WHITE CELL DISORDERS
Disorders of white cells include deficiencies (leukopenias) and proliferations, which may be reactive or neoplastic. Reactive proliferation in response to an underlying primary, often microbial, disease is fairly common. Neoplastic disorders, though less common, are more ominous.

NON-NEOPLASTIC DISORDERS OF WHITE CELLS

Leukopenia is most commonly the result of a decrease in neutrophils (the most prevalent circulating white cells).

Neutropenia
Neutropenia: a reduction below normal of the number of neutrophils in peripheral blood; when severe, it is referred to as agranulocytosis, where affected persons are extremely susceptible to bacterial and fungal infections, which can lead to death.

Etiology and Pathogenesis
The mechanisms that cause neutropenia can be broadly divided into two categories:

1. Inadequate or ineffective granulopoiesis, which is a manifestation of:
   A. Generalized marrow failure as in:
      - Aplastic anemia
      - A variety of leukemias
      - Megaloblastic anemia
   B. Isolated neutropenia; there is involvement of neutrophilic precursors only as is seen with
      - Congenital
      - Idiopathic benign (racial or familial e.g. Africans and in the Middle East)
      - Cyclical neutropenia syndrome (with 3-4 weeks periodicity)

2. Accelerated removal or destruction of neutrophils:
   - Acquired: drug-induced (immune-mediated or direct toxicity)
   - Overwhelming bacterial (typhoid, miliary tuberculosis), viral (hepatitis, influenza, HIV), fungal infections
   - Splenomegaly that leads to sequestration and accelerated removal of neutrophils

Pathologic features
The changes in the bone marrow (BM) depend on the underlying mechanism.
- Hypercellular marrow; is seen when the neutropenia results from excessive destruction of the mature neutrophils or from ineffective granulopoiesis, as occurs in megaloblastic anemia.
- Marked decrease in maturing granulocytic precursors in the marrow; as associated with the use of certain drugs that suppress granulopoiesis.
- All marrow elements are suppressed; seen after treatment with most myelotoxic drugs but erythropoiesis and megakaryopoiesis can be normal if the responsible agent specifically affects the granulocytes.

The main problem with neutropenia is infection. They commonly take the form of ulcerating, necrotizing lesions of the mouth, pharynx, or other sites within the oral cavity. These lesions often show a massive growth of microorganisms.

Lymphopenia: a reduction below normal of the number of lymphocytes in peripheral blood and are associated with:
1. Congenital immunodeficiency diseases
2. Acquired:
   - Advanced HIV infection
   - Treatment with corticosteroids and other immunosuppressive therapy
   - Hodgkin disease
   - Widespread irradiation

**Reactive Leukocytosis**
An increase in the number of white cells is common in a variety of reactive inflammatory states caused by microbial and non-microbial stimuli. Leukocytosis is relatively non-specific and can be classified on the basis of the particular white cell series affected.

- **Neutrophilic Leukocytosis (Neutrophilia)**
  - a. Acute bacterial infections (especially pyogenic)
  - b. Sterile inflammation caused by tissue necrosis (myocardial infarction, burns)
  - c. Metabolic disorders (uremia, eclampsia, acidosis, gout)
  - d. Neoplasms of all types
  - e. Acute hemorrhage or hemolysis
  - f. Treatment with myeloid growth factors (G-CSF, GM-CSF)

- **Eosinophilic Leukocytosis (Eosinophilia)**
  - a. Allergic disorders such as asthma, hay fever, allergic skin diseases
  - b. Parasitic infestations
  - c. Drug sensitivity
  - d. Collagen vascular disorders (polyarteritisnodosa, vasculitis)
  - e. Certain malignancies (e.g., Hodgkin disease and some non-Hodgkin lymphomas)
  - f. Treatment with GM-CSF
  - g. Idiopathic (Hypereosinophilic syndrome)
  - h. Neoplastic; as seen in myeloproliferative neoplasms, and chronic eosinophilic leukemia

- **Basophilic Leukocytosis (Basophilia)**: often indicative of myeloproliferativeneoplasms (e.g., chronic myeloid leukemia). Reactive modest increase is seen in ulcerative colitis, myxoedema, drug allergies and smallpox or chickenpox infections.

- **Monocytosis**
  - a. Chronic bacterial infections (e.g., tuberculosis, brucellosis, endocarditis, typhoid)
  - b. Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
  - c. Rickettsiosis
  - d. Malaria
  - e. Hodgkin disease, acute myeloid leukemia and other malignancies
  - f. Myelodysplastic syndrome
  - g. Inflammatory bowel diseases (e.g., ulcerative colitis)

- **Lymphocytosis**
  - a. Acute infections: infectious mononucleosis (Epstein-Barr virus), rubella, mumps, infectious hepatitis, cytomegalovirus, HIV, herpes, *B. pertussis*
  - b. Chronic infections: brucellosis,typhoid fever, syphilis, healingTB, toxoplasmosis
  - c. Chronic lymphoid leukemias
  - d. Acute lymphoblastic leukemia
  - e. Non-Hodgkin lymphoma (some)
  - f. Thyrotoxicosis
NEOPLASTIC PROLIFERATIONS OF WHITE CELLS

A. Lymphoid neoplasms, which include Hodgkin and non-Hodgkin lymphomas, acute and chronic lymphoid leukemias, and plasma cell dyscrasias and related disorders.

