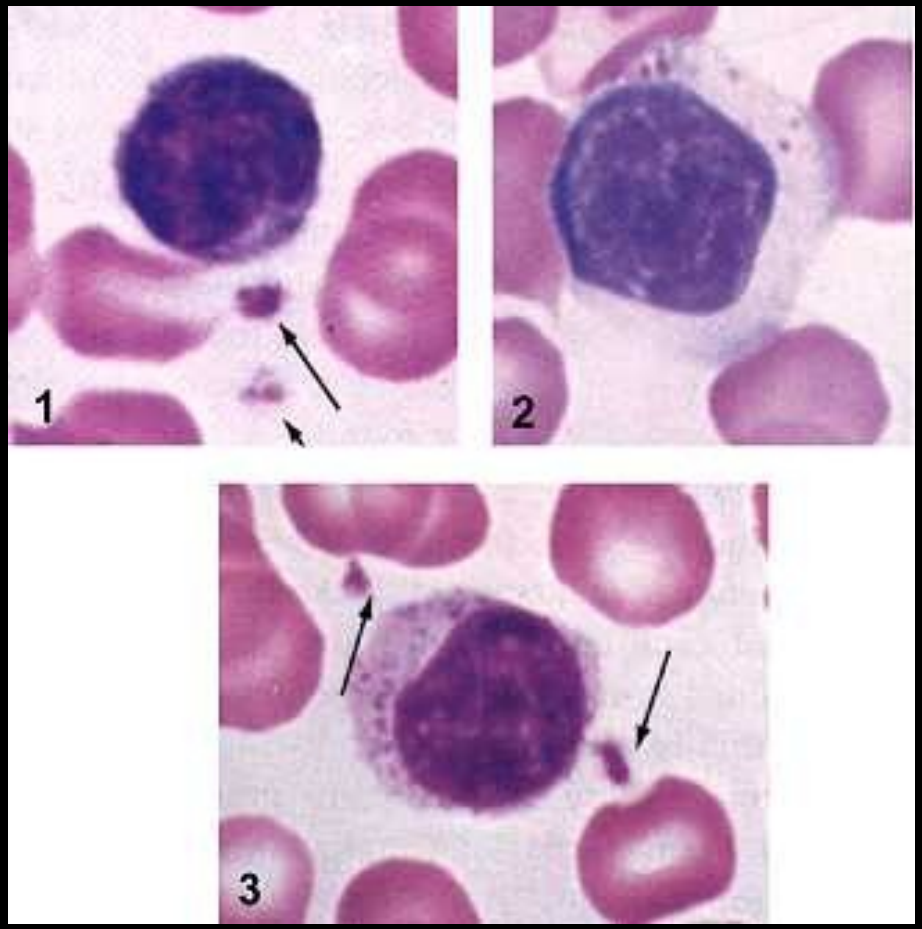
-CD8+ cytotoxic T cells: T cells displaying co-receptor CD8 are known as CD8+ T cells. These cells bind antigens presented on MHC I complex of virus-infected or tumour cells and kill them. Nearly all nucleated cells display MHC I.

-γδ T cells possess an alternative T cell receptor (different from the αβ TCR found on conventional CD4+ and CD8+ T cells). Found in tissue more commonly than in blood, γδ T cells share characteristics of helper T cells, cytotoxic T cells, and natural killer cells.

- **Natural killer cells**

  They are able to kill cells of the body that do not display MHC class I molecules, or display stress markers such as MHC class I polypeptide-related sequence A (MIC-A). Decreased expression of MHC class I and up-regulation of MIC-A can happen when cells are infected by a virus or become cancerous.

