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Disorders of red and white blood cells, such as anemia and leukemia

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***Abstract*---Background:** Disorders of red and white blood cells, such as anemia and leukemia, can reflect both hematological and non-hematological conditions. Anemia, a common clinical challenge, necessitates thorough evaluation when accompanied by symptoms like splenomegaly, lymphadenopathy, or bleeding tendencies. **Aim:** This article aims to explore the diagnostic approach to blood disorders, emphasizing the significance of initial screening tests and their interpretations. **Methods:** A comprehensive review of laboratory tests, including hemoglobin concentration, white blood cell count, and peripheral blood smear examination, is conducted. The article discusses the interpretation of results, considering factors such as age, sex, and ethnic background. **Results:** The findings illustrate that abnormalities in blood cell counts can indicate various underlying conditions. Increased cell counts may suggest myeloproliferative neoplasms, while decreased counts may arise from factors such as hypersplenism, infections, or myelosuppressive agents. The article further categorizes anemia into microcytic, macrocytic, and normocytic types, with flowcharts outlining the investigation sequence

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for each type. **Conclusion:** Understanding the complexities of blood disorders requires a systematic approach to diagnosis. Utilizing basic screening tests effectively can guide further investigations, ultimately aiding in the identification and management of underlying hematological conditions.

***Keywords*---**anemia, leukemia, blood disorders, hematological testing, screening tests, diagnostics.

Introduction

An atypical blood count or abnormal morphology of blood cells does not inherently signify a primary hematological disorder, as it could also reflect an underlying non-hematological condition or result from therapeutic interventions. Anaemia is prevalent in numerous conditions; however, a primary hematological disorder should be considered if a patient exhibits splenomegaly, lymphadenopathy, a tendency to bleed, thrombosis, and/or nonspecific symptoms indicative of leukemias and lymphomas, such as malaise, night sweats, or weight loss.

As with any clinical challenge, the initial steps in establishing a diagnosis involve collecting a comprehensive clinical history, including travel and medication use, alongside a meticulous physical examination. The results of these assessments, in conjunction with the patient's age, sex, ethnic background, social and familial history, and knowledge of locally prevalent diseases, will inform subsequent laboratory investigations. While the array of hematological tests available to support clinical and public health initiatives is extensive, it is frequently the simplest investigations that prove most valuable in guiding diagnosis. Even laboratories with limited resources can typically provide an initial battery of tests, such as hemoglobin concentration (Hb), white blood cell count (WBC), and platelet count, as well as examination of a peripheral blood smear for differential leukocyte count and cellular morphology. These screening tests often facilitate the rapid identification of underlying pathological processes and direct attention to a few key diagnostic tests.

Interpretation of Screening Test Results

The outcomes of laboratory screening tests should always be interpreted with an awareness of the tests' limitations and the physiological variations that arise with factors such as sex, age, ethnic group, and conditions like pregnancy and exercise. Abnormalities in red blood cells, white blood cells, or platelets may manifest as quantitative (increased or decreased numbers) or qualitative (abnormal morphology and/or function).

Quantitative Abnormalities of Blood Cells:
Increased Cell Counts:

An elevation involving more than one cell lineage suggests excessive production originating from a common early precursor cell. This phenomenon is observed in

myeloproliferative neoplasms, where one cell type may dominate; for instance, there may be an increase in platelets in essential thrombocythemia and red blood cells in polycythemia vera.

Erythrocytosis: Patients exhibiting a persistently elevated venous hematocrit (Hct) (e.g., > 2 months) (> 0.52 in males, > 0.48 in females) warrant investigation to ascertain the underlying cause. Erythrocytosis may be classified as relative or absolute and, if absolute, can be further categorized as primary or secondary. **Relative:** This indicates a normal total red blood cell volume accompanied by reduced plasma volume (e.g., dehydration). **Absolute:** Males and females presenting with Hct values exceeding 0.60 and 0.56, respectively, are presumed to have absolute erythrocytosis and do not require confirmatory tests. However, the cause of the elevated Hct must still be elucidated. **Primary:** This typically refers to polycythemia vera (PV), part of the spectrum of myeloproliferative neoplasms. The JAK2 V617F mutation is present in approximately 95% of PV patients, and mutations affecting exon 12 are found in many individuals lacking the V617F mutation. **Secondary:** Causes include chronic hypoxia (e.g., chronic lung disease, congenital heart defects, high-affinity hemoglobins) or aberrant erythropoietin production. Secondary polycythemia can generally be excluded based on clinical history and examination, assessment of serum erythropoietin levels and arterial oxygen saturation, hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), along with an oxygen dissociation curve and abdominal ultrasound examination. Should initial screening tests yield negative results for a JAK2 mutation and no obvious secondary cause for the elevated Hct be found, then studies to assess red cell mass are warranted.

