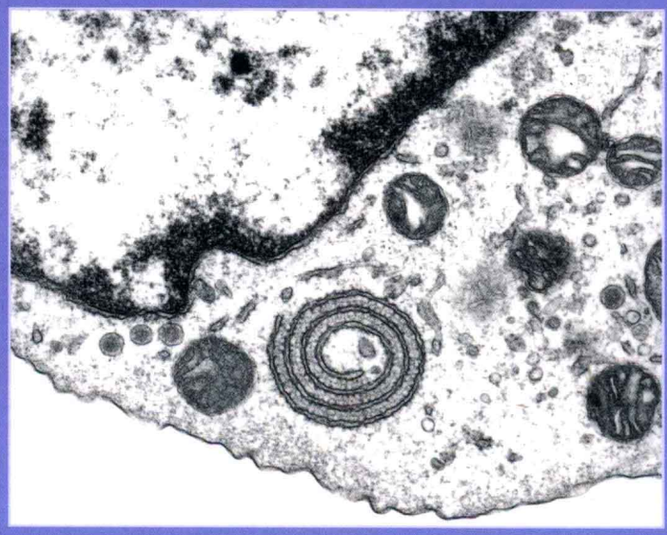
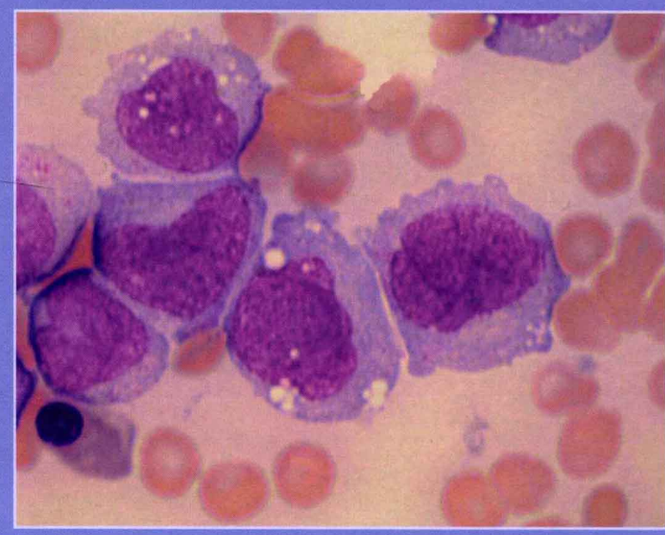
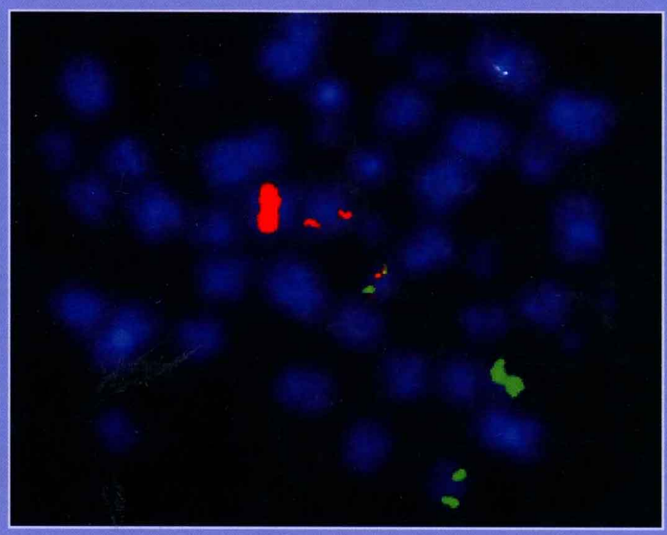
An Atlas of Investigation and Diagnosis

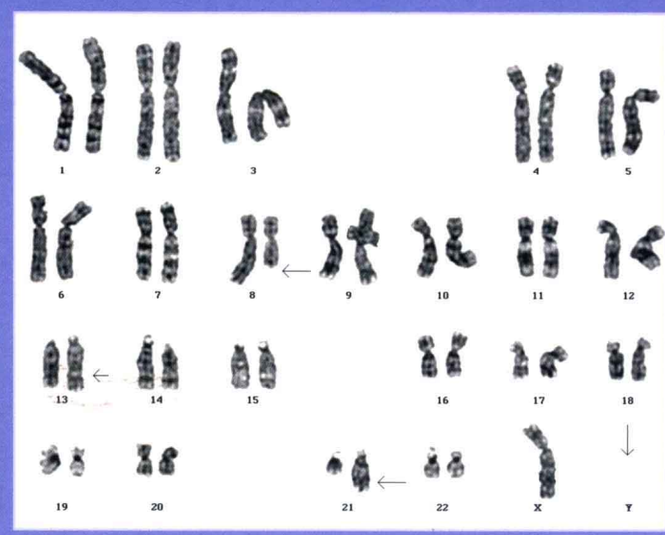
MYELOID MALIGNANCIES

Barbara J Bain • Estella Matutes









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An Atlas of Investigation and Diagnosis

MYELOID MALIGNANCIES

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Barbara J Bain
Estella Matutes

Abbreviations

aCML atypical chronic myeloid leukaemia
ALIP abnormal localization of immature precursors
ALL acute lymphoblastic leukaemia
AML acute myeloid leukaemia
ATRA all-*trans*-retinoic acid
BM bone marrow
c cytoplasmic
CAE chloroacetate esterase
CD cluster of differentiation
CEL chronic eosinophilic leukaemia
CML chronic myeloid leukaemia
CMML chronic myelomonocytic leukaemia
CNS central nervous system
DIC disseminated intravascular coagulation
FAB French–American–British
FISH fluorescence *in situ* hybridization
FSC forward light scatter
G-CSF granulocyte colony-stimulating factor
H&E haematoxylin and eosin
Hb haemoglobin concentration
Hct haematocrit
HIV human immunodeficiency virus
ICUS idiopathic cytopenia of undetermined significance
IPSS international prognostic scoring system
ITD internal tandem duplication
JMD juxtamembrane domain
JMML juvenile myelomonocytic leukaemia
LDC lymphoid dendritic cell
MDS myelodysplastic syndrome/syndromes
MGG May–Grünwald–Giemsa
MPD myeloproliferative disorder/disorders
MPN myeloproliferative neoplasm/neoplasms
MPO myeloperoxidase
NK natural killer
NSE non-specific esterase
PAS periodic acid-Schiff
PCR polymerase chain reaction
Ph Philadelphia
PTD partial tandem duplication
RAEB refractory anaemia with excess blasts
RARS-T refractory anaemia with ring sideroblasts and thrombocytosis
RBC red cell count
RCMD refractory cytopenia with multilineage dysplasia
RCMD-RS refractory cytopenia with multilineage dysplasia and ringed sideroblasts
RCUD refractory cytopenia with unilineage dysplasia
RT-PCR reverse transcriptase polymerase chain reaction
RQ-PCR real time quantitative polymerase chain reaction
SBB Sudan black B
SSC sideways light scatter
TdT terminal deoxynucleotidyl transferase
TKD tyrosine kinase domain
WBC white cell count
WHO World Health Organization
wt wild type