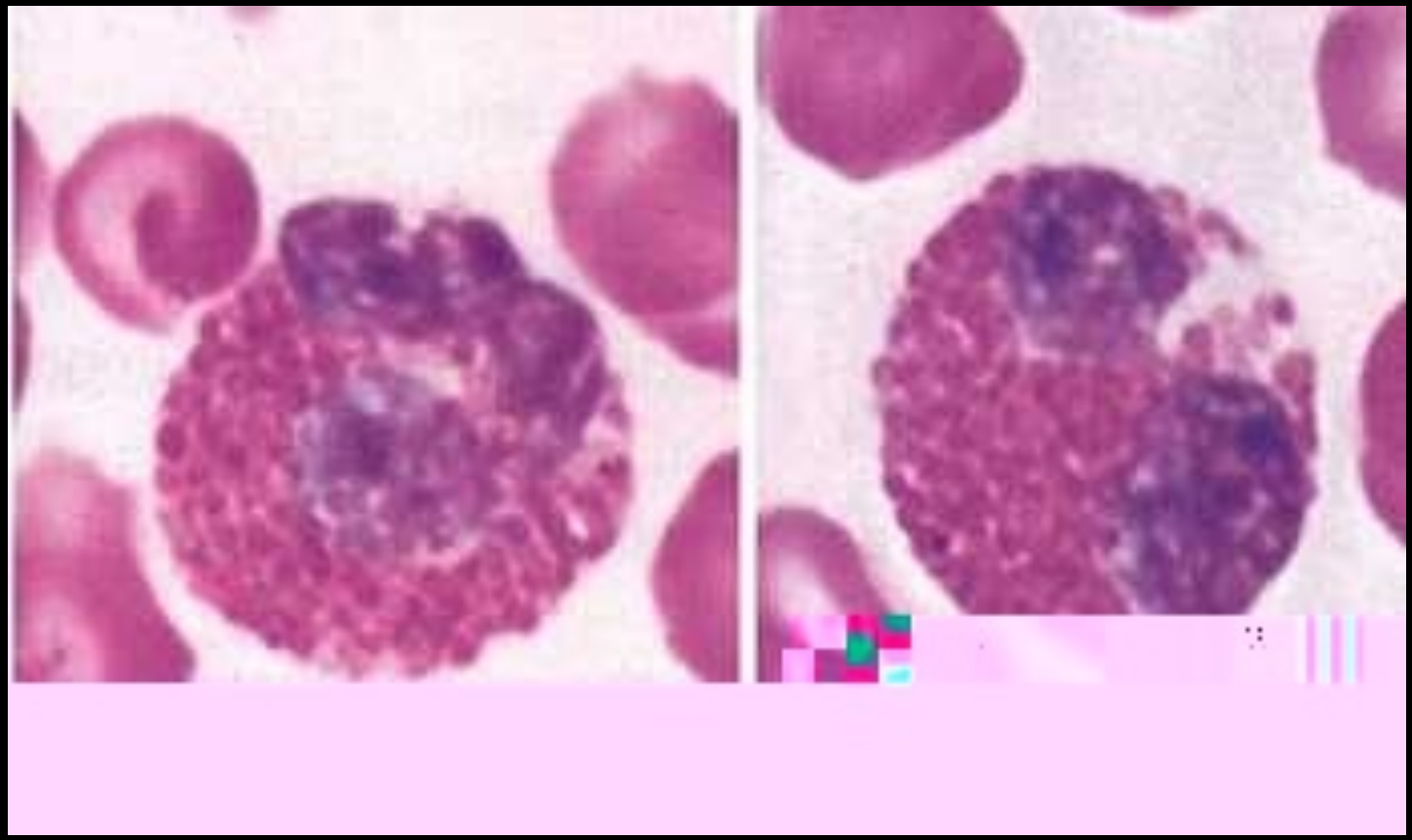
Lymphocytes- types



Eosinophils

- Eosinophils are present in the blood in relatively small quantity (1-5% in norm) but their number increases (eosinophilia), and sometimes signifi-cantly, in allergic processes (serum sickness or bronchial asthma), in helmin-thiasis, and itching dermatosis. Eosinophilia in allergic processes is asso-ciated with the role played by eosinophils in removal of toxic substances pro-duced in these reactions. Decreased number of eosinophils (eosinopenia), to their complete absence, occurs in sepsis, severe forms of tuberculosis, typhus, and poisoning. Basophils are carriers of important mediators of tissue metabolism. Their number (0-1% in norm) increases in sensitization of patients and de-creases markedly during decomposition caused by the repeated administra-tion of the allergen. Combined increase of the number of basophils and eosi-nophils (basophil –eosinophil association) may be in chronic myeloid leuco-sis.