Leukocytosis

Neutrophilia:

Neutrophil levels commonly rise during pregnancy and in the context of acute infections, inflammation, alcohol intoxication, corticosteroid therapy, and acute blood loss or red cell destruction. Additional findings from a complete blood count can aid in identifying the etiology of neutrophilia. The combination of anemia and neutrophilia may occur in chronic infection or inflammation and in malignant conditions; a high Hct alongside neutrophilia may indicate polycythemia vera. Neutrophilia combined with an elevated platelet count is typically associated with infectious or inflammatory processes, malignant conditions, or during bone marrow recovery. Neutrophilia alongside thrombocytopenia is classically observed in sepsis and occasionally in microangiopathic hemolytic anemia. Examination of the peripheral blood smear can provide further insights to confirm or rule out specific diagnoses. For instance, neutrophilia characterized by heavy cytoplasmic granulation (“toxic” granulation) is commonly noted in severe bacterial infections. In the absence of an identifiable underlying cause, a high neutrophil count accompanied by immature myeloid cells suggests chronic myelogenous leukemia (CML), warranting cytogenetic and molecular studies to assess for t(9;22) and the presence of the BCR–ABL1 fusion gene.

Lymphocytosis:

Lymphocytosis is characteristic of certain infections, particularly those affecting children. It may be particularly pronounced in conditions such as pertussis, infectious mononucleosis, cytomegalovirus infection, infectious hepatitis,

tuberculosis, and brucellosis. Elderly individuals with lymphoproliferative disorders, including chronic lymphocytic leukemia and lymphomas, often present with lymphadenopathy and lymphocytosis. The morphology and immunophenotyping of cells, combined with histological examination of a bone marrow trephine biopsy specimen (and, if necessary, other tissue biopsies), are employed to classify these disorders and provide insight into management and prognosis. If lymph nodes are enlarged, a lymph node biopsy for histology and immunohistochemistry may assist in diagnosis. Differentiating between reactive and neoplastic lymphocytosis can occasionally be challenging. In such cases, immunophenotyping, which provides evidence of light chain restriction, and polymerase chain reaction for immunoglobulin or T-cell receptor gene rearrangements can indicate the presence of a monoclonal lymphocyte population, thereby supporting a diagnosis of neoplastic rather than reactive lymphoproliferation.

Monocytosis:
A mild to moderate monocytosis may occur in conjunction with certain protozoal, rickettsial, and bacterial infections, including malaria, typhus, and tuberculosis. The presence of monocytosis alongside neutrophilia raises suspicion for chronic myelomonocytic leukaemia. In elderly patients, elevated monocyte levels (monocyte count > 1 × 10^9/l) may indicate chronic myelomonocytic leukaemia or, less commonly, atypical chronic myeloid leukaemia. These disorders are categorized within the myelodysplastic/myeloproliferative neoplasm spectrum , and the diagnosis can be corroborated by the observation of splenomegaly, quantitative and qualitative abnormalities in other cell lines, or the identification of a clonal cytogenetic anomaly.

Eosinophilia:
Eosinophilia is predominantly linked to parasitic infections, skin conditions, and allergic responses. Eosinophils tend to infiltrate and inflict damage on tissues such as the heart, lungs, and gastrointestinal tract; therefore, a comprehensive assessment of these organs is warranted in eosinophilic patients. Typically, the etiology of eosinophilia can be deduced from the clinical history, which should encompass details of all medications and international travel, as well as stool and urine examinations for parasites, cysts, and ova.

Causes of eosinophilia:
- **Parasitic Infections** – Particularly with helminths
- **Neoplastic Diseases**:
  - Primary (or neoplastic) hypereosinophilia, e.g., linked to the FIP1L1-PDGFRA fusion gene (or occasionally to PDGFRB or FGFR1 rearrangements or PCM1-JAK2 fusion)
  - Other acute or chronic eosinophilic leukaemias
  - Other myeloproliferative neoplasms, such as chronic myeloid leukaemia and systemic mastocytosis
  - Reactive eosinophilia due to other neoplasms, such as B- or T-cell lymphoma or solid tumors
- **Allergic Disorders**:
  - Gastrointestinal disorders, which may be associated with tissue eosinophilia rather than peripheral blood eosinophilia

  - Drug reactions, including DRESS syndrome (drug reaction with eosinophilia and systemic symptoms)
  - Allergic rhinitis, asthma, and atopic dermatitis
- **Immunodeficiency Disorders**:
  - Hyper IgE (Job) syndrome
  - Autoimmune lymphoproliferative syndrome
  - Graft-versus-host disease
- **Connective Tissue/Rheumatological Disorders**

Basophilia:
The occurrence of basophilia as an isolated finding is relatively rare; however, it is a frequent characteristic of myeloproliferative neoplasms, particularly chronic myeloid leukaemia (CML). In this scenario, an escalating basophil count may represent the initial indication of an accelerated phase of the disease. Basophilia can also arise from endocrinopathies, such as myxoedema and estrogen imbalances, infections, allergic disorders, and, infrequently, other hematological malignancies.