B. Myeloid neoplasms arise from stem cells that normally give rise to the formed elements of the blood: granulocytes (neutrophils, eosinophils and basophils), red cells and platelets. The myeloid neoplasms fall into three fairly distinct subcategories:

1. Acute myeloid leukemias: immature progenitor cells accumulate in the BM
2. Chronic myeloproliferative neoplasms: in which inappropriately increased production of formed blood elements leads to elevated blood cell counts
3. Myelodysplastic syndromes, which are characteristically associated with ineffective hematopoiesis and cytopenias.

ACUTE LEUKEMIAS (AL)

There are two major types of AL; acute lymphoblastic (ALL) and acute myeloblastic (AML). The pathophysiology, laboratory findings, and clinical features of one closely resemble those of the other.

Acute leukemia is usually an aggressive clonal malignant transformation involving the hematopoietic stem cells or early progenitors and characterized by uncontrolled proliferation of blasts in the BM with spillage into the peripheral blood and variable infiltration of other organs.

Etiology of AL

Several factors have been linked to the occurrence of AL including:

I. Environmental Agents

A. Ionizing Radiation

Exposure to atomic bomb explosions is associated with increased incidence of AL; younger age and those who are closer to the hypocenter are at particularly high risk. The predominant type is AML though ALL is reported in younger individuals. Exposure to diagnostic X-rays or radioisotopes at diagnostic levels (low dose) does not increase the risk. Infants whose mothers were exposed to X-rays during pregnancy are at higher risk.

B. Chemicals

Exposure to the following has been noted to be associated with a higher incidence

- **Benzene**
  a. Benzene and other petroleum derivatives
  b. Shoe makers and plastic glues
  c. Handling buses and trucks
- **Alkylating agents**: (cytotoxic drugs used in the treatment of certain malignancies)

II. Host susceptibility to AL is determined by

A. Genetic factors

- If one identical twin is affected, the other twin has a 20% chance of developing ALL.
- Those with Down's syndrome have 10-30 fold ↑ risk (> 3y; lymphoid, < 3y; myeloid).
- Patients with Bloom's syndrome, Fanconi anemia and Ataxia telangiectasia are associated with increased risk.

B. Acquired factors; AL show increased incidence in association with the following

- Myelodysplasia (myelodysplastic syndrome).
- After chemotherapy ± radiotherapy
• Chronic myeloproliferative neoplasms.
• Aplastic anemia.
• Paroxysmal nocturnal hemoglobinuria.

III. Oncogenic viruses: there is no good evidence except for HTLV-1, which may cause adult T-cell leukemia/lymphoma.

IV. Others: there is a significant correlation between infants with AL and alcohol intake, smoking and exposure to benzene and petroleum derivatives of their mothers during pregnancy.

Pathophysiology of Acute Leukemias

• *In AL there is a block in differentiation* which leads to the accumulation of immature leukemic blasts in the BM, which suppress the function of normal hematopoietic stem cells by physical displacement and other poorly understood mechanisms.

• Eventually BM failure results, which accounts for the major clinical manifestations of AL.

The acute leukemias have the following clinical characteristics:

• **Variable age of onset:** childhood AL (age <15 years) is usually ALL (80%) whereas adult AL (age ≥15 years) is usually AML (80%).

• **Abrupt onset especially in children**

• **Symptoms related to depression of normal marrow function.** These include:
  a. Fatigue (due mainly to anemia)
  b. Fever (reflecting mainly infections resulting from neutropenia)
  c. Bleeding such as aspetechiae, ecchymoses, epistaxis, gum bleeding (secondary to thrombocytopenia).

• **Symptoms related to organ or tissue infiltration.**
  Generalized lymphadenopathy, splenomegaly, hepatomegaly and testicular involvement these are more pronounced in ALL than in AML. Central nervous system manifestations these include headache, vomiting, and nerve palsies resulting from meningeal spread; these features are more common in children than in adults and are also more common in ALL than AML. Gum infiltration is more common in AML. Arthralgia, bone pain and tenderness.

Laboratory diagnosis of Acute Leukemias

The diagnosis of AL is based on the presence of ≥ 20 % blasts in the BM and/or peripheral blood. However; it can be diagnosed with even < 20 % blasts if specific leukemia-associated cytogenetic or molecular genetic abnormalities are present.