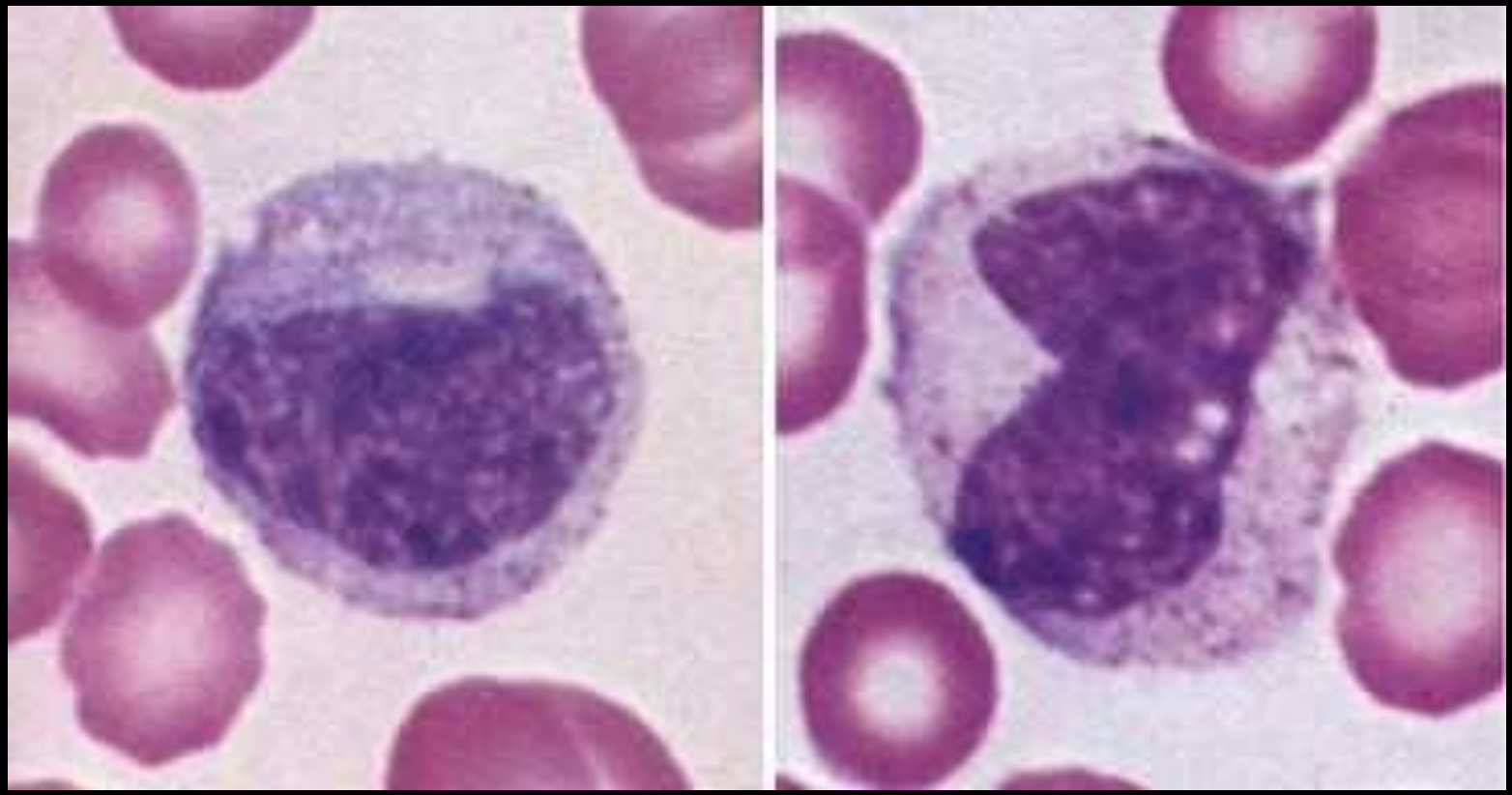
Eosinophils



Monocytes

- Monocyte count is 4-9% in norm. Increased number of monocytes (monocytosis) indicates development of the immune processes. Monocytosis occurs in some chronic diseases (e.g. tuberculosis, malaria, visceral leishma-niasis, syphilis) and in infectious mononucleosis. Monocytopenia sometimes occurs in severe septic (hypertoxic) forms of typhoid fever and other infec-tions. In rare cases, apart from the mentioned cells, normal blood contains plasma cells. Their number increases in pathology. The cells have an eccentr-ically arranged dense nucleus (often a wheel-like structure) and a markedly basophilic vacuolized cytoplasm. Their number increases in plasmacytoma (myeloma), certain infectious diseases, wound sepsis, hypernephroma, mye-loma, etc.

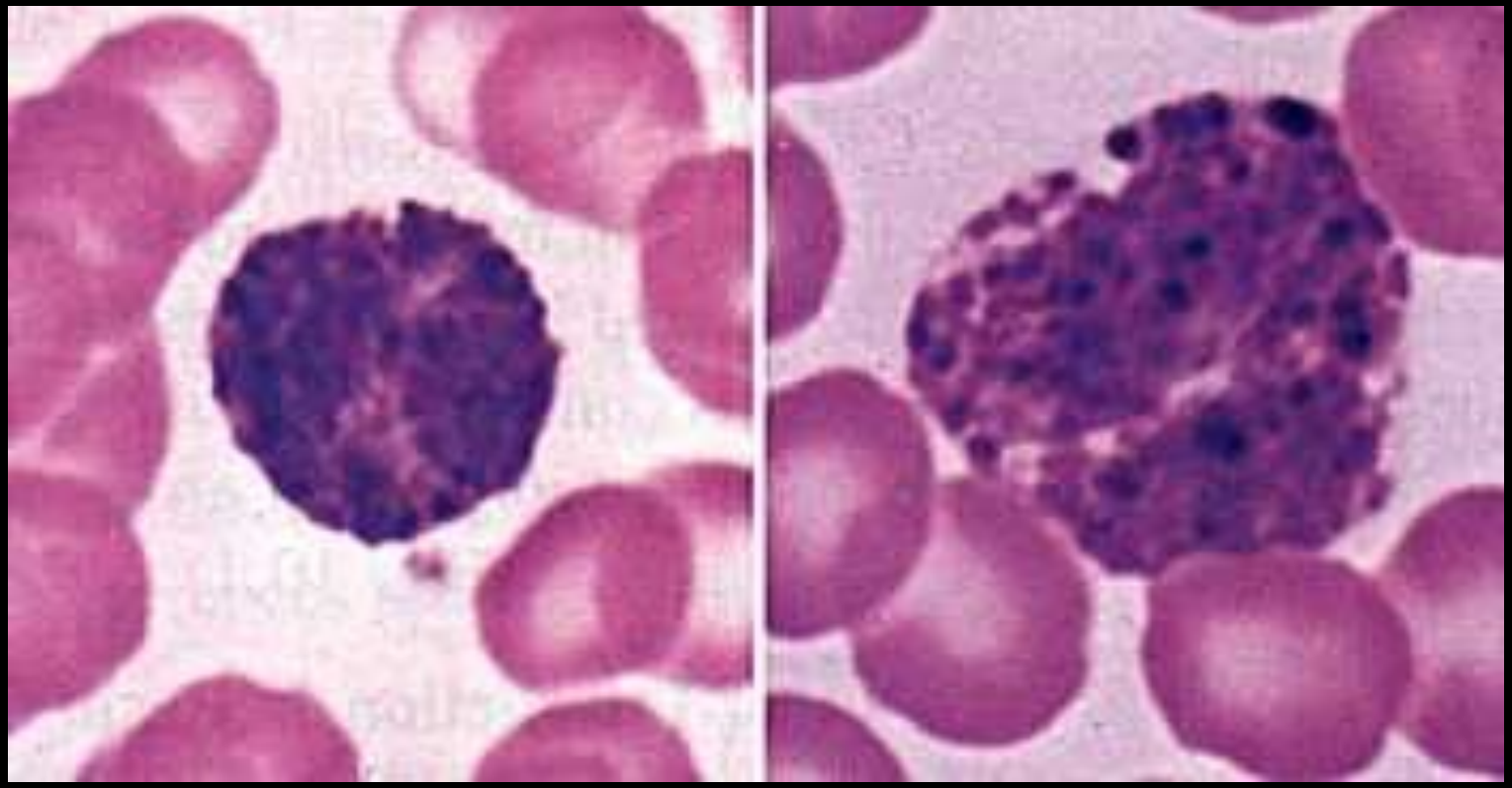
Monocytes



Basophils

- Basophils are chiefly responsible for allergic and antigen response by releasing the chemical histamine causing the dilation of blood vessels. Because they are the rarest of the white blood cells (less than 0.5% of the total count) and share physicochemical properties with other blood cells, they are difficult to study. They can be recognized by several coarse, dark violet granules, giving them a blue hue. The nucleus is bi- or tri-lobed, but it is hard to see because of the number of coarse granules that hide it.
- They excrete two chemicals that aid in the body's defenses: histamine and heparin. Histamine is responsible for widening blood vessels and increasing the flow of blood to injured tissue. It also makes blood vessels more permeable so neutrophils and clotting proteins can get into connective tissue more easily. Heparin is an anticoagulant that inhibits blood clotting and promotes the movement of white blood cells into an area. Basophils can also release chemical signals that attract eosinophils and neutrophils to an infection site.