Contents

Chapter 1

Molecular basis and classification of myeloid neoplasms

Normal haemopoiesis

In the adult, normal haemopoiesis occurs predominantly in the bone marrow, although haemopoietic stem cells circulate in the blood stream and the potential for haemopoiesis in liver, spleen or other tissues is retained. All blood cells are derived ultimately from a pluripotent haemopoietic stem cell, able to give rise to lymphoid and myeloid lineages [1]. The pluripotent stem cells are capable not only of self renewal but also of generating multipotent myeloid stem cells and the common lymphoid stem cells (**Figure 1.1**). The multipotent stem cell gives rise in turn to committed progenitor cells from which cells of the major myeloid lineages are derived. Differentiation and maturation are controlled by a variety of cytokines which are to some extent specific for particular cell lines. In addition, the microenvironment and accessory cells such as fibroblasts and fat cells have a role in the differentiation and maturation of stem cells. Cells of haemopoietic origin include mast cells and osteoclasts.

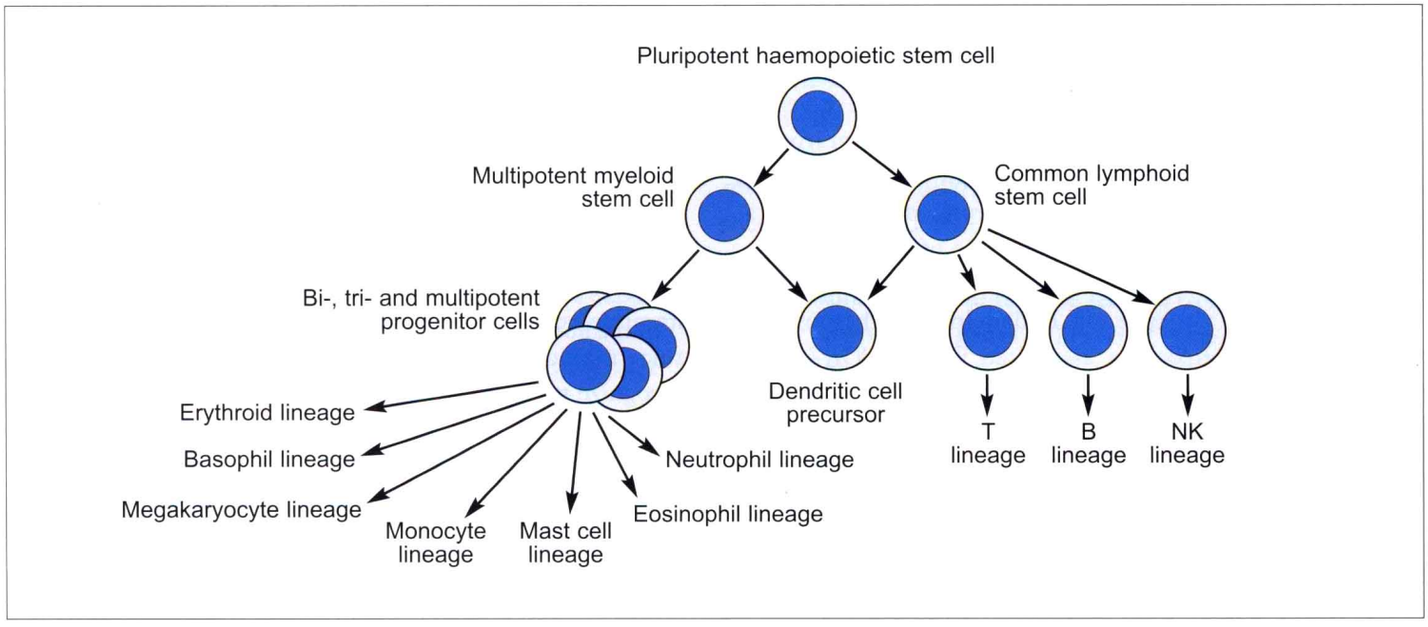

Figure 1.1 A diagram of the stem cell hierarchy and myeloid and lymphoid differentiation pathways. Abbreviation: NK, natural killer.