It is of great practical importance to distinguish ALL from AML. The nuclei of lymphoblasts have somewhat coarse and clumped chromatin and one or two nucleoli; myeloblasts tend to have finer chromatin with multiple nucleoli and more cytoplasm, which may contain granules or Auer rods.

• **Blood film:**
  a. RBCs: anemia is almost always present.
  b. WBCs: total WBC count may show high count (where blasts are self-evident), or low count (blasts may be present or absent).
  Neutropenia is also a common finding in the peripheral blood.
  c. Platelet count is reduced in most cases (i.e. <150,000/μL or <150 × 10^9/L).
• **BM aspirate is necessary to confirm the diagnosis (especially when low counts).**
• **BM trephine biopsy is only essential when:**
1. BM aspirate is inadequate; this is commonly due to BM fibrosis.
2. To distinguish whether a poor aspirate is due to hypocellularity or persistent leukemia.

Investigations

Hematological: BF and BM findings are already mentioned.

Biochemical tests may reveal increased S. uric acid, S. LDH, and hypercalcemia.

Liver and Renal Function Tests are performed as a baseline before treatment begins.

Radiological Examination may reveal lytic bone lesions, mediastinal widening caused by enlargement of the thymus and/or mediastinal lymphadenopathy.

CSF examination may show blast cells, indicating CNS involvement.

Cytochemistry is useful if the leukemia is not obviously myeloid.

Immunophenotyping is indicated in all patients in whom the leukemia is not obviously myeloid.

Cyto genetic analysis is essential in all patients, best performed on BM aspirate.

Classification of acute leukemia is based on:

1. Morphology of blasts
2. Cytochemistry through the use of special stains like; SBB, PAS, MPO, Estrases…etc
3. Immunophenotyping (cell surface marker analysis by flow cytometry).
4. Cytogenetic analysis
5. Molecular genetic analysis

Morphological classification

I. French American British (FAB) classification (1976)

A. Acute Lymphoid Leukemia (ALL) is classified into three subtypes:
   - ALL- L1: Monomorphic blasts, majority are small, high nucleo-cytoplasmic (N/C) ratio, and scanty cytoplasm with small or inconspicuous nucleoli.
   - ALL- L2: Heterogeneous blasts, variable sizes and N/C ratios, more prominent nucleoli with nuclear membrane irregularities.
   - ALL- L3: Monomorphic large blasts with prominent nucleoli and strongly basophilic, vacuolated cytoplasm.

B. Acute Myeloid Leukemia (AML) is classified into eight subtypes:
   - M0: AML with minimal evidence of myeloid differentiation
   - M1: AML without maturation
   - M2: AML with maturation
   - M3: Acute promyelocytic leukemia
   - M4: Acute myelomonocytic leukemia
   - M5: Acute monoblastic(M5a), acute monocytic(M5b) leukemia
   - M6: Acute erythroleukemia
   - M7: Acute megakaryoblastic leukemia

II. WHO classification (2000 & 2002)

There was a consensus that FAB L1, L2 and L3 of ALL are no longer relevant, since L1 and L2 morphology do not predict immunophenotype, genetic abnormalities, or clinical behavior. ALL-L3 is generally equivalent to Burkitt lymphoma in leukemic phase and should be diagnosed as such.

The WHO classification of AML had reduced the blast threshold for diagnosis from 30% (in FAB classification) to 20% in the peripheral blood and/or BM. In addition, patients with
certain clonal, recurrent cytogenetic abnormalities should be considered to have AML regardless the blast percentage.

**Cytochemistry of AL**
- ALL is negative for Myeloperoxidase, Sudan Black B, and Non-specific estrases. Periodic Acid Schiff is positive in many cases.
- AML is positive for Myeloperoxidase, Sudan Black B, and Non-specific estrases. PAS is positive in AML-M6

**Immunophenotyping of AL**
This is very useful in typing and subtyping of AL. The specific marker for B-cells is CD79a;CD3 for T-cells. The most specific myeloid marker is anti-MPO.

**Karyotyping of AL**
**ALL:** the most common karyotypic abnormalities in pre-B-cell tumors is hypoploidy (>50 chromosomes/cell) which is associated with t(12:21) chromosomal translocation. The presence of these aberrations correlates with a good prognosis. Poor outcomes are observed with pre-B-cell tumors that have translocations involving chromosome 11q23 or the Philadelphia (Ph+) chromosome.

**AML:** good outcome correlates with t(8:21) and t(15:17). Conversely, poor outcome correlates with Ph+, t(6:9) and hyperploidy.

**Course and Prognosis of AL**
If untreated, patients will only survive for few months, and they will usually die either of severe infection or bleeding due to progressive BM replacement by blast cells. ALL in general carries a better prognosis than AML. Children 2 to 10 years of age have the best prognosis; most can be cured. Other groups of patients do less well.