Basophils



Leucocyte count (WBC count)

- Blood for counting leucocytes is diluted either in a special mixer or a test tube. A 3-5 per cent solution of acetic acid destroying erythrocytes is mixed with a small amount of a suitable aniline dye to stain leucocyte nuclei. The counting chamber is filled as for counting erythrocytes. It is convenient to count leucocytes in 100 greater (undivided) squares. **The normal leucocyte count are 4,0-9,0×109/1 of blood**. The total quantity of leucocytes alone is of great diagnostic signific-ance, because it characterizes the condition of the hemopoietic system and its response to harmful effects.

Disorders

- The increased number of leucocytes (leucocyto-sis) is the result of activation of leucopoiesis.
- The decreased number of leu-cocytes (leucopenia) may be in affection of the bone marrow by infectious causative agents, some medicinal preparations, ionizing radiation, and in au-to-immune processes.
- The leucocyte formula (leukogram, differential blood count) is counted in stained smears. Romanovsky-Giemsa staining method is commonly used. The stain is a mixture of weakly acid (eosin) and weakly alkaline (azure II) stains. Depending on the reaction of the medium, the cells and their parts dif-ferently accept the stain: acid (basophilic) substances are coloured blue by azure, while alkaline (oxyphilic) substances are coloured red by eosin. Neu-tral substances accept both dyes and turn violet. Azure II, which is generally blue, contains a small quantity of azure I. In some cells the cytoplasm con-tains grains which selectively accept red azure I. The grains are called azuro-philic.

- **Leucocyte formula** is the percentage of separate forms of blood leuco-cytes. Leucocytes quickly respond to various environmental factors and changes inside the body. Shifts in their counts are very important diagnosti-cally. But individual variations in leucocyte composition are quite significant and it is therefore necessary to compare individual findings not with the average values, but with a certain range within which these variations are normal.
- When assessing the composition of leucocytes, it is necessary to bear in mind that changes in percentage ratios can give an incorrect picture of the shifts occurring in the blood. For example, an increase in the absolute amount of a given type of cells in the blood decreases the percentage of all other cell elements. The picture is reverse with decreasing absolute amount of this given type of blood cells. A correct conclusion can be derived not from relative (percentage) but absolute values.

Examination of hemopoietic organs

- The morphological composition of the blood does not always show the changes occurring in the hemopoietic organs. For example, the cell composi-tion of blood remains almost unaltered in aleukemic form of leucosis despite significant changes in the bone marrow.
- M. Arinkin (1928) proposed *sternal puncture for intravital study of the bone marrow. Owing to the simplicity and safety of the procedure, it is used* for the study of almost all patients with diseases of the hemopoietic system. After fixation and staining (Romanovsky-Giemsa), not less than 500 ele-ments containing nuclei are counted in the smear. A *myelogram is then de-rived. The marrow specimen can show upset maturation of the cells: in-creased number of juvenile forms or prevalence of primary undifferentiated elements, upset proportion between the red and white cells, changes in the total number of cells, presence of the pathological forms, etc. Apart from the sternum, other bones (e.g. iliac bone) can also be used for taking the bone marrow. More accurate information on the composition of the bone marrow is given by trepanobiopsy. A special needle (troacar) is passed into the iliac crest to cut out a column consisting of the bone-marrow tissue, which is then used for making histological preparations. The structure of the bone-marrow remains unchanged in the preparations while the absence of blood makes it possible to evaluate its cells composition and to reveal focal and diffuse changes in it.*

- Enlarged lymph nodes are often punctured. It makes it possible to es-tablish the character of changes in the cell composition and to verify the diagnosis of some systemic diseases of the lymph apparatus (lymphoid leucosis, lymphogranulomatosis, lymphosarcomatosis), to reveal metastases of tu-mours, etc. More accurate data can be obtained with biopsy of the lymph node. The puncture is made without anesthesia, by a simple injection needle attached to a 10-ml syringe. The obtained material is used to prepare smears. The spleen is punctured by the same method. The patient is asked to keep breath at the inspiration height to prevent possible injury of the spleen during respiratory movements. Combined study of cell composition of the bone marrow, spleen and lymph nodes reveals the relations between these organs of the hemopoietic system and the presence of extramedullar hemopoiesis which develops in some affections of the bone marrow.

Common white blood cells diseases

Leukaemias

- **Leukaemias are malignant disorders of the haematopoietic** stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood. The course of leukaemia may vary from a few days or weeks to many years, depending on the type.

Leukaemias

Epidemiology and aetiology

- The incidence of leukaemia of all types in the population is approximately 10/100 000 per annum, of which just under half are cases of acute leukaemia. Males are affected more frequently than females, the ratio being about 3:2 in acute leukaemia, 2:1 in chronic lymphocytic leukaemia and 1.3:1 in chronic myeloid leukaemia. Geographical variation in incidence does occur, the most striking being the rarity of chronic lymphocytic leukaemia in the Chinese and related races. Acute leukaemia occurs at all ages. Acute lymphoblastic leukaemia shows a peak of incidence in children aged 1–5 years. All forms of acute myeloid leukaemia have their lowest incidence in young adult life and there is a striking rise over the age of 50. Chronic leukaemias occur mainly in middle and old age. The cause of the leukaemia is unknown in the majority of patients. Several risk factors, however, are known.

Leukaemias

Terminology and classification

Leukaemias are traditionally classified into four main groups:

- Acute lymphoblastic leukaemia (ALL)
- Acute myeloid leukaemia (AML)
- Chronic lymphocytic leukaemia (CLL)
- Chronic myeloid leukaemia (CML).

Leukaemias

- The diagnosis of leukaemia is usually suspected from an abnormal blood count, often a raised white count, and is confirmed by examination of the bone marrow. This includes the morphology of the abnormal cells, analysis of cell surface markers (immunophenotyping), clone-specific chromosome abnormalities and molecular changes. These results are incorporated in the World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues; the subclassification of acute leukaemias. The features in the bone marrow not only provide an accurate diagnosis but also give valuable prognostic information, allowing therapy to be tailored to the patient's disease.