Thrombocytosis:
Thrombocytosis may be classified as either primary or secondary (reactive) to surgical interventions, infectious and inflammatory conditions, hyposplenism, blood loss, and malignancies, and it can manifest as a rebound phenomenon following the recovery from marrow suppression. Additionally, spurious thrombocytosis can occur in instances of severe burns and cryoglobulinaemia due to the similarity in size between red cell fragments or cryoglobulin particles and platelets. A moderately elevated platelet count (e.g., 450–800 × 10^9/l) frequently does not signify a primary hematological disorder. When isolated persistent thrombocytosis occurs in the context of a myeloproliferative neoplasm, essential thrombocythaemia is the likely diagnosis, provided that the presence of a BCR–ABL1 fusion gene has been ruled out. Thrombotic or hemorrhagic complications may accompany thrombocytosis, although the diagnosis is often made incidentally . Individuals diagnosed with essential thrombocythaemia have been found to harbor mutations such as JAK2 V617F (50%), MPL (10%), or CALR mutations, with the JAK2 mutation correlating with an elevated risk of thrombosis.

Reduced Numbers of Cells
Reductions in More Than One Cell Line:
A decrease in cell numbers may arise from increased destruction, decreased production, or excessive pooling in the spleen or other organs. Reduced production of cells can result from several conditions, including aplastic anemia, deficiencies in essential hematinics such as folate or cobalamin, or disruption of normal hematopoiesis due to infiltration (e.g., leukemia), infections (e.g., human immunodeficiency virus (HIV), tuberculosis, leishmaniasis), exposure to toxins (e.g., alcohol), or the influence of myelosuppressive agents (e.g., hydroxycarbamide or methotrexate). Certain myeloid neoplasms, such as primary myelofibrosis and myelodysplastic syndromes (MDS), are characterized by cytopenias resulting, at least in part, from ineffective hematopoiesis. Cytopenia can also occur in acute myeloid leukemia (AML), where it arises due to both ineffective hematopoiesis and the replacement of normal hematopoietic stem cells

by leukemic cells. A common cause of a global reduction in circulating cells is the pooling of cells in an enlarged spleen, a condition known as hypersplenism. This can be secondary to diseases like primary myelofibrosis and portal hypertension. When the cause of cytopenias is not readily apparent, examination of a bone marrow aspirate and trephine biopsy specimen can provide valuable diagnostic insights.

Anemia:

The mechanisms leading to anemia include decreased production, reduced red blood cell lifespan, blood loss, and splenic pooling. Anemia is classified into three main types: microcytic (characterized by low mean cell volume (MCV)), macrocytic (high MCV), and normocytic (normal MCV). The selection of investigations is primarily determined by MCV and red cell morphology, alongside clinical features. The examination of a blood film typically offers the most rapid diagnostic route, although confirmation may necessitate more specialized tests.

- **Basophilic Stippling:** The presence of basophilic stippling in conjunction with microcytic red cells can indicate thalassemia trait or, less frequently, lead poisoning.
- **Dimorphic Blood Film:** A dimorphic blood film is commonly associated with congenital sideroblastic anemia but is more frequently observed in cases of iron deficiency that respond to treatment.
- **Pappenheimer Bodies:** The identification of Pappenheimer bodies suggests that microcytic anemia may be a result of sideroblastic erythropoiesis.

In summary, understanding the mechanisms underlying reductions in cell numbers and the classification of anemia is crucial for accurate diagnosis and effective management. The evaluation of blood films and subsequent investigations can guide clinicians toward identifying the underlying causes and implementing appropriate treatment strategies.

Microcytic Anemia:

The most prevalent cause of anemia globally is **iron deficiency**, which can be suspected from a low mean cell volume (MCV) and the presence of hypochromic, microcytic red cells. Laboratory confirmation of iron deficiency can be achieved through several methods:

1. Measurement of **serum ferritin**
2. Measurement of **serum iron** along with either **total iron-binding capacity** or **transferrin**
3. Assessment of **red cell protoporphyrin**
4. Staining of bone marrow aspirates for iron

Once iron deficiency is diagnosed, it is crucial to investigate the underlying cause. This investigation should encompass inquiries related to blood loss, dietary insufficiency, and may necessitate stool examinations for parasites and occult blood. Endoscopic examination of the gastrointestinal tract may be required to rule out occult malignancies, alongside tests for coeliac disease. The differential diagnosis for iron deficiency anemia includes **anemia of chronic disease** (or anemia of inflammation). Clinical and laboratory features indicative of inflammation or chronic infection may lead to this diagnosis, which is confirmed by observing normal or high serum ferritin levels alongside reduced serum iron, transferrin, and iron-binding capacity. Serum soluble transferrin receptors may

be advantageous in differentiating between iron deficiency anemia and anemia of chronic disease when ferritin levels are ambiguous; however, further research is needed to establish the overall diagnostic accuracy of these tests.