**THE CHRONIC LYMPHOID LEUKEMIA**
A number of disorders are included in this group characterized by accumulation in the blood of mature lymphocytes of either B- or T-cell type. In general the diseases are incurable but tend to run a chronic and fluctuating course.

**Diagnosis**
This group is characterized by a chronic persistent lymphocytosis. Subtypes are distinguished by:
1. Morphology.
2. Immunophenotype.
3. Cytogenetics.
4. DNA analysis may be useful in showing a monoclonal rearrangement of either immunoglobulin (Ig) gene (for B-cells) or T-cell receptor (TCR) gene (for T-cells).

**CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)**
CLL is a low grade clonal lymphoproliferative disorder characterized by progressive accumulation of usually well-differentiated CD5+ lymphocytes in the BM with an accompanying peripheral lymphocytosis. Involvement of lymph nodes (LN), spleen and liver invariably occurs sometimes during the disease course. The etiology is unknown. There is seven-fold increased risk of CLL in the close relatives of the patient. CLL is the most common of the chronic lymphoid leukemia, accounting for 60% of cases, and it is the most common in the West representing about 25% of all leukemias in adults > 50 years. CLL is rare in the Far East.

**Clinical features of CLL**
1. The majority of patients are over 50 years.
2. Most cases are diagnosed when routine blood test is performed.
3. Lymphadenopathy: Symmetrical enlargement of cervical, axillary oringuinal LNs is usually discrete and non-tender.
4. Splenomegaly and less commonly hepatomegaly are common in intermediate stage.
5. Features of anemia and thrombocytopenia present in advanced disease.
6. Early bacterial infections predominate but with advanced disease viral and fungal infections such as herpes zoster are also seen. This is due to immunosuppression which is a significant problem resulting from hypogammaglobulinemia and cellular immune dysfunction.

Laboratory findings
- **Lymphocytosis**: the absolute lymphocyte count is > 5 × 10⁹/L (up to 300 × 10⁹/L or more). The predominant cells are small lymphocytes with compact dark-staining round nuclei, scanty cytoplasm, and little variation in size. The CLL lymphocytes are fragile and are frequently disrupted during the preparation of smears, which produces characteristic smudge cells. Variable numbers of larger activated lymphocytes are also usually present in the blood smear.
- **Anemia** and **Thrombocytopenia** are seen in later stages due to BM failure, hypersplenism or autoimmune process.
- **BM examination** shows lymphocyte infiltration >30 % of all nucleated marrow cells. BM biopsy reveals early interstitial, nodular, mixed (nodular & interstitial) and late diffuse pattern of involvement.
- **Immunophenotype** shows pan-B-cell markers (CD19⁺ & CD22⁺) with CD5⁺, CD23⁺ and weak expression of SmIg (surface membrane immunoglobulin for IgM or IgD) with weak or negative FMC7 and CD79b.
- **Serum Ig reduction** becomes more marked with advanced disease.
- **Karyotype**. The most common cytogenetic abnormalities are: deletion of 13q14 (15-20%) which is associated with good prognosis. Triosomy 12 (10-15%), deletion at 11q23 (20%) and structural abnormalities of 17p involving the p53 gene (all carry bad prognosis).

Staging of CLL
It is useful to stage patients at presentation both for prognosis and for deciding on therapy. The stage is determined by several variables such as peripheral lymphocyte count, BM lymphocyte percentage, presence or absence of lymphadenopathy, hepatosplenomegaly. The presence of anemia < 10 gm/dL and/or thrombocytopenia < 100,000/µL indicates advanced disease stage.

Course and prognosis
Many patients, in early stage, never need therapy. Survival ranges from 12 years for early stage to < 3 years for advanced stage. Cure is rare. CLL may transform to:
- CLL/PL or frank prolymphocytic leukemia (PLL) that is resistant to treatment
- Richter's transformation (Immunoblastic lymphoma, localized high grade NHL)

PROLYMPHOCYTIC LEUKEMIA
The prolymphocyte is around twice the size of a CLL lymphocyte and has a larger central nucleolus. PLL typically presents with splenomegaly without lymphadenopathy and with a high and rapidly rising lymphocyte count. Diagnosis is made by appearance of > 55% prolymphocytes in blood film. Anemia is a poor prognostic feature. Response to treatment is poor.

HAIRY CELL LEUKEMIA
HCL patients typically present with infections, anemia or splenomegaly. Lymphadenopathy is very uncommon. Lymphocyte count is rarely > 20 × 10⁹/L. The peripheral blood shows
pancytopenia and monocytopenia with variable number of unusually large lymphocytes with villous cytoplasmic projections. BM biopsy; shows a characteristic appearance of mild fibrosis and a loose diffuse cellular infiltrate. Patients can expect long-term remission with treatment.