Acute leukaemia

There is a failure of cell maturation in acute leukaemia.

Proliferation of cells which do not mature leads to an accumulation of useless cells which take up more and more marrow space at the expense of the normal haematopoietic elements. Eventually, this proliferation spills into the blood.

Acute myeloid leukaemia (AML) is about four times more common than acute lymphoblastic leukaemia (ALL) in adults. In children the proportions are reversed, the lymphoblastic variety being more common. The clinical features are usually those of bone marrow failure (anaemia, bleeding or infection.

Acute leukaemia

- In acute leukaemia there is proliferation of primitive stem cells leading to an accumulation of blasts, predominantly in the bone marrow, which causes bone marrow failure.
- In chronic leukaemia the malignant clone is able to differentiate, resulting in an accumulation of more mature cells. Lymphocytic and lymphoblastic cells are those derived from the lymphoid stem cell (B cells and T cells). Myeloid refers to the other lineages, i.e. precursors of red cells, granulocytes, monocytes and platelets.

- The word leukemia, which means 'white blood', is derived from the characteristic high white blood cell count that presents in most afflicted people before treatment. The high number of white blood cells is apparent when a blood sample is viewed under a microscope, with the extra white blood cells frequently being immature or dysfunctional. The excessive number of cells can also interfere with the level of other cells, causing further harmful imbalance in the blood count.

- Some people diagnosed with leukemia do not have high white blood cell counts visible during a regular blood count. This less-common condition is called aleukemia. The bone marrow still contains cancerous white blood cells which disrupt the normal production of blood cells, but they remain in the marrow instead of entering the bloodstream, where they would be visible in a blood test. For a person with aleukemia, the white blood cell counts in the bloodstream can be normal or low. Aleukemia can occur in any of the four major types of leukemia, and is particularly common in hairy cell leukemia.

Clinical features

- The most common symptoms in children are easy bruising, pale skin, fever, and an enlarged spleen or liver.

- Damage to the bone marrow, by way of displacing the normal bone marrow cells with higher numbers of immature white blood cells, results in a lack of blood platelets, which are important in the blood clotting process. This means people with leukemia may easily become bruised, bleed excessively, or develop pinprick **bleeds (petechiae).**

- White blood cells, which are involved in fighting pathogens, may be suppressed or dysfunctional. This could cause the person's immune system to be unable to fight off a simple infection or to start attacking other body cells. Because leukemia prevents the immune system from working normally, some people experience **frequent infection**, ranging from infected tonsils, sores in the mouth, or diarrhea to life-threatening pneumonia or opportunistic infections.

- Finally, the red blood cell deficiency leads to anemia, which may cause **dyspnea and pallor.**

Clinical features

- Some people experience other symptoms, such as feeling sick, having fevers, chills, night sweats, feeling fatigued and other flu-like symptoms. Some people experience nausea or a feeling of fullness due to an enlarged liver and spleen; this can result in unintentional weight loss. Blasts affected by the disease may come together and become swollen in the liver or in the lymph nodes causing pain and leading to nausea.

- If the leukemic cells invade the central nervous system, then neurological symptoms (notably headaches) can occur. Uncommon neurological symptoms like migraines, seizures, or coma can occur as a result of brain stem pressure. All symptoms associated with leukemia can be attributed to other diseases. Consequently, leukemia is always diagnosed through medical tests.

Acute leukaemia

- Blood examination usually shows anaemia with a normal or raised MCV. The leucocyte count may vary from as low as 1 × 109/L to as high as 500 × 109/L or more. In the majority of patients the count is below 100 × 109/L. Severe thrombocytopenia is usual but not invariable. The appearance of blast cells in the blood film is usually diagnostic. Sometimes the blast cell count may be very low in the peripheral blood and a bone marrow examination is necessary to confirm the diagnosis. The bone marrow is usually hypercellular, with replacement of normal elements by leukaemic blast cells in varying degrees (but more than 20% of the cells. The presence of Auer rods in the cytoplasm of blast cells indicates a myeloblastic type of leukaemia.

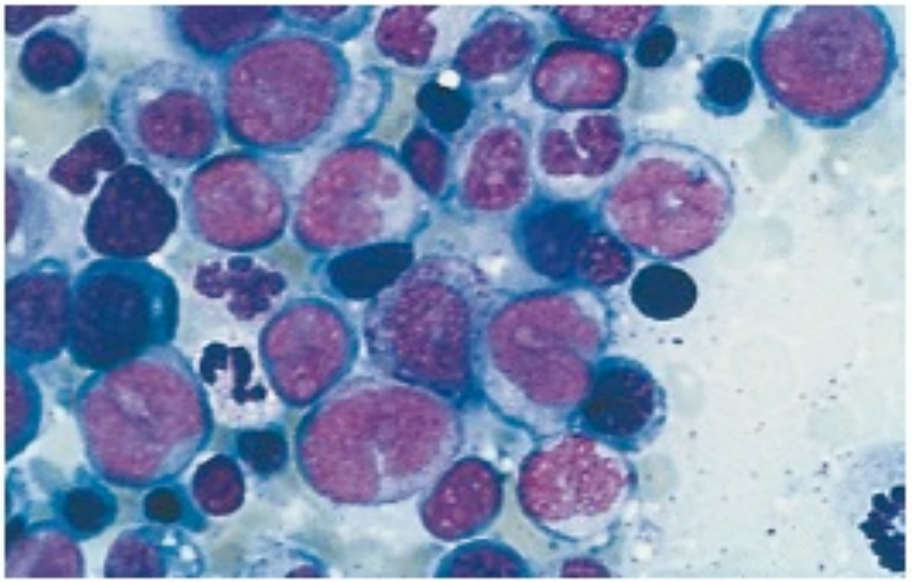
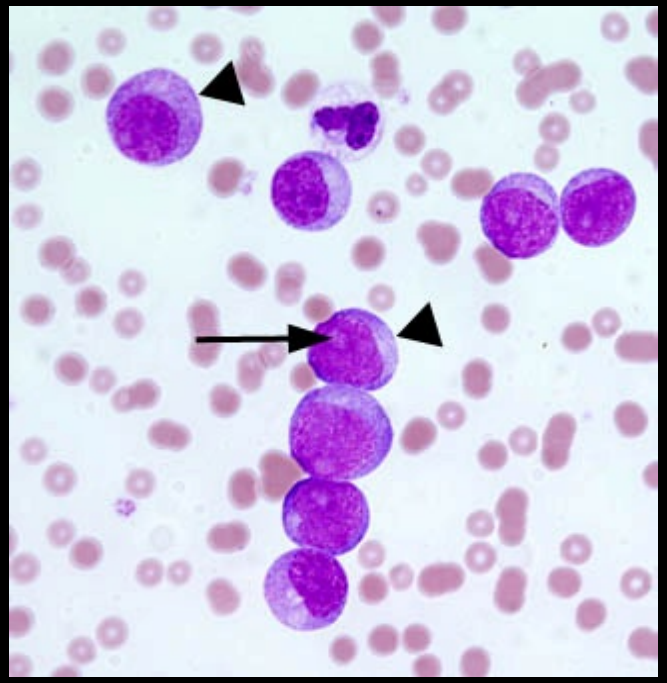