The **thalassemias** also result in microcytosis, but both α and β thalassemia traits are typically associated with an increased red blood cell (RBC) count and normal or near-normal hemoglobin levels, despite a considerable reduction in MCV and mean cell hemoglobin (MCH). In contrast, in iron deficiency anemia, the MCV and MCH do not decrease until hemoglobin levels are significantly reduced. Further investigations, such as **high-performance liquid chromatography (HPLC)** or **hemoglobin electrophoresis**, supplemented by measurements of hemoglobin A2 and hemoglobin F, usually confirm the diagnosis of β thalassemia trait. Diagnosing α thalassemia trait is more challenging; detection of infrequent hemoglobin H inclusions is generally feasible in α^0 thalassemia trait, but definitive diagnosis requires **deoxyribonucleic acid (DNA)** analysis. The identification of α^0 thalassemia heterozygosity is clinically significant for predicting the risk of hemoglobin Bart's hydrops fetalis.

Macrocytic Anemia:
A high MCV, characterized by oval macrocytes and hypersegmented neutrophils, suggests **folate** or **cobalamin deficiency**, warranting assays of these vitamins. Plasma methylmalonic acid assays can serve as a useful second-line test to clarify uncertainties regarding biochemical or functional cobalamin deficiencies. Serum folate is the first-line test to evaluate folate status and possesses equivalent diagnostic capability to red cell folate.
Subsequent investigations may include:

- Malabsorption studies
- Tests for coeliac disease
- Screening for intrinsic factor antibodies

In patients exhibiting these blood film findings alongside normal folate and cobalamin assays, hematinic deficiency cannot be completely excluded, necessitating further investigations. Since there is no definitive test for cobalamin deficiency, treatment should be initiated if there is a strong clinical suspicion, regardless of test results, to prevent neurological impairment. In cases lacking intrinsic factor antibodies, the diagnosis of **pernicious anemia** may be presumed. Pernicious anemia is often associated with autoimmune thyroid disease and other autoimmune disorders, such as diabetes mellitus.

A high MCV may also result from **alcohol excess**, **liver disease**, or the use of certain drugs like **hydroxycarbamide**. Macrocytosis due to chronic hemolysis is characterized by increased numbers of immature red cells, which appear larger and bluer than normal red cells (known as polychromatic macrocytes) on a Romanowsky-stained peripheral blood film. An automated reticulocyte count or supravital staining of blood films can confirm reticulocytosis. Untreated anemia associated with polychromasia typically indicates blood loss or hemolysis. The combination of red cell fragments, thrombocytopenia, and polychromasia suggests **microangiopathic hemolytic anemia**. This condition is a medical emergency as it may be indicative of **thrombotic thrombocytopenic purpura**, which necessitates immediate treatment, often via plasma exchange. Therefore, these findings should trigger further tests, including platelet counts, coagulation

studies, renal function assessments, measurement of **ADAMTS13** concentration, and investigation for infection or neoplastic disease.

Normocytic Anemia:

Normochromic, normocytic anemia frequently results from an underlying chronic, non-hematological disease. Investigations should encompass screening for renal insufficiency, subclinical infections, autoimmune diseases, and neoplasia. In cases of anemia characterized by a lack of polychromasia, confirmed by reticulocytopenia, this points to a primary failure of erythropoiesis or a lack of compensatory increased red cell production in blood loss or hemolysis. Examination of the bone marrow may assist in identifying hematological causes for normochromic, normocytic anemia, such as **myelodysplastic syndromes (MDS)** or **aplastic anemia**. Staining for iron may also reveal a blockage in iron metabolism, suggestive of anemia associated with chronic inflammatory disease.

Leucopenia

Neutropenia:

After excluding physiological variations, ethnicity, and familial or cyclic neutropenia, the nonhaematological causes of isolated neutropenia that should be considered include overwhelming infections, autoimmune disorders (e.g., systemic lupus erythematosus), radiation exposure, drug effects (particularly from anticancer agents), and large granular lymphocytic leukaemia. A bone marrow examination can help differentiate between peripheral destruction (indicated by increased marrow myeloid precursors) and stem cell failure (characterized by a lack of marrow myeloid precursors). Typical bone marrow findings in drug-induced neutropenia show a relative paucity of mature neutrophils, while in infant genetic agranulocytosis (Kostmann syndrome), there is a maturation arrest at the promyelocytic stage.