CLASSIC CHRONIC MYELOPROLIFERATIVE NEOPLASMS (MPN)
This term covers a group of clonal disorders of the hemopoietic stem cells that lead to effective proliferation of one or more hematopoietic component in the BM, and in many cases, in the liver and spleen leading to elevated blood levels of one or more myeloid cell lineages (i.e. erythrocytosis, leukocytosis, and thrombocytosis). The classic MPNs include:

1. Chronic myeloid leukemia (CML - Ph^+ve)
2. Polycythemia vera (PV)
3. Essential thrombocythemia (ET)
4. Primary myelofibrosis (MF)

These disorders are closely related to each other and transitional forms and evolution from one entity into another occurs during the course of the disease.

Karyotype and Molecular Features
- The vast majority of CML show the Philadelphia chromosome, in(90-95%) and M-BCR-ABL p210 in (99% of patients). Ph chromosome is a minute chromosome 22 from which the long arms are deleted (22q-). It is part of reciprocal translocation between chromosome 9 & 22 t(9; 22) in which part of 22 is clearly visible on 9 but the part of 9 on 22 is too small to be distinguished cytogenetically. This translocation is detected by PCR or FISH techniques.
- Almost all PV patients and about 50% of ET and MF cases show Janus-Associated Kinase 2 (JAK2) mutation that occurs in the BM and in the peripheral blood granulocytes. This mutation is not found in secondary polycythemia, or reactive thrombocytosis. JAK2plays a major role in normal myeloid development.

POLYCYTHEMIA
Polycythemia (erythrocytosis): is an increase in the hemoglobin (Hb) concentration above the upper limit of normal for the patient's age and sex in specific population. It is classified according to its pathophysiology:
A. Absolute
   1. Primary
      o Polycythemia vera
      o Familial (congenital) Polycythemia.
   2. Secondary
      Caused by compensatory erythropoietin increase in:
      • High altitudes
      • Pulmonary disease and alveolar hypoventilation (sleep apnoea)
      • Cardiovascular disease, especially congenital with cyanosis.
      • Increased affinity hemoglobin (familial Polycythemia).
      • Heavy cigarette smoking
      Caused by inappropriate erythropoietin increase in:
      • Renal diseases (e.g. hydronephrosis, vascular impairment, cysts, carcinoma)
      • Tumors (such as uterine leimyoma, renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma).
B. Relative (Stress or pseudopolycythemia):
a. Cigarette smoking
b. Dehydration: water deprivation, vomiting.

POLYCYTHEMIA VERA (PV)

PV is an insidious clonal MPN characterized by generalized hyperplasia of all marrow elements, but dominated by expansion of the red blood cell volume >25% above mean normal predicted value or Hb > 18.5 g/dl for men and > 16.5 g/dl for women. In 50% of patients, there is also neutrophilia and thrombocytosis. There is endogenous erythroid colony growth despite subnormal serum erythropoietin level. The clinical features include headache, dyspnea, blurred vision, night sweats, pruritus (characteristically after hot bath) and plethoric appearance. Splenomegaly occurs in 75% of patients. Hypertension occurs in one-third of patients. The course may be complicated by hemorrhage, thrombosis, gout and peptic ulceration. Typically, the prognosis is good with a median survival of 10-16 years. Thrombosis and hemorrhage are the major clinical problems. Transition from PV to MF and AL may occur.

ESSENTIAL THROMBOCYTHEMIA (ET)

ET is characterized by a sustained increase in platelet count > 400 × 10^9/L (400,000 /µL), because of megakaryocytic proliferation and overproduction of platelets. There is endogenous megakaryocyte growth independent of thrombopoietin. Other causes of raised platelet count need to be fully excluded before the diagnosis can be made. Many cases are symptomless and diagnosed on routine blood counts. Thrombosis in about 25% of the patients may occur in venous or arterial systems. Hemorrhage as a result of abnormal platelet function may cause either chronic or acute bleeding. Erythromelalgia is a characteristic symptom (it is a burning sensation felt in hands or feet and relieved by aspirin). Up to 40% of patients will have palpable splenomegaly, whereas in others there may be splenic atrophy because of infarction. Abnormal large platelets and megakaryocyte fragments may be seen on blood film. BM typically shows an excess proliferation of abnormal large and mature megakaryocyte, and no or little granulocyte or erythroid proliferation. Often the disease is stationary for 10-20 years or more and has a lesser risk to transform to MF, AL and PV.

MYELOFIBROSIS (MF)

MF is a clonal MPN of the pluripotent hematopoietic stem cell, characterized by proliferation of multiple cell lineages and accompanied by progressive BM fibrosis, with development of hematopoiesis in the spleen and liver. The onset is insidious with symptoms of anemia. About ≥ ⅓ of the patients have previous history of PV. Massive splenomegaly is the main physical sign.