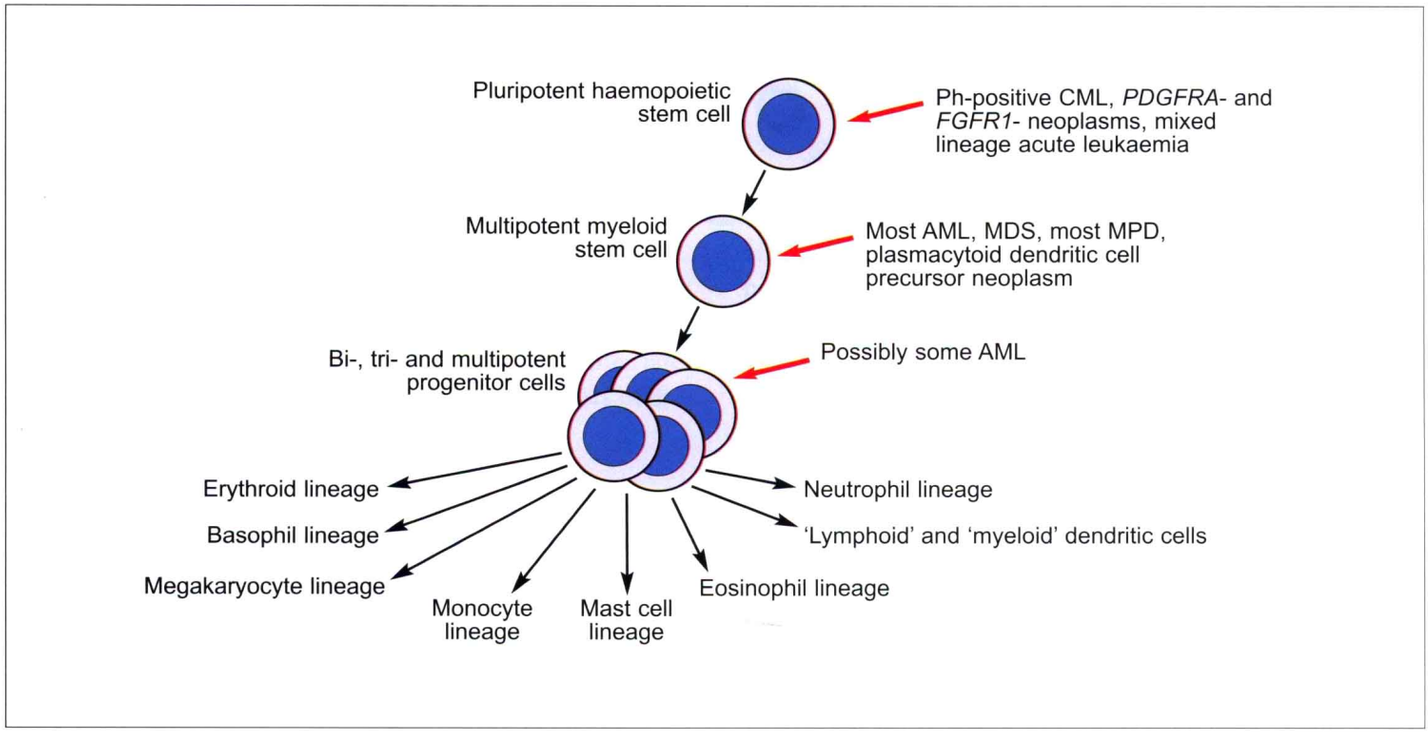

Figure 1.2 A diagram of the stem cell hierarchy and myeloid differentiation pathways showing the cell in which the causative mutation appears to occur in various haematological neoplasms. Abbreviations: AML acute myeloid leukaemia; CML chronic myeloid leukaemia; MDS myelodysplastic syndrome(s); MPD myeloproliferative disorder(s).

Myeloid neoplasms arise from mutation in a haemopoietic stem cell or progenitor cell (**Figure 1.2**). Many neoplasms, including most types of acute myeloid leukaemia (AML) and the myelodysplastic syndromes (MDS) arise from a mutated multipotent stem cell. Some chronic myeloid leukaemias arise from mutation in a pluripotent stem cell so that at one stage of the disease the leukaemia may manifest itself as a lymphoid leukaemia or lymphoma. This is true of Philadelphia (Ph)-positive chronic myeloid leukaemia associated with a *BCR-ABL1* fusion gene (in which B-lineage and less often T-lineage blast transformation can occur) and of *FGFR1*-related neoplasms, which at various stages of the disease may be manifest as chronic eosinophilic leukaemia, T-lineage lymphoblastic leukaemia/lymphoma, B-lineage lymphoblastic leukaemia/lymphoma or AML. It is possible that some subtypes of AML arise in a mutated committed progenitor cell without the capacity to differentiate into cells of erythroid or megakaryocyte lineages.

The molecular basis of haematological neoplasms

In common with other neoplasms, haematological neoplasms can be viewed as acquired genetic diseases in the sense that they result from genetic alteration in a stem cell that gives rise to an abnormal clone of cells, the behaviour of which is responsible for the disease phenotype. The host immune response also has a role in disease development since the body's immune response includes some ability to recognize tumour cells and destroy them.

Classification of haematological neoplasms

Classification of haematological neoplasms is moving from a period when classification was largely based on clinicopathological features, including morphology and, to a

lesser extent, immunophenotype, to a period when definitions are based to some extent on identified molecular abnormalities. Although certain syndromes are defined mainly on the basis of the genetic abnormality these must be interpreted in the light of the clinicopathological features. Thus t(9;22)(q34;q11) and *BCR-ABL1* fusion are the hallmark of chronic myelogenous leukaemia (CML) but they can also be observed in acute lymphoblastic leukaemia (ALL) and, uncommonly, AML. Similarly t(15;17)(q22;q12) is the hallmark of acute promyelocytic leukaemia, including its variant form but can be observed, albeit rarely, in transformation of a chronic myeloproliferative neoplasm (MPN). The conditions that are defined largely on a molecular basis are CML, the *FIP1L1-PDGFRA* syndrome and MPD associated with rearrangement of *PDGFRB* and *FGFR1* genes. A second group of disorders are currently defined on the basis of clinicopathological/morphological features supplemented by cytogenetic/molecular genetic information. This applies to AML, MDS, polycythaemia vera, essential thrombocythaemia, primary myelofibrosis, systemic mastocytosis and juvenile myelomonocytic leukaemia (JMML). There remains a third group of disorders where the disease definition is essentially based on clinicopathological/morphological features, even though relevant cytogenetic/molecular genetic abnormalities are sometimes found. At present chronic myelomonocytic leukaemia (CMML) and atypical chronic myeloid leukaemia (aCML) fall into this group. Although MDS has been placed in the second group, there is only a single cytogenetically defined entity and otherwise its definition remains largely clinicopathological and morphological; it has long been suspected that specific genetic abnormalities should be identifiable in subgroups of MDS but these have been slow to reveal themselves.

Myeloid neoplasms have been classified by various expert groups under the aegis of the World Health Organization (WHO) as shown, in simplified form, in *Table 1.1* (overleaf).

Oncogenic mechanisms

Oncogenic mechanisms differ between the chronic MPN and AML. The essential difference between the genetic events in the two groups of disorders is that in MPN they result in an expanded clone of proliferating cells able to differentiate into end cells of one or more myeloid lineages, whereas in AML cells continue to proliferate but are mainly unable to differentiate to end cells.