Reduced Numbers of Other Blood Cells:

Lymphocytes, eosinophils, and basophils may also decrease due to physical stressors such as surgery, trauma, and infections. A combination of lymphopenia with neutrophilia is common in severe acute respiratory syndrome and various other acute illness scenarios. Lymphopenia, especially affecting CD4 cells, is associated with HIV infection and renal failure. Monocytopenia (defined as a monocyte count < 0.2 × 10^9/L) is typically seen in hairy cell leukaemia, which also presents with pancytopenia, distinct bone marrow histology, and lymphocytes with characteristic cytology and immunophenotype.

Thrombocytopenia:

Thrombocytopenia, the isolated finding of reduced platelet counts, requires confirmation that the laboratory result reflects a true reduction. Common causes of spurious thrombocytopenia include blood clots in the sample, platelet clumping, and platelet satellitism. Platelet clumping can occur in vitro due to temperature- or anticoagulant-dependent autoantibodies or from finger-prick samples. True thrombocytopenia often results from immune mechanisms (immune thrombocytopenia), infections (e.g., HIV), anticancer chemotherapy, medications (e.g., thiazide diuretics), alcohol excess, hypersplenism, or myelodysplastic syndromes (MDS). Recognition of heparin-induced thrombocytopenia and thrombosis is critical. In assessing thrombocytopenia, a

blood film examination is the first step. Combining the clinical context with findings from the blood film and bone marrow examination usually helps identify the causes of thrombocytopenia. An association with thrombosis, renal or hepatic dysfunction, and hemolytic anemia should prompt investigations for conditions like thrombotic thrombocytopenic purpura or, in pregnant women, the HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count). In cases where atypical features are present in the blood film, a bone marrow examination may be warranted to rule out acute leukaemia, especially in children.

Pancytopenia

Pancytopenia refers to a reduction in white blood cells (WBC), hemoglobin (Hb), and platelet count, commonly resulting from anticancer chemotherapy, HIV infection, hypersplenism, or bone marrow infiltration or failure. Bicytopenia, which involves a reduction in two cell lineages, shares similar causes with pancytopenia. A careful examination of the blood film is crucial when the cause of cytopenia is unclear from the clinical history. If no cause is evident, bone marrow aspiration and trephine biopsy may be necessary.

Qualitative Abnormalities of Blood Cells

In a healthy state, only mature cell forms are present in the peripheral blood. However, conditions that lead to overactive or functionally abnormal bone marrow may result in the release of immature cells, such as nucleated red blood cells, polychromatic red cells, myelocytes, and metamyelocytes into the bloodstream. Their presence indicates active hematopoiesis.

Abnormalities of All Cell Lines

The combination of anisopoikilocytosis, mild macrocytosis, hypogranular neutrophils with abnormal nuclear morphology, and platelet anisocytosis, often accompanied by quantitative abnormalities, is almost pathognomonic of myelodysplastic syndromes (MDS). These features reflect disturbances in the normal developmental pathways in the bone marrow, sometimes associated with nuclear-cytoplasmic asynchrony. Cytogenetic studies can confirm the diagnosis, particularly when cytological abnormalities are minimal, and assist in prognostic assessment.

Abnormalities of Individual Cell Lines

Red Cells:

Congenital abnormalities affecting the structure and content of red blood cells can lead to distinct morphological changes. Conditions such as **spherocytosis** and **elliptocytosis** may alter the shape of the cells, while **haemoglobinopathies** and **enzymopathies** can affect their content. The specific morphological changes observed can direct further diagnostic investigations, including:

- **Structural protein analysis**
- **Haemoglobin electrophoresis or High-Performance Liquid Chromatography (HPLC)**
- **Enzyme assays**

Certain red cell abnormalities can also hint at underlying pathologies. For instance, the presence of **target cells** may suggest the need for liver function tests, whereas increased **rouleaux formation** may warrant investigations for conditions such as **multiple myeloma** or other inflammatory diseases.

White Cells:
Congenital abnormalities in neutrophils are rare; however, morphological changes similar to those seen in congenital disorders, such as **pseudo-Pelger–Huët cells**, can be observed in acquired conditions like **myelodysplastic syndromes (MDS)**. Reactive lymphocyte changes, including increased cell size, irregular shape, and basophilic cytoplasm, are frequently seen in **infectious mononucleosis**. This condition can be diagnosed through:

- **Serological screening tests**
- If serological tests are negative, **demonstration of IgM antibodies** to the **Epstein–Barr virus (EBV)** may be performed.