Laboratory findings:
1. Anemia is usual.
2. The WBC and platelet counts are frequently high at presentation but with advanced disease, leucopenia and thrombocytopenia are common.
3. A leukoerythroblastic blood film is found and the red cell morphology shows characteristic 'tear-drop' poikilocytes.
4. BM is usually unobtainable by aspiration (dry tap). Trephine biopsy shows hypercellular marrow; granulocytic proliferation and increased numbers of atypical megakaryocytes are frequently seen with often decreased erythropoiesis in pre-fibrotic phase with extensive marrow fibrosis in fibrotic phase.
In 10% of cases there is increased bone formation with increased bone density on X-ray (osteomyelosclerosis).

Neutrophil alkaline phosphotase (NAP) score is usually increased.

MF has the poorest prognosis of the MPNs; the median survival is 3-5 years (range 1-15 years). Causes of death include: heart failure, infection and in 10-20% of cases transformation to AML.

CHRONIC MYELOID LEUKEMIA (CML)

CML is a clonal genetic change in a pluripotential hematopoietic stem cell, which proliferates and generates a population of differentiated cells that gradually replaces normal hematopoiesis and leads to a greatly expanded total myeloid mass. CML represents about 15% of leukemia.

CML usually passes into 3 phases during its course:
A. Chronic Phase (CP),
B. Accelerated Phase (AP),
C. Blastic Phase (BP).

The Chronic phase (CP) usually lasts 2-7 years and in 50% of cases it is transformed to blastic phase directly. In up to 50% of cases the diagnosis is made incidentally from a routine blood count (asymptomatic). There may be features of anemia and of abnormal platelet function (bruising, epistaxis, menorrhagia, etc). Splenomegaly is nearly always present and is frequently massive. Gout and renal impairment (caused by hyperuricemia) may occur.

Laboratory findings
- Anemia; usually normochromic normocytic.
- Leukocytosis: usually in the range of 20-200 ×10⁹/L, occasional patients may present with leukocytosis >200 ×10⁹/L causing features of hyperviscosity.
- Blood film shows a full spectrum of granulocytic cells, ranging from blast forms (usually <10%) to mature neutrophils, with myelocytes and neutrophils predominating.
- The percentages of eosinophils and basophils are usually increased.
- Platelet numbers are usually ↑ in the range of 300-600 ×10⁹/L, but may be normal or ↓.
- NAP score is decreased or absent.

BM Aspirate:
- Markedly hypercellular marrow
- Blast cells < 10% of all nucleated cells (ANC).
- Eosinophils and basophils are usually prominent.
- Megakaryocytes are small, hypolobed and increased in numbers.

BM Biopsy shows complete loss of fat spaces due to dense hypercellularity.

The Advanced disease (AP & BP); the clinical features are quite variable
- Asymptomatic
- Patients may develop fever, excessive sweating, anorexia and weight loss or bone pain.
- Occasionally, patients present with generalized lymphadenopathy; LN biopsy shows nodal infiltration with blast cells that may be myeloid or lymphoid.
- Localized skin infiltrates may be seen. Discrete masses of blast cells may develop at almost any site; these are referred to as "Myeloid Sarcomas."

Laboratory findings
In AP: Blasts range (10-19%) in BF and/or BM, basophils ≥20%, platelet count <100 × 10⁹/L or persistently >1000 × 10⁹/L, increasing spleen size and WBCs unresponsive to therapy. There may be megakaryocytic proliferation in sizable sheets and clusters, associated with marked fibrosis, and/or severe granulocytic dysplasia.
In BP: Blasts ≥20%, or extramedullary blast proliferation (LN, skin, elsewhere), or detection of large foci or clusters of blats in BM biopsy.

**Course and prognosis**
- Patients with CML-CP usually show an excellent response to treatment with imatinib.
- Those who respond have prolonged survival and may never relapse.
- Transformation to AL ends with death within 2-6 months.
- Death usually occurs from blastic transformation or intercurrent hemorrhage or infection.

**MYELODYSPLASTIC SYNDROME (MDS)**

MDS is a group of clonal disorders of multipotent hematopoietic stem cells which are characterized by increasing BM failure with quantitative and qualitative abnormalities of megakaryocytes, erythroid and granulocytic cells. MDS is either primary or it is secondary to chemotherapy ± radiotherapy.

**Pathogenesis**

MDS starts following genetic damage to multipotent hematopoietic progenitor cell, leading to increased stem cell proliferation but **ineffective differentiation and maturation, resulting in a hypercellular BM with peripheral blood pancytopenia; this is the hallmark of the disease.**

Neutrophils, monocytes and platelets are often functionally impaired.

**Clinically,** the evolution of disease is often slow. The patients may be asymptomatic or present with anemia (transfusion-dependent), recurrent infections and easy bruising or bleeding.