Mutations in myeloid malignancies include novel fusion genes and mutated genes. Fusion genes can result from a translocation, inversion, insertion or cryptic deletion. Mutated genes may harbour a point mutation, a partial duplication or a small insertion or deletion that alters the reading frame. Genes can be triplicated as the result of trisomy. Genes can be amplified (multiple copies) in double minute chromosomes or in homogeneously staining regions within chromosomes. There can also be epigenetic effects, such as an altered methylation status that alters gene expression. All these changes are related to the formation or activation of oncogenes. In addition, deletion or inactivation of tumour suppressor genes can contribute to oncogenesis.

In MPN there is often a mutation in a gene encoding a protein on a signalling pathway between the surface membrane and the nucleus; often this protein is a tyrosine kinase that becomes constitutively activated as a result of the mutation. The neoplastic cells are thus able to proliferate and differentiate without being dependent on growth factors. Examples of such constitutively activated tyrosine kinases include the product of the *BCR-ABL1* fusion gene in CML, and the product of a mutated *JAK2* gene (*JAK2* V617F) in almost all cases of polycythaemia vera and in some cases of essential thrombocythaemia, primary myelofibrosis and refractory anaemia with ring sideroblasts and thrombocytosis (RARS-T).

In AML there appears to be a need for at least two mutations to convey the leukaemic phenotype to the neoplastic cells and in some types of AML there are multiple mutations. Particularly in AML with multilineage dysplasia, secondary AML, therapy-related AML and AML in the elderly there are likely to have been multiple mutational events (which can include those leading to loss of activity of tumour suppressor genes). The first genetic subtypes of AML recognized were those associated with recurrent cytogenetic abnormalities that gave rise to fusion genes. Specifically these were: t(15;17)(q22;q12) associated with a *PML-RARA* fusion gene; t(8;21)(q22;q22) associated with *RUNX1-CBFA2T1*; and either inv(16)(p13q22) or t(16;16)(p13;q22) associated with *CBFB-MYH11*. Each of these subtypes was found to have characteristic cytological features. More recently, genetic subtypes of AML have been recognized, mainly among patients with normal cytogenetic analysis, that are characterized by gene mutation without

Table 1.1 An overview of the classification of myeloid neoplasms

Category	*Important subcategories*
Acute myeloid leukaemia (AML)	Therapy-related myeloid neoplasms AML with recurrent cytogenetic/genetic abnormalities AML with myelodysplasia-related changes AML not otherwise categorized
The myelodysplastic syndromes (MDS)	Refractory cytopenia, including refractory anaemia, with unilineage dysplasia Refractory anaemia with ring sideroblasts Refractory cytopenia with multilineage dysplasia (with or without ring sideroblasts) Refractory anaemia with excess blasts 5q– syndrome Myelodysplastic syndrome, unclassifiable Childhood myelodysplastic syndrome
Myeloproliferative neoplasm (MPN)	Chronic myelogenous leukaemia (with *BCR-ABL1* fusion gene) Chronic neutrophilic leukaemia (occasionally associated with *JAK2* V617F mutation) Chronic eosinophilic leukaemias and other chronic myeloid leukaemias (including those associated with rearrangement of the *PDGFRA*, *PDGFRB* and *FGFR1* genes)* Polycythaemia vera (usually has *JAK2* V617F mutation) Essential thrombocythaemia (often has *JAK2* V617F mutation) Myelofibrosis (often has *JAK2* V617F mutation) Mast cell disease: Cutaneous mastocytosis including urticaria pigmentosa Systemic mastocytosis (usually associated with KIT^{D816V} mutation) Mast cell leukaemia
The myelodysplastic/ myeloproliferative neoplasms (MDS/MPN)	Chronic myelomonocytic leukaemia Atypical chronic myeloid leukaemia Juvenile myelomonocytic leukaemia (often associated with either *PTPN11* or *NF1* or *RAS* mutation)

* In the WHO 2008 classification, myeloid and lymphoid neoplasms associated with rearrangement of neoplasms PDGFRA, PDGFRB and FGFR1 are assigned to a separate category.

chromosomal rearrangement. Specifically these are associated with mutations in either *NPM1* [2] or *CEBPA* [3]. Neither is associated with distinctive cytological features. It has been postulated that for any case of AML there is a need for two different types of mutation, one designated type I to indicate a mutation that conveys a proliferation or survival advantage to the cells and another, designated type II, which interferes with differentiation [4].

Table 1.2 Type I and type II mutations that can interact in the pathogenesis of AML

Class II mutation (interferes with differentiation)	*Class I mutation (conveys proliferation or survival advantage) (reported incidence in subtype shown in brackets)*
RUNX1-CBFA2T, usually resulting from t(8;21)(q22;q22)	*KIT* mutation (12–47% of cases) *NRAS* (c 10%) *FLT3*-ITD (c 4%)
CBFB-MYH11, usually resulting from inv(16)(p13q22) or t(16;16)(p13;q22)	*NRAS* (c 30–40%) *FLT3*-ITD (c 7%) *KIT* mutation (22–47% of cases)
PML-RARA, usually resulting from t(15;17)(q22;q12)	*FLT3*-ITD (c 30%) *NRAS* (c 2%)
CEBPA mutated	*FLT3*-ITD
NPM1 mutated	*FLT3*-ITD

ITD, internal tandem duplication

Type I and type II mutations are associated with each other in a non-random manner. It is the type II mutation that can be related to the clinical and haematological phenotype of the disease but the type I mutation is also likely to be essential for leukaemogenesis and often affects prognosis (*Table 1.2*).

In MDS, multiple genetic events occur, which can include changes in oncogenes and tumour suppressor genes. These processes are generally poorly understood. The net result is continuing cell proliferation but with ineffective haemopoiesis, i.e. with an increased rate of apoptotic death of haemopoietic cells in the bone marrow and a resultant failure of production of adequate numbers of end cells. The only subtype of MDS so far linked to a specific cytogenetic abnormality is the 5q– syndrome, in which there is an interstitial deletion of part of the long arm of chromosome 5; several candidate genes that are often deleted have been identified of which *RPS14* appears the most likely to be relevant [5]. A deletion of the tumour suppressor gene *TP53* at 17p13.1 occurs in some patients with MDS.