Atypical lymphocytes in infectious mononucleosis can sometimes be mistaken for lymphoma cells, necessitating further evaluation through **immunophenotyping studies** and assessing lymphocyte clonality, which can involve:

- **Light chain restriction**
- **Gene rearrangement studies**

Platelets:
Platelets may not show morphological abnormalities despite poor function, although some may appear hypogranular or larger than normal. A normal platelet count combined with abnormal results from in vitro platelet function tests typically indicates a platelet function disorder, although some patients may also experience thrombocytopenia. Hereditary platelet function disorders are rare and often manifest as bleeding diatheses. When a qualitative disorder is suspected, platelet examination should assess:

- **Size**
- Cytological features indicative of **platelet alpha-granule deficiency** (e.g., **grey platelet syndrome**)

Neutrophils should also be examined for inclusions suggestive of **MYH9-related disorders**, such as the **May–Hegglin anomaly**. Qualitative platelet disorders can generally be categorized into two main types:

1. **Abnormalities of platelet membrane glycoproteins** (e.g., **Bernard–Soulier syndrome**, **Glanzmann thrombasthenia**)
2. **Abnormalities of platelet secretory function** (e.g., **storage pool diseases**)

Acquired disorders of platelet function are more prevalent than hereditary ones. Hematological conditions linked to platelet dysfunction include:

- **Myeloproliferative neoplasms**
- **MDS**
- **Dysproteinaemias** (associated with plasma cell neoplasms)

Numerous commonly prescribed medications, including **aspirin** and **nonsteroidal anti-inflammatory drugs (NSAIDs)**, can interfere with platelet function. Additionally, systemic conditions such as **chronic renal failure** and **cardiopulmonary bypass** are associated with a bleeding tendency due to qualitative platelet defects. Most acquired functional defects do not result in observable abnormalities in platelet morphology. However, in cases of MDS and, to a lesser extent, in myeloproliferative neoplasms, **hypogranular** and **giant platelets** may be noted.

Specific Tests for Common Haematological Disorders:
This section outlines common haematological disorders along with recommended investigations to aid in diagnosis. The tests provided are indicative and may vary based on local expertise and technology available within a general haematology department.

Red Cell Disorders
Microcytic Hypochromic Anaemias:
For more detailed information, refer to Chapters 9 and 14. Suggested investigations include:

- **Measurement of serum ferritin** or iron levels, alongside total iron-binding capacity or transferrin assay, red cell protoporphyrin, or soluble transferrin receptors.
- **Bone marrow aspirate** with staining for iron.
- **Stool examination** for occult blood.
- **Gastrointestinal imaging and endoscopy**, with biopsies as needed; in rare cases, blood loss studies with **51Cr-labelled red cells** may be warranted.
- **Tests for malabsorption**.
- **Serological tests for coeliac disease**, such as tissue transglutaminase antibodies.
- **Serum lead levels** of lead poisoning is suspected.

If **thalassaemia** is suspected, further tests should include:

- **HPLC** or haemoglobin electrophoresis with haemoglobin A2 and F measurements.
- **Haemoglobin H preparation**.
- **Family studies**.
- **DNA analysis** if the diagnosis is clinically significant.

Macrocytic Anaemias:
If macrocytic and megaloblastic erythroid maturation is confirmed, further investigations as described in Chapter 10 should be performed. Typical assays and investigations for megaloblastic anaemia can often lead to a diagnosis without requiring a bone marrow aspirate. Causes of macrocytosis may also include alcohol excess, liver disease, MDS, hydroxycarbamide administration, and hypothyroidism. Additionally, reticulocytosis can elevate the mean corpuscular volume (MCV).

Aplastic Anaemia:
Investigations include:

- **Cobalamin and folate assays** (note that bone marrow hypoplasia is rare).
- **Viral studies**, especially for EBV, HIV, and hepatitis viruses.
- **Bone marrow aspirate and trephine biopsy**, including cytogenetic analysis.
- **Flow cytometry** for glycosylphosphatidylinositol-anchored proteins to detect a **paroxysmal nocturnal haemoglobinuria (PNH)** clone, followed by urine examination for haemosiderin if positive.

- **Peripheral blood gene mutation analysis** for **dyskeratosis congenita** if there are relevant clinical features or lack of response to immunosuppressive therapy.

If **Fanconi anaemia** is suspected:

- Conduct studies on the **sensitivity of chromosomes** to breakage by DNA cross-linking agents.

Haemolytic Anaemias:

A haemolytic process may be suspected with the following signs:

- **Falling haemoglobin levels**.
- **Reticulocytosis**.
- **Jaundice** with an increase in unconjugated bilirubin levels (refer to Chapters 9, 10, and 11).

White Cell Disorders

The blood film plays a critical role in differentiating white cell disorders, although it may appear normal in some cases (e.g., certain patients with lymphoma or neutrophil functional defects). Changes in white cell numbers or morphology can occur rapidly in response to local or systemic conditions. In chronic leukaemias, bone marrow aspiration might not significantly contribute to diagnosis; however, the pattern of neoplastic cell infiltration observed on trephine biopsy can have diagnostic or prognostic implications (e.g., in lymphoma and chronic lymphocytic leukaemia).