**Laboratory findings**

**A. Peripheral Blood:**
- Pancytopenia is frequent
- Anemia
- Granulocytes are often decreased in number and frequently lack granulation
- Pelger anomaly (neutrophil with single or bilobed nucleus) is often present
- Platelets may be improperly large or small and are usually decreased in number
- Blasts in variable numbers are present in poor prognosis cases

**B. Bone Marrow:**
- Usually hypercellular
- Multinucleate normoblasts are seen
- Ring sideroblasts may be seen (>4 perinuclear iron granules/normoblast & covering ≥ ⅓ of the nuclear circumference)
- Granulocyte precursors show defective granulation
- Megakaryocytes are abnormal (micronuclear, small binuclear or polynuclear)

At least 10% of the cells in a lineage should be dysplastic to consider the diagnosis of MDS.

**PLASMA CELL DYSCRASIAS**

PCDs originate from a clone of B cells that differentiates into plasma cells and secretes a single complete and/or partial immunoglobulin (Ig). These disorders are also called monoclonal gammopathies, due to the presence of usually excessive amounts of serum Igs, referred to asparaprotein or M-protein.

**The plasma cell dyscrasias can be divided into many variants:**

1. Multiple Myeloma (MM)
MMis the most common of the malignant plasma cell dyscrasias. It is a neoplastic proliferation characterized by accumulation of clonal plasma cell in the BM, the presence of paraprotein in the serum and/or urine and related tissue damage that is usually associated with multifocal lytic lesions throughout the skeletal system. The etiology of the disease is unknown; dysregulation or increased expression of cyclin D1 and D3 is an early unifying event and IL6 is a potent growth factor for myeloma cells and is often active by autocrine mechanism. Hyperploidy is present in about half of cases whereas non-hyperploid cases have a high incidence of translocations involving the Ig heavy-chain gene (IGH) on chromosome 14. Monoallelic loss of 13q is frequent in both categories. All these genetic abnormalities are also seen in monoclonal gammopathy of undetermined significance (MGUS). The most common paraprotein is IgG (60%), followed by IgA (20% to 25%). In the remaining 15% to 20% of cases, the plasma cells produce only κ or λ light chains. Because of their low molecular weight, the free light chains are rapidly excreted in the urine, where they are termed Bence-Jones proteins (BJP). Even more commonly, malignant plasma cells produce both serum paraprotein and BJP in urine. The excess light chains have adverse effects on renal function.

**Gross pathologic features**
- Multiple myeloma presents most often as multifocal destructive bone lesions throughout the skeletal system. The affected bones are; vertebral column (65%), ribs (45%), skull (40%), pelvis (30%), and femur (25%). There are often pathological fractures and vertebral collapse.
- These focal lesions generally begin in the medullary cavity, erode the cancellous bone, and progressively destroy the cortical bone. The osteolytic lesions are caused by osteoclast activation resulting from high serum level of RANKL (receptor activator of nuclear factor-κB ligand), produced by plasma cells and BM stroma, which binds to RANK receptors on the osteoclast surface, which promotes the differentiation and activation of osteoclasts.

**Microscopic features**
- BM examination reveals an increased number of plasma cells (10 - 90%) of the cellularity.
- The neoplastic cells can resemble normal mature plasma cells, but they more often show abnormal features, such as prominent nucleoli or abnormal cytoplasmic inclusions containing immunoglobulin.
- Plasma cell infiltrations of soft tissues (plasmacytomas) can be encountered in the spleen, liver, kidneys, lungs, and lymph nodes early or with disease progression.
- Terminally, a leukemic picture may emerge (plasma cell leukemia or acute leukemia).
- **Metastatic calcification** stemming from bone resorption and hypercalcemia.
- **Myeloma nephrosis** refers to renal involvement; it is a distinctive feature of MM.
  - Proteinaceous casts are prominent in the distal convoluted tubules and collecting ducts. Most of these casts are made up of BJPs.
  - Some casts have tinctorial properties of amyloid.
  - Multinucleate giant cells created by the fusion of infiltrating macrophages usually surround the casts.
  - Very often the epithelial cells lining the cast-filled tubules become necrotic or atrophic because of the toxic actions of the Bence-Jones proteins.
  - Pyelonephritis can also occur as a result of the increased susceptibility to bacterial infections. Less commonly, interstitial infiltrates of abnormal plasma cells are seen.

**The clinical manifestations:**
1. **Bone pain,** especially backache is extremely common resulting from plasma cell infiltration, vertebral collapse and pathologic fractures.
2. **Features of anemia** result from BM replacement and inhibition of hematopoiesis.

3. **Recurrent bacterial infections** result from severe suppression of normal Ig secretion, abnormal cell-mediated immunity and neutropenia.

4. **Features of renal failure and/or hypercalcemia.** Renal insufficiency occurs in as many as 50% of patients as a result of proteinaceous deposit from heavy BJ proteinuria, hypercalcemia, uric acid, amyloid and pyelonephritis.

5. **Bleeding tendency.** Paraproteins may interfere with platelet function and coagulation factors; thrombocytopenia occurs in advanced disease.