Aetiology

The aetiology of most instances of myeloid neoplasms is unknown. AML, MDS and MDS/MPN can result from exposure to radiation, anticancer chemotherapy and chemical carcinogens such as benzene. Cigarette smoking also increases the incidence of AML. CML can follow exposure to irradiation or topoisomerase-II-interactive drugs. Genetic predisposition also has an aetiological role. Down's syndrome predisposes to transient leukaemia in the neonatal period and to acute megakaryoblastic leukaemia in infants. Inherited defects in proto-oncogenes can predispose to leukaemia, e.g. germline mutation in *RUNX1* and in *CEBPA* predispose to AML. Germline mutation of *NF1* in neurofibromatosis type 1 and of *PTPN11* in Noonan syndrome predispose to JMML. Inherited defects in tumour suppressor genes likewise predispose to various types of leukaemia. Germline mutation of *TP53* in the Li Fraumeni syndrome, of *RB1* in familial retinoblastoma families and of *WT1* in familial Wilms' tumour families predispose to AML.

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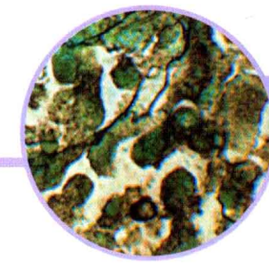
Chapter 2

Acute myeloid leukaemia



Acute myeloid leukaemia (AML) is a malignant disease, usually resulting from mutation in a multipotent haemopoietic stem cell. Normal polyclonal haemopoietic cells in the bone marrow are replaced by a clone of neoplastic cell with a growth advantage over normal cells and with a pronounced defect in differentiation. There is usually neutropenia, anaemia and thrombocytopenia as a result both of the differentiation defect of the neoplastic cells and of the crowding out of normal cells. Leukaemic cells may also suppress the growth of normal cells. Occasionally AML results from a mutation in a pluripotent haemopoietic stem cell able to give rise to both lymphoid and myeloid cells. In other categories of acute leukaemia the mutated cell that gives rise to the leukaemic clone may be a cell already committed to the granulocyte–monocyte lineages. The point in the stem cell hierarchy where mutations occur in cases of apparently pure erythroid leukaemia and megakaryoblastic leukaemia has not been defined.

Acute myeloid leukaemia usually arises *de novo*. However, a significant minority of cases represent evolution of a preceding haematological disorder, which may have been a myeloproliferative or myelodysplastic disorder, aplastic anaemia or paroxysmal nocturnal haemoglobinuria; these cases are referred to as secondary AML. Others are therapy-related, following prior administration of cytotoxic drugs or exposure to radiation. Further aetiological factors include benzene and cigarette smoking. AML is more common in men than women. The prevalence rises exponentially with age to about 18/100 000/year above the age of 65 years [1]. The median age of onset is about 65 years.

Clinical features

Clinical manifestations result either from the proliferation of leukaemic cells or from bone marrow failure that leads to a lack of normal cells. Leukaemic cells can infiltrate tissues, leading to hepatomegaly, splenomegaly, skin infiltrates and swollen gums. Tissue infiltration is particularly a feature when there is monocytic differentiation. As an indirect effect of the leukaemic proliferation there may be hyperuricaemia and occasionally renal failure. The lack of normal cells leads to clinical features of anaemia, neutropenia and thrombocytopenia. Thus there may be pallor, fatigue, breathlessness, fever due to opportunistic infections, purpura and visual impairment (due to retinal haemorrhage). In several subtypes of acute leukaemia, particularly but not only acute promyelocytic leukaemia, there is a profound coagulation defect as a result of both disseminated intravascular coagulation (DIC) and increased fibrinolysis. In such patients purpura and haemorrhagic manifestations are much more pronounced and can be life-threatening.

Occasionally patients with AML present with a tumour at an extramedullary site, e.g. soft tissues such as orbit, lymph nodes, or central nervous system (CNS), while the blood and bone marrow are still apparently normal. A tumour of this type is known as a granulocytic sarcoma or a myeloid sarcoma and it is more frequent in AML with differentiation, either granulocytic or monocytic (French–American–British (FAB) M2, M4 and M5 subtypes).

Haematological and pathological features

Typically patients with AML have an increased white cell count (WBC) as the result of the presence in the blood of a large number of blast cells. These may be myeloblasts, monoblasts or megakaryoblasts. Because of the lack of differentiation, there are usually few maturing cells so that the neutrophil count is reduced, but occasionally differentiation occurs with the production of dysplastic neutrophils. Sometimes monocytes are increased and occasionally eosinophils. There is a normocytic normochromic anaemia with an inappropriately low reticulocyte count. In patients with dysplastic features or a preceding myelodysplastic syndrome (MDS), the anaemia may be macrocytic. The platelet count is often reduced.

A bone marrow aspirate shows hypercellularity with an increase in blast cells. These may comprise almost all the bone marrow cells or there may also be maturing cells of neutrophil, eosinophil or monocyte lineage. As incorporated into the World Health Organization (WHO) classification, a blast cell count of 20% or more is now considered sufficient for a diagnosis of AML [2]. In some specific instances with recurring cytogenetic abnormalities, the blast cell percentage can be even lower (see below) and in patients with myeloid sarcoma, the blast count is not considered in the diagnosis of AML. Erythropoiesis is usually greatly reduced but may be increased. Megakaryocytes are usually reduced but occasionally increased. There may be dysplasia of one, two or three lineages. Trephine biopsy sections show the features that would be expected from the aspirate; if a particulate, cellular aspirate is obtained trephine biopsy is not essential but if the marrow is hypocellular or fibrotic it becomes important.

In rare cases, the bone marrow (aspirate and trephine biopsy specimen) is hypocellular with an increase in fat spaces but with blasts constituting a high percentage of the cells present. This group has been designated hypocellular or hypoplastic AML and does not correspond to a specific morphological or genetic category (**Figures 2.1–2.4**).