Acute Leukaemia:

Key investigations include:

- **Full blood count and peripheral blood film**.
- **Bone marrow aspirate and trephine biopsy**.
- **Blood or marrow immunophenotyping** for monitoring minimal residual disease (cytochemical stains may be used if immunophenotyping is unavailable).
- **Cytogenetic analysis**.
- **Molecular studies** (e.g., **fluorescence in situ hybridisation (FISH)**) for identifying specific mutations, such as:
    - **Acute lymphoblastic leukaemia (ALL)** with hyperdiploidy or ETV6–RUNX1 fusion.
    - **BCR–ABL1 fusion** in adults with ALL.
    - Other oncogene mutations (e.g., **NPM1**, **CEBPA**, and possibly **FLT3** in AML).

Neutropenia

Investigations may include:

- **Cobalamin and folate assays**.
- **Autoantibody screen**, including rheumatoid factor and investigations for systemic lupus erythematosus.
- **Serial neutrophil counts** for cyclical neutropenia.
- **Tests for antineutrophil antibodies**.
- **Bone marrow aspirate and trephine biopsy**.
- **Flow cytometry** for PNH (as noted above).

- Consider **clonality studies** to investigate for abnormal T-cell populations.

Chronic Myelogenous Leukaemia:
Investigations include:

- **Full blood count and peripheral blood film**.
- **Bone marrow aspirate**.
- **Cytogenetic analysis**.
- **Molecular studies** (e.g., real-time quantitative reverse transcriptase or FISH) for BCR–ABL1 transcripts.
- **Neutrophil alkaline phosphatase score** using cytochemistry (only if cytogenetic and molecular genetic analyses are not available).

Common Haematological Disorders and Investigations

1. Red Cell Disorders

Microcytic Hypochromic Anaemias

- **Tests:**
  - Serum ferritin or iron plus total iron-binding capacity or transferrin assay, red cell protoporphyrin, or soluble transferrin receptors.
  - Bone marrow aspirate with iron staining.
  - Stool examination for occult blood.
  - Gastrointestinal imaging and endoscopy, with biopsies as appropriate.
  - Tests for malabsorption (e.g., serological tests for coeliac disease).
  - Serum lead level (if lead poisoning suspected).
- **If Thalassaemia is suspected:**
  - HPLC or haemoglobin electrophoresis with A2 and F measurements.
  - Haemoglobin H preparation.
  - Family studies.
  - DNA analysis (if clinically significant).

Macrocytic Anaemias

- **Tests:**
  - Cobalamin and folate assays.
  - Viral studies (EBV, HIV, hepatitis).
  - Bone marrow aspirate and trephine biopsy.
  - Flow cytometry for PNH (if indicated).

Aplastic Anaemia

- **Tests:**
  - Cobalamin and folate assays.
  - Bone marrow aspirate and trephine biopsy with cytogenetic analysis.
  - Peripheral blood gene mutation analysis (for dyskeratosis congenita).
- **If Fanconi Anaemia is suspected:**
  - Chromosome breakage sensitivity studies.

Haemolytic Anaemias

- **Tests:**
  - Full blood count and reticulocyte count.
  - Unconjugated bilirubin levels.

2. White Cell Disorders

Acute Leukaemia

- **Tests:**
  - Full blood count and peripheral blood film.
  - Bone marrow aspirate and trephine biopsy.
  - Immunophenotyping of blood or marrow.
  - Cytogenetic analysis.
  - Molecular studies (e.g., FISH analysis).

Neutropenia

- **Tests:**
  - Cobalamin and folate assays.
  - Autoantibody screen.
  - Serial neutrophil counts.
  - Bone marrow aspirate and trephine biopsy.

Chronic Myelogenous Leukaemia

- **Tests:**
  - Full blood count and peripheral blood film.
  - Bone marrow aspirate.
  - Cytogenetic analysis for BCR–ABL1 transcripts.
  - Neutrophil alkaline phosphatase score.

3. Chronic Lymphoproliferative Disorders / Lymphadenopathy

- **Tests:**
  - Full blood count and peripheral blood film.
  - Serum protein electrophoresis and immunoglobulin concentrations.
  - Bone marrow aspirate and trephine biopsy.
  - Flow cytometry immunophenotyping.
  - Cytogenetic or molecular genetic analysis.

Myelomatosis (Plasma Cell Myeloma)

- **Tests:**
  - Full blood count and peripheral blood film.
  - Serum and urine protein electrophoresis.
  - Bone marrow aspirate with cytogenetic or FISH analysis.
  - Radiologic skeletal survey.

4. Other Disorders

Thrombocytopenia

- **Tests:**
  - Full blood count and blood film.
  - Reticulocyte count.
  - Direct antiglobulin test.
  - HIV and hepatitis screening.

Myeloproliferative Neoplasms

- **Tests:**
  - Full blood count and blood film.
  - JAK2 and CALR mutation analysis.
  - Bone marrow aspirate and trephine biopsy.