Fig. 24.26 Acute myeloid leukaemia. Bone marrow aspirate showing infiltration with large blast cells which display nuclear folding and prominent nucleoli.



•Paraleucoblasts in peripheral blood - these are cells of different size, circular, concave or strongly incised nucleus; with young chromatin and 2-3 large blue nucleoli; cytoplasm is narrower or wider; colored in bluish, with eosinophilic inclusions (Auer sticks) or numerous eosinophilic granules.

Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia is a myeloproliferative stem-cell disorder resulting in proliferation of all haematopoietic lineages but manifesting predominantly in the granulocytic series. Maturation of cells proceeds fairly normally. The disease occurs chiefly between the ages of 30 and 80 years, with a peak incidence at 55 years. It is rare, with an annual incidence in the UK of 1.8/100 000, and accounts for 20% of all leukaemias. The disease is found in all races. Approximately 95% of patients with CML have a chromosome abnormality known as the Philadelphia (Ph) chromosome. This is a shortened chromosome 22 resulting from a reciprocal translocation of material with chromosome 9. The break on chromosome 22 occurs in the breakpoint cluster region (BCR). The fragment from chromosome 9 that joins the BCR carries the *abl* oncogene, which forms a chimeric gene with the remains of the BCR. This *BCR ABL* chimeric gene codes for a 210 kDa protein with tyrosine kinase activity, which plays a causative role in the disease as an oncogene, influencing cellular proliferation, differentiation and survival. In some patients in whom conventional chromosomal analysis does not detect a Ph chromosome, the BCR ABL gene product is detectable by molecular techniques.

Chronic myeloid leukaemia (CML)

Natural history

The disease has three phases:

- *A chronic phase*, in which the disease is responsive to treatment and is easily controlled, typically lasting 3–5 years. With the introduction of imatinib therapy this phase has been prolonged to longer than 5 years in many patients.
- *An accelerated phase* (not always seen), in which disease control becomes more difficult.
- *Blast crisis*, in which the disease transforms into an acute leukaemia, either myeloid (70%) or lymphoblastic (30%), which is relatively refractory to treatment. This is the cause of death in the majority of patients; therefore survival is dictated by the timing of blast crisis, which cannot be predicted. Prior to imatinib therapy (see below) approximately 10% of patients per year would transform. In those treated with imatinib for up to 5 years, only between 0.5-2.5% have transformed each year. Patients who are Ph chromosome-negative and *BCR ABL*-negative tend to be older, mostly male, with lower platelet counts and higher absolute monocyte counts, and respond poorly to treatment, with a median survival of less than 1 year.

Chronic myeloid leukaemia (CML)

Clinical features

The common symptoms at presentation are:

- **Splenomegaly** is present in 90%; in about 10% the enlargement is massive, extending to over 15 cm below the costal margin.
- **A friction rub** may be heard in cases of splenic infarction.
- **Hepatomegaly** occurs in about 50%.
- **Lymphadenopathy is unusual.**

Chronic myeloid leukaemia (CML)

Investigations

- FBC results are variable between patients. There is usually a normocytic, normochromic anaemia. The leucocyte count can vary from 10 to 600 × 109/L. In about one-third of patients there is a very high platelet count, sometimes as high as 2000 × 109/L. In the blood film the full range of granulocyte precursors from myeloblasts to mature neutrophils is seen but the predominant cells are neutrophils and myelocytes. Myeloblasts usually constitute less than 10% of all white cells. There is often an absolute increase in eosinophils and basophils, and nucleated red cells are common. If the disease progresses through an accelerated phase, the percentage of more primitive cells increases. Blast transformation is characterised by a dramatic increase in the number of circulating blasts. In patients with thrombocytosis, very high platelet counts may persist during treatment, in both chronic and accelerated phases, but usually drop dramatically at blast transformation. Basophilia tends to increase as the disease progresses.
- Bone marrow should be obtained to confirm the diagnosis and phase of disease by morphology, chromosome analysis to demonstrate the presence of the Ph chromosome, and RNA analysis to demonstrate the presence of the BCR ABL gene product. Blood LDH levels are elevated and the uric acid level may be high due to increased cell breakdown.