Other relevant tests include a coagulation screen,

Table 2.1 A summary of the FAB classification of AML

FAB category	*Characteristics*
M0	AML with minimal evidence of differentiation: MPO, SBB and NSE stains positive in fewer than 3% of blast cells
M1	AML without maturation: MPO and SBB stains positive in at least 3% of blast cells but fewer than 10% of maturing cells of granulocyte or monocyte lineage
M2	AML with maturation: more than 10% of maturing cells of granulocyte lineage and fewer than 20% of monocyte lineage
M3	Acute promyelocytic leukaemia: the dominant cell is either a hypergranular promyelocyte or a dysplastic hypogranular promyelocyte with a lobulated nucleus
M4	Acute myelomonocytic leukaemia: more than 20% of cells are of granulocyte lineage and more than 20% are of monocyte lineage
M5	Acute monocytic/monoblastic leukaemia: NSE positive, fewer than 20% of cells are of granulocyte lineage
M6	Erythroleukaemia: more than 50% of cells are erythroid with blasts constituting at least 30% of non-erythroid cells
M7	Acute megakaryoblastic leukaemia: the dominant cell is a megakaryoblast with megakaryocytes sometimes being increased in number and dysplastic

AML, acute myeloid leukaemia; MPO, myeloperoxidase; NSE, non-specific esterase; SBB, Sudan black B

including fibrinogen assay and assay of D-dimer, to identify DIC. Uric acid may be elevated and renal and liver function may be impaired.

The FAB group classified AML, mainly on the basis of morphological features, into seven subtypes, which are summarized in *Table 2.1* [3–7]. Diagnosis of AML according to the FAB classification, requires a minimum of 30% bone marrow blast cells (whereas in the WHO classification it has been modified to 20% blast cells). Assigning cases to the M0 and M7 categories requires immunophenotyping as well as morphology and cytochemistry. Haematological features differ between the FAB categories.

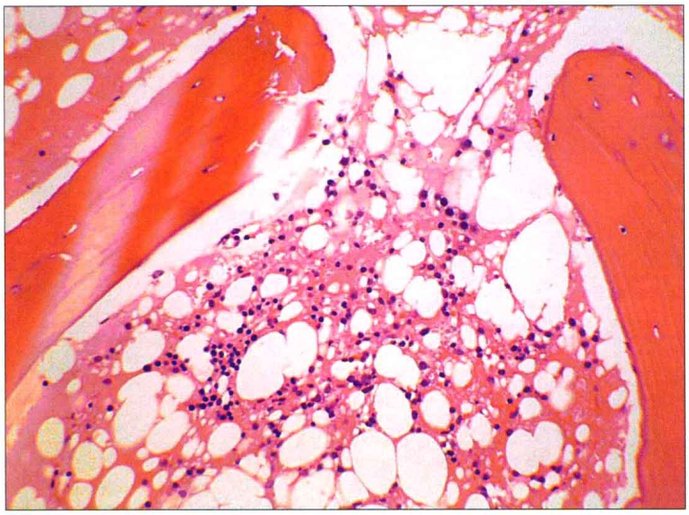


Figure 2.1 Trephine biopsy section from a patient with hypoplastic AML showing a markedly hypocellular bone marrow with blast cells. H&E, × 20 objective.

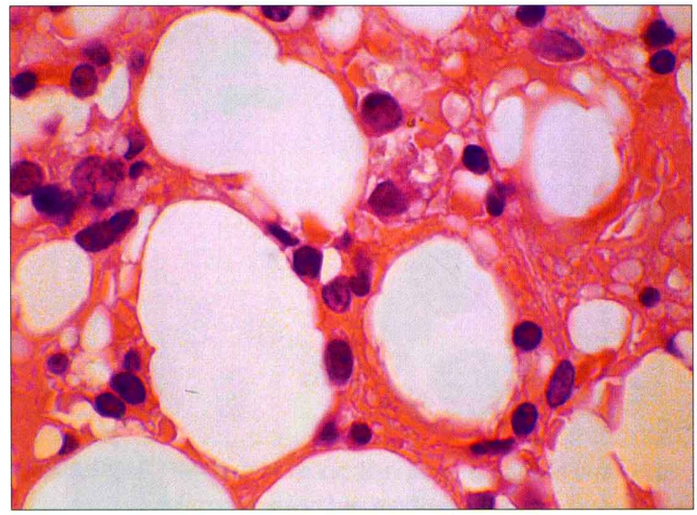


Figure 2.2 Trephine biopsy section from a patient with hypoplastic AML (same patient as **Figure 2.1**) showing that most cells present are blast cells. H&E, × 100 objective.

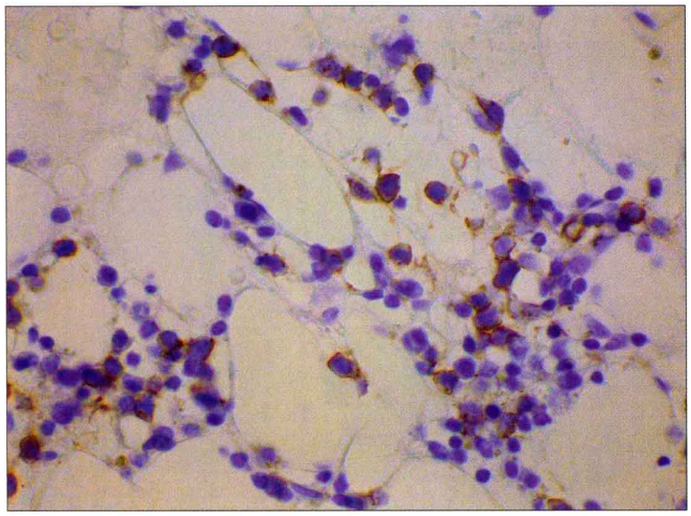


Figure 2.3 Trephine biopsy section from a patient with hypoplastic AML (same patient as **Figure 2.1**) showing that the majority of cells express the stem cell marker, CD34. Immunoperoxidase, CD34, × 50 objective.