6. **Amyloidosis** develops in 5% to 10% of patients with features such as macroglossia, carpal tunnel syndrome and diarrhea.

7. **Hyperviscosity syndrome** may occur in 2% of MM cases due to excessive production and aggregation of myeloma paraproteins. Purpura, hemorrhages, visual failure, CNS symptoms, neuropathies and heart failure may be present.

**Diagnosis of multiple myeloma** depends on three principal findings:

1. Paraprotein in serum and/or urine.
2. Presence of clonal plasma cells in the BM often with abnormal forms or plasmacytoma. The characteristic clonal immunophenotype is CD38<sup>high</sup>, CD138<sup>high</sup> and CD45<sup>low</sup>.
3. Complications related to organ damage or tissue impairment such as bone disease, renal impairment, anemia, hypercalcemia, hyperviscosity, amyloidosis or recurrent infection.

**Investigations in MM:**

- Electrophoresis of the serum and urine is an important diagnostic tool. In 97% of cases a monoclonal spike of complete Ig or Ig light chain can be detected in the serum and/or urine.
- Anemia is usually normochromic normocytic or macrocytic. Rouleaux formation is marked. Neutropenia and thrombocytopenia occur in advanced disease.
- Few plasma cells appear in the blood film in 15% of cases.
- High ESR and C-reactive protein.
- BM plasma cells are increased (usually >10% of ANC).
- Radiological; the diagnosis is strongly suspected when the characteristic focal, osteolytic *punched-out lesions* in the bone are present (in 60% of cases) especially when located in the vertebrae or calvarium. Generalized osteoporosis (20%) can also be seen and no *bone lesions* in (20%). In addition, pathological fractures or vertebral collapse are common.
- S. Calcium increased in 45% of patients. Typically, the serum alkaline phosphatase is normal (except following pathological fractures).
- S. Creatinine is raised in 20% of cases.
- S. Albumin decreases with advanced disease.
- S. β<sub>2</sub>-microglobulin is often raised (level < 4 mg/L imply a relatively good prognosis).

**Prognosis**

Multiple myeloma is a progressive disease. Patients with serum β<sub>2</sub>-microglobulin > 5.5 mg/L and serum albumin level < 35 g/L have poor survival as do those with frequent circulating plasma cells. The median survival with non-intensive chemotherapy is 3 - 4 years.

2. **Monoclonal Gammapathy of Undetermined Significance (MGUS)**

A serum paraprotein may sometimes be detected in asymptomatic individuals without any evidence of MM (related organ damage or tissue impairment) and is termed MGUS. It has a high prevalence (3.2% and 5.8% in individuals over 50 and 70 years of age, respectively), making this the most common plasma cell dyscrasia. There are no bone lesions, no BJP in urine and the
percentage of plasma cells in the BM is normal (<4%) or only slightly increased (<10%). Serumparaproteins are <30 g/L and serum light chains are ↑ in ⅓ of patients. Patients with MGUS develop a well-defined plasma cell dyscrasia (MM, LPL, or amyloidosis) at a rate of 1% per year. Moreover, MGUS cells often contain the same chromosomal translocations that are found in full-blown MM. Thus, the diagnosis of MGUS should be made with caution and only after careful exclusion of all other forms of monoclonal gammopathies, particularly MM.

3. **Localized Plasmacytomas** (solitary plasmacytoma)
   These are isolated plasma cell tumors involving the skeleton or the soft tissues. Extraosseous lesions occur mainly in mucosa of the upper respiratory tract (sinuses, nasopharynx, and larynx), GIT or the skin. The associated paraprotein disappears following radiotherapy to the primary lesion. Most of those with *solitary skeletal plasmacytomas* develop full-blown MM over a period of 5 to 10 years.

4. **Plasma cell leukemia**
   PCL occurs either as a late complication of MM or as a primary disease characterized by the presence of ≥ 20% plasma cells in the peripheral blood. There is pancytopenia, organomegaly, hypercalcemia, renal involvement and bone disease. The outlook is poor.

5. **Lymphoplasmacytic Lymphoma (LPL) / Waldenström macroglobulinemia (WM)**
   It is an indolent B-cell lymphoma with an IgM paraprotein that often behaves as cryoglobulin causing Raynaud’s phenomenon. Anemia, hepatosplenomegaly, lymphadenopathy and mucosal bleeding are common. Hyperviscosity syndrome is evident in 70% of patients especially with IgM levels >30 g/L, where plasmapheresis is a dramatically effective treatment. Bone lesions are rare, as is renal failure. Peripheral blood lymphocytosis is usually a feature of late disease. BM shows a pleomorphic, diffuse infiltrate of lymphocytes, plasmacytoid lymphocytes and plasma cells >30% of cells. The M-protein light chain is lambda λ in 75% of patients and 70% have BJP. Median survival is approximately 6 years.