Chronic lymphocytic leukaemia (CLL)

- This is the most common variety of leukaemia, accounting for 30% of cases. The male:female ratio is 2:1 and the median age at presentation is 65–70 years. In this disease B lymphocytes, which would normally respond to antigens by transformation and antibody formation, fail to do so. An ever-increasing mass of immuno-incompetent cells accumulates, to the detriment of immune function and normal bone marrow haematopoiesis.

Chronic lymphocytic leukaemia (CLL)

Clinical features

- The onset is very insidious. Indeed, in around 70% of patients the diagnosis is made incidentally on a routine FBC. Presenting problems may be anaemia, infections, painless lymphadenopathy, and systemic symptoms such as night sweats or weight loss. However, these more often occur later in the progress of the disease.

Chronic lymphocytic leukaemia (CLL)

Investigations

- The diagnosis is based on the peripheral blood findings of a mature lymphocytosis (> 5 × 109/L) with characteristic morphology and cell surface markers. Immunophenotyping reveals the lymphocytes to be monoclonal B cells expressing the B cell antigens CD19 and CD23, with either kappa or lambda immunoglobulin light chains and, characteristically, an aberrant T cell antigen, CD5. Other useful investigations in CLL include a reticulocyte count and a direct Coombs test as autoimmune haemolytic anaemia may occur (p. 1025). Serum immunoglobulin levels should be estimated to establish the degree of immunosuppression, which is common and progressive. Bone marrow examination by aspirate and trephine is not essential for the diagnosis of CLL, but may be helpful in difficult cases, for prognosis (patients with diffuse marrow involvement have a poorer prognosis) and to monitor response to therapy. The main prognostic factor is stage of disease (Box 24.53); however, newer markers such as CD38 expression, mutations of IgV н genes, and cytogenetic abnormalities of chromosome 11 or 17 may also suggest a poorer prognosis.

Myelodysplastic syndrome (MDS)

- This syndrome consists of a group of clonal haematopoietic disorders which represent steps in the progression to the development of leukaemia. It presents with consequences of bone marrow failure (anaemia, recurrent infections or bleeding), usually in older people (median age at diagnosis is 69 years). The overall incidence is 4/100 000 in the population, rising to more than 30/100 000 in the over-seventies. The blood film is characterised by cytopenias and abnormal-looking (dysplastic) blood cells, including macrocytic red cells and hypogranular neutrophils with nuclear hyper- or hyposegmentation. The bone marrow is hypercellular with dysplastic changes in all three cell lines. Blast cells may be increased but do not reach the 20% level which indicates acute leukaemia. Chromosome analysis frequently reveals abnormalities, particularly of chromosome 5 or 7.

Lymphomas

These neoplasms arise from lymphoid tissues, and are diagnosed from the pathological findings on biopsy as Hodgkin or non-Hodgkin lymphoma. The majority are of B cell origin. Non-Hodgkin lymphomas are classified as low- or high-grade tumours on the basis of their proliferation rate.

- *High-grade tumours* divide rapidly, are typically present for a matter of weeks before diagnosis and may be life-threatening.
- *Low-grade tumours* divide slowly, may be present for many months before diagnosis and typically behave in an indolent fashion.

Hodgkin lymphoma

The histological hallmark of HL is the presence of Reed–Sternberg cells, large malignant lymphoid cells of B cell origin. They are often only present in small numbers but are surrounded by large numbers of reactive non-malignant T cells, plasma cells and eosinophils. Nodular lymphocyte-predominant HL is slow-growing, localised and rarely fatal. Classical HL is divided into four histological subtypes from the appearance of the Reed–Sternberg cells and surrounding reactive cells. The nodular sclerosing type is more common in young patients and in women. Mixed cellularity is more common in the elderly. Lymphocyte-rich HL usually presents in men. Lymphocyte-depleted HL is rare and probably represents large-cell or anaplastic non-Hodgkin lymphoma.

Hodgkin lymphoma

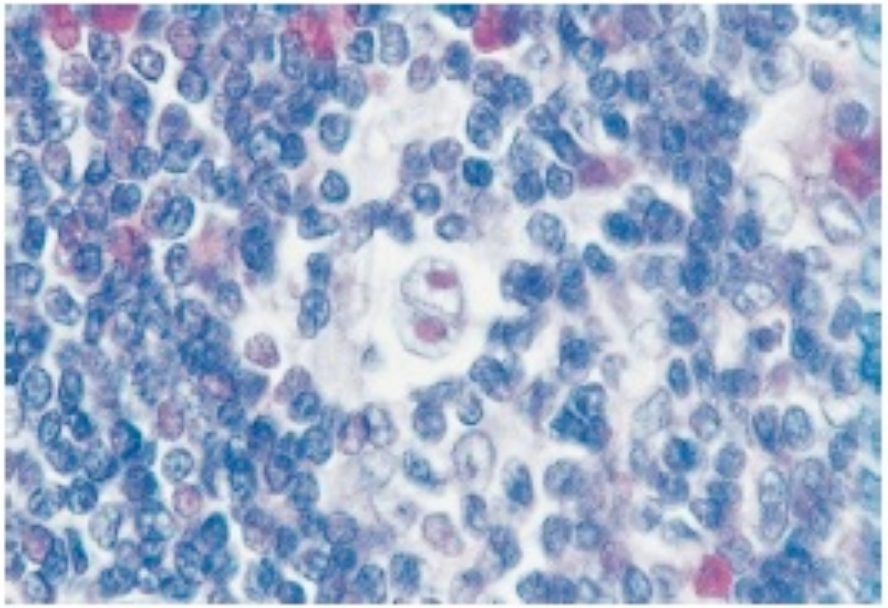


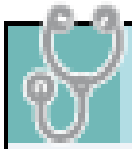
Fig. 24.29 Hodgkin lymphoma. In the centre of this lymph node biopsy is a large typical Reed–Sternberg cell with two nuclei containing a prominent eosinophilic nucleolus.