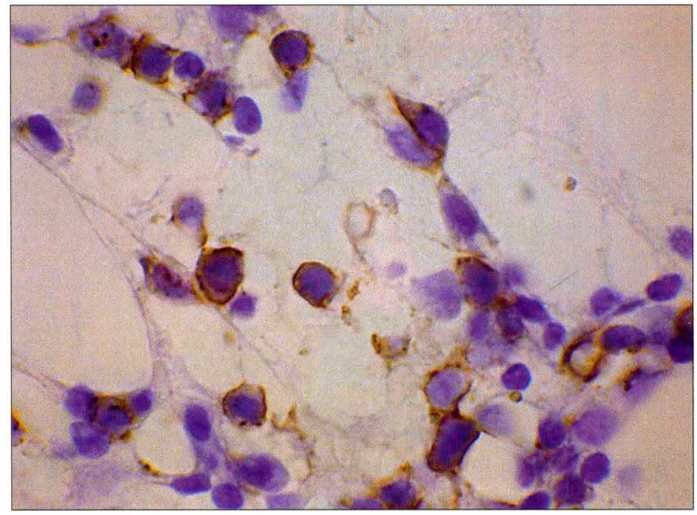


Figure 2.4 Trephine biopsy section from a patient with hypoplastic AML (same patient as **Figure 2.1**) showing that the majority of cells express the stem cell marker, CD34. Immunoperoxidase, CD34, × 100 objective.

The FAB classification

The FAB categories are still of relevance since the initial assessment of any case is morphological; in FAB M3 AML the rapid and accurate morphological diagnosis is of considerable clinical importance. The features of the FAB categories will therefore be summarized and illustrated.

M0 AML

In FAB M0 AML (**Figures 2.5–2.7**) the dominant cell in the bone marrow is a blast cell which has no morphological features that identify it as myeloid. There are no Auer rods and no Sudan black B (SBB)- or myeloperoxidase (MPO)-positive granules. The leukaemia is identified as myeloid by immunophenotyping or by ultrastructural cytochemistry (**Figure 2.8**).

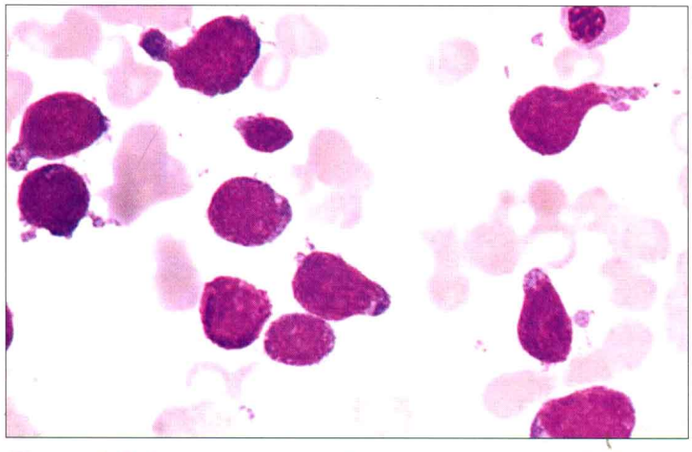


Figure 2.5 Peripheral blood film of a patient with FAB M0 AML showing agranular blast cells with basophilic cytoplasm and a high nucleocytoplasmic ratio; some have a hand-mirror configuration. MGG, low power.

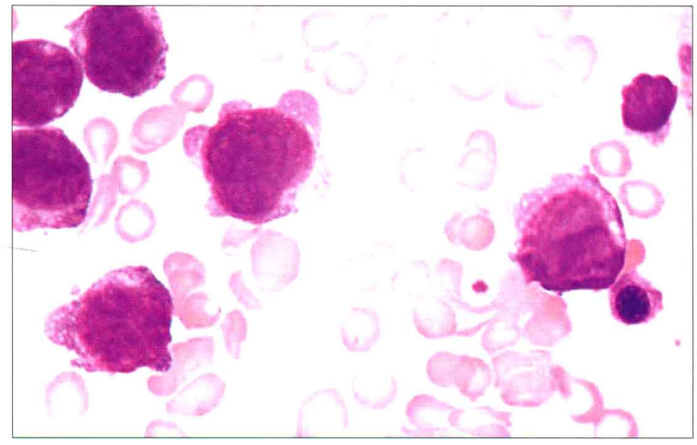


Figure 2.6 Bone marrow aspirate film from a patient with FAB M0 AML showing agranular blast cells with basophilic cytoplasm, which is forming blebs; cytoplasmic blebs are more characteristic of FAB M7 AML. MGG, high power.

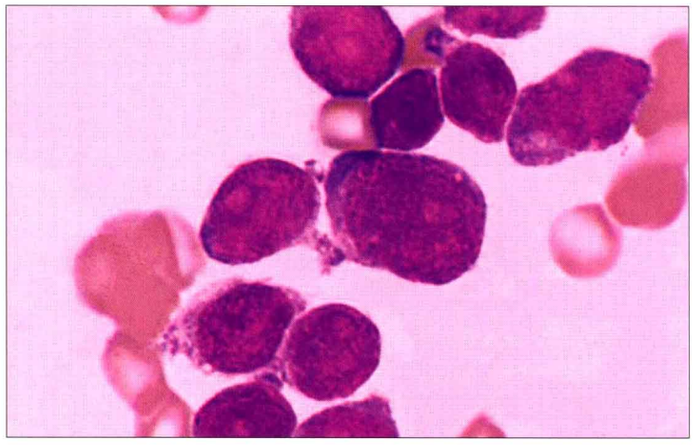


Figure 2.7 Bone marrow aspirate film from a patient with FAB M0 AML showing agranular blast cells with a high nucleocytoplasmic ratio and basophilic cytoplasm; the blast cells show considerable variation in cell size. MGG, high power.

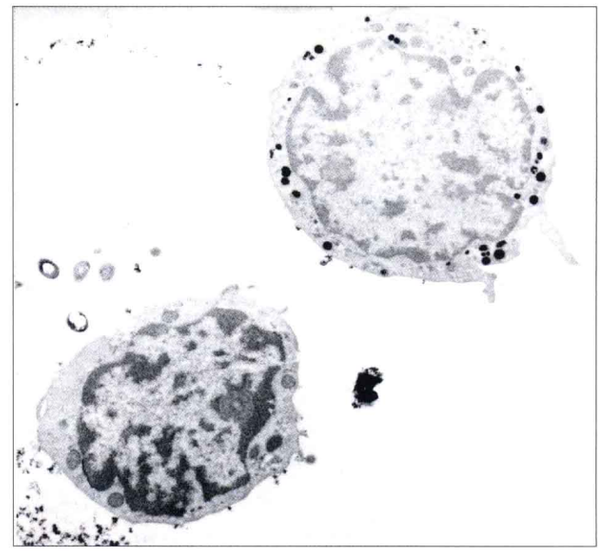


Figure 2.8 Ultrastructural cytochemistry showing MPO activity in blast cells from a patient with M0 AML. Unstained section, MPO reaction.