Myelodysplastic Syndromes

- **Tests:**
  - Full blood count and blood film.
  - Bone marrow aspirate and trephine biopsy.

- Cytogenetic analysis.

Pancytopenia with Splenomegaly

- **Tests:**
  - Cobalamin and folate assays.
  - Bone marrow aspirate and trephine biopsy.
  - Biopsy of palpable lymph nodes or liver biopsy.

Classification of Haematological Neoplasms

Standards for Assessment and Diagnosis

- Classifications are based on the World Health Organisation (WHO) guidelines, which include:
  - Clinical history and physical examination.
  - Morphology (cytology or histology).
  - Immunophenotyping.
  - Cytogenetic analysis.
  - Molecular genetic analysis (if applicable).

Provisional Diagnoses

- The previous French–American–British (FAB) classification may be used for provisional diagnoses when advanced techniques are unavailable, particularly in acute leukaemia cases.

Consistency Across Centres

- Strict adherence to classification criteria is essential for consistency in diagnosis and treatment across different healthcare settings.

Conclusion

Disorders affecting red and white blood cells, including anemia and leukemia, represent significant clinical challenges that necessitate a nuanced understanding of hematological testing and diagnosis. While abnormalities in blood cell counts can often be symptomatic of primary hematological disorders, they may also reflect a range of non-hematological conditions or therapeutic influences. The initial diagnostic approach involves a comprehensive clinical history and meticulous physical examination, which are paramount in directing subsequent laboratory investigations. The interpretation of screening test results requires an appreciation of the physiological variations due to factors such as age, sex, and ethnicity, as well as the inherent limitations of each test. Quantitative abnormalities, such as erythrocytosis, leukocytosis, and thrombocytosis, can provide critical insights into the underlying pathology. For instance, conditions like polycythemia vera, characterized by elevated hematocrit levels, and chronic myelogenous leukemia, associated with neutrophilia and immature myeloid cells, highlight the importance of targeted investigations. Similarly, the characterization of anemia into microcytic, macrocytic, and normocytic forms, accompanied by tailored investigation strategies, underscores the need for a systematic approach. For example, the presence of basophilic stippling in microcytic cells may suggest thalassemia or lead poisoning, while dimorphic blood films may indicate congenital sideroblastic anemia. Ultimately, the effective use of basic hematological tests not only facilitates the rapid identification of underlying pathologies but also directs attention to more specific diagnostic assessments. By integrating clinical findings with laboratory results, healthcare providers can ensure accurate diagnoses and tailored treatment plans for patients with blood

disorders. This comprehensive understanding is essential for improving patient outcomes and enhancing public health initiatives in hematology.

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اضطرابات كريات الدم الحمراء والبيضاء، مثل فقر الدم واللوكيميا

الملخص:
الخلفية :يمكن أن تعكس اضطرابات كريات الدم الحمراء والبيضاء، مثل فقر الدم واللوكيميا، حالات دموية وغير دموية. يُعتبر فقر الدم تحديًا سريريًا شائعًا، مما يستدعي تقييمًا دقيقًا عند اقترانه بأعراض مثل تضخم الطحال، تضخم العقد اللمفاوية، أو ميول النزيف.
الهدف :يهدف هذا المقال إلى استكشاف المنهج التشخيصي لاضطرابات الدم، مع التأكيد على أهمية اختبارات الفحص الأولية وتفسيراتها.
الطرق :تم إجراء مراجعة شاملة للاختبارات المعملية، بما في ذلك تركيز الهيموجلوبين، وعدد كريات الدم البيضاء، وفحص اللطخة الدموية الطرفية. يناقش المقال تفسير النتائج، مع مراعاة عوامل مثل العمر والجنس والخلفية العرقية.
النتائج :توضح النتائج أن الشذوذات في عدد خلايا الدم يمكن أن تشير إلى حالات مرضية مختلفة. قد تشير الزيادة في عدد الخلايا إلى الأورام النخاعية، بينما قد تنشأ الأعداد المنخفضة من عوامل مثل فرط الطحال، أو العدوى، أو العوامل المثبطة لنخاع العظم. يصنف المقال فقر الدم أيضًا إلى أنواع مكروسيتية، ماكروسيتية، ونورموسيتية، مع مخططات تدفق توضح تسلسل التحقيق لكل نوع.
الاستنتاج :يتطلب فهم تعقيدات اضطرابات الدم منهجًا منهجيًا للتشخيص. يمكن أن يؤدي الاستخدام الفعال للاختبارات الأساسية إلى توجيه التحقيقات الإضافية، مما يساعد في النهاية على تحديد وإدارة الحالات الدموية الكامنة.
الكلمات المفتاحية :فقر الدم، اللوكيميا، اضطرابات الدم، اختبار الدم، اختبارات الفحص، التشخيص.