Hodgkin lymphoma

Clinical features

- There is painless rubbery lymphadenopathy, usually in the neck or supraclavicular fossae; the lymph nodes may fluctuate in size. Young patients with nodular sclerosing disease may have large mediastinal masses which are surprisingly asymptomatic but may cause dry cough and some breathlessness. Isolated subdiaphragmatic nodes occur in fewer than 10% at diagnosis.
- Hepatosplenomegaly may be present but does not always indicate disease in those organs. Spread is contiguous from one node to the next and extranodal disease, such as bone, brain or skin involvement, is rare.

Hodgkin lymphoma Clinical stages



24.57 Clinical stages of Hodgkin lymphoma (Ann Arbor classification)

Stage	Definition
I	Involvement of a single lymph node region (I) or extralymphatic* site (I_E)
II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm with (III_E) or without (III) localised extralymphatic involvement or involvement of the spleen (III_S) or both (III_{SE})
IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow

Each stage is subclassified:

A	No systemic symptoms
B	Weight loss, drenching sweats

*The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches.

Hodgkin lymphoma

Investigations

Treatment of HL depends upon the stage at presentation; therefore investigations aim not only to diagnose lymphoma but also to determine the extent of disease.

- *FBC* may be normal. If a normochromic, normocytic anaemia or lymphopenia is present, this is a poor prognostic factor. An eosinophilia or a neutrophilia may be present.
- *ESR* may be raised.
- *Renal function tests* are required to ensure function is normal prior to treatment.
- *Liver function* may be abnormal in the absence of disease or may reflect hepatic infiltration. An obstructive pattern may be caused by nodes at the porta hepatis.
- *LDH measurements* showing raised levels are an adverse prognostic factor.
- *Chest X-ray* may show a mediastinal mass.
- *CT scan* of chest, abdomen and pelvis permits staging. Bulky disease (> 10 cm in a single node mass) is an adverse prognostic feature.
- *Lymph node biopsy* may be undertaken surgically or by percutaneous needle biopsy under radiological guidance.

Non-Hodgkin lymphoma

NHL represents a monoclonal proliferation of lymphoid cells of B cell (70%) or T cell (30%) origin. The incidence of these tumours increases with age, to 62.8/million population per annum at age 75 years, and the overall rate is increasing at about 3% per year.

It has been difficult to establish a reproducible and clinically useful histological classification. The current WHO classification stratifies according to cell lineage. Clinically, the most important factor is grade, which is a reflection of proliferation rate. High-grade NHL has high proliferation rates, rapidly produces symptoms, is fatal if untreated, but is potentially curable. Low-grade NHL has low proliferation rates, may be asymptomatic for many months before presentation, runs an indolent course, but is not curable by conventional therapy. Of all cases of NHL, 85% are either high-grade diffuse large B-cell NHL or low-grade follicular NHL. Other forms of NHL, including mantle cell lymphoma and malt lymphomas, are less common.

Non-Hodgkin lymphoma

Clinical features

- Unlike Hodgkin lymphoma, NHL is often widely disseminated at presentation, including in extranodal sites. Patients present with lymph node enlargement which may be associated with systemic upset: weight loss, sweats, fever and itching. Hepatosplenomegaly may be present. Extranodal involvement is more common in T cell disease and involves the bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone. Bone marrow involvement is more common in low-grade (50–60%) than high-grade (10%) disease. Compression syndromes may occur, including gut obstruction, ascites, superior vena caval obstruction and spinal cord compression.
- The same staging system is used for both HL and NHL, but NHL is more likely to be stage III or IV at presentation.

Non-Hodgkin lymphoma

Investigations

These are as for HL, but in addition the following should be performed:

- *Routine bone marrow aspiration and trephine*.
- *Immunophenotyping of surface antigens to distinguish T and B cell tumours*. This may be done on blood, marrow or nodal material.
- *Immunoglobulin determination*. Some lymphomas are associated with IgG or IgM paraproteins, which serve as markers for treatment response.
- *Measurement of uric acid levels*. Some very aggressive high-grade NHLs are associated with very high urate levels, which can precipitate renal failure when treatment is started.
- *HIV testing*. This may be appropriate if risk factors are present.

Non-Hodgkin lymphoma

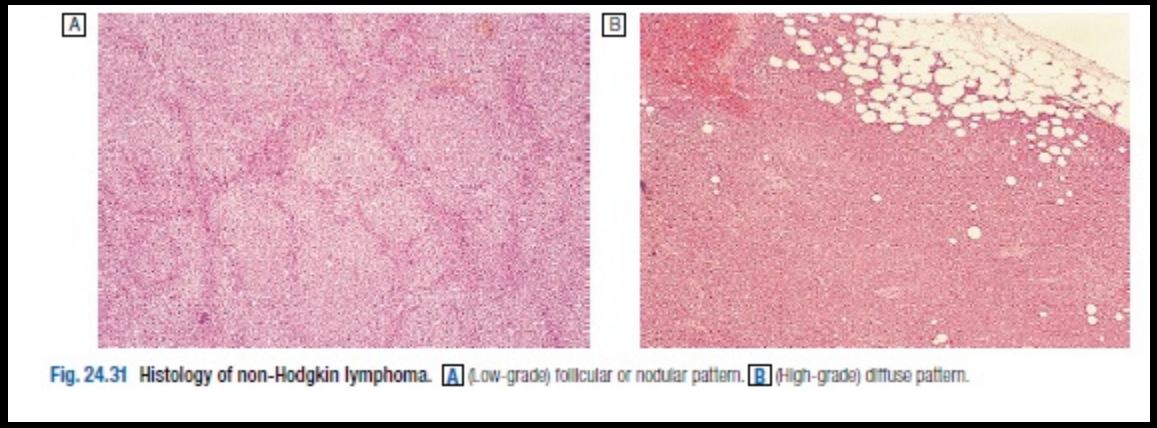


Fig. 24.31 Histology of non-Hodgkin lymphoma. A (Low-grade) follicular or nodular pattern. B (High-grade) diffuse pattern.

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