M1 AML

In FAB M1 AML (**Figures 2.9–2.14**) the dominant cell in the bone marrow is a myeloblast, identified as such by the presence of Auer rods and by SBB or MPO positivity in at least 3% of blast cells; positivity in a lower percentage of cells is not significant since a low number of cytochemically-positive blast cells may represent residual normal cells. Auer rods are also positive for SBB and MPO. Blast cells also give positive reactions for naphthol AS-D chloroacetate esterase (CAE). This subtype of AML is distinguished from M2 and M4 AML by the lower number of maturing cells.

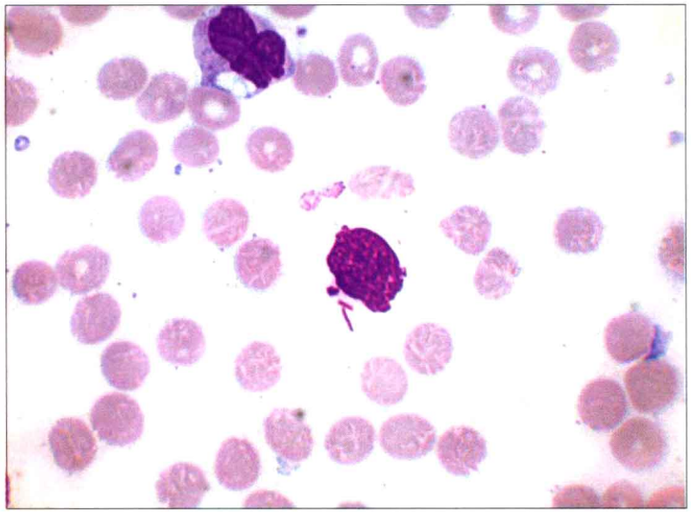


Figure 2.9 Bone marrow aspirate film from a patient with FAB M1 AML showing two Auer rods adjacent to the nucleus of a crushed blast cell. Sometimes Auer rods are more easily discernible when a cell is crushed. MGG, low power.

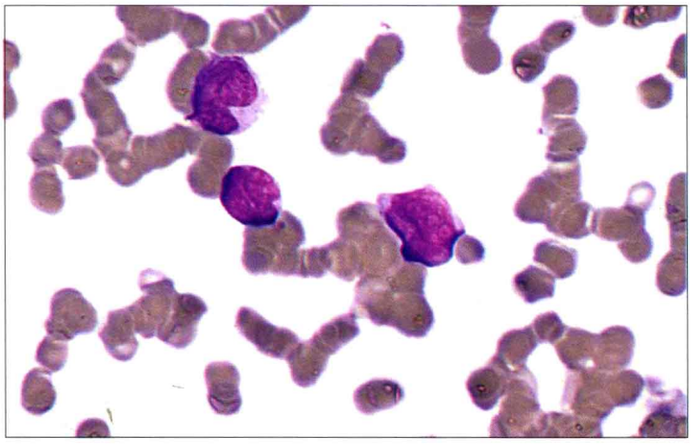


Figure 2.10 Peripheral blood film from a patient with FAB M1 AML showing pleomorphic medium sized to large blast cells with no obvious granules or Auer rods. MGG, low power.

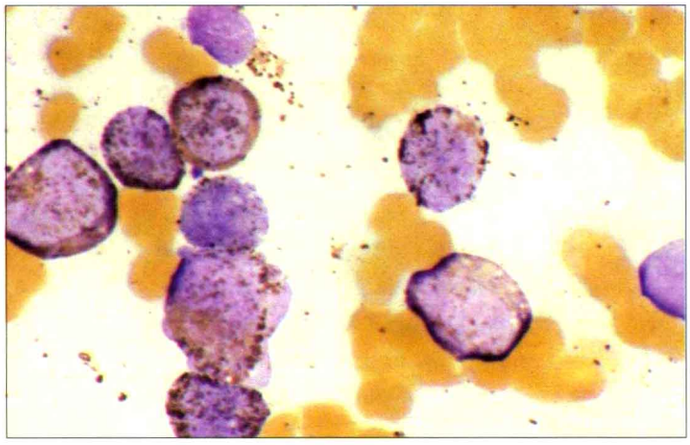


Figure 2.11 Peripheral blood film of a patient with FAB M1 AML (same patient as **Figure 2.10**) showing strong myeloperoxidase activity that identifies the blast cells as myeloid. MPO, high power.

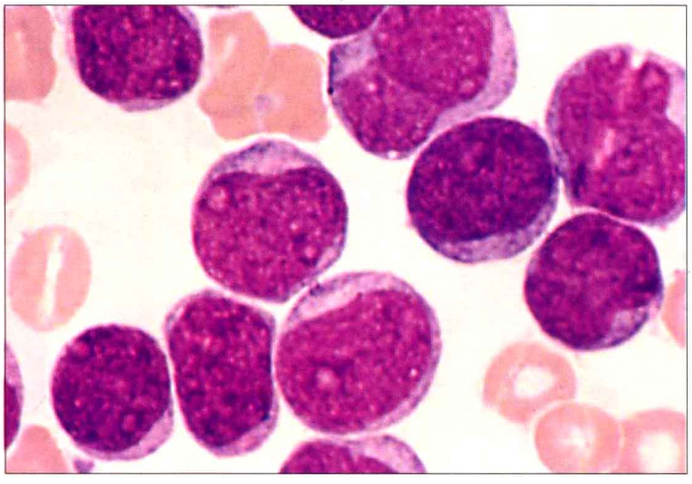


Figure 2.12 Bone marrow aspirate film from a patient with FAB M1 AML showing medium sized blast cells with no granules or Auer rods. MGG, high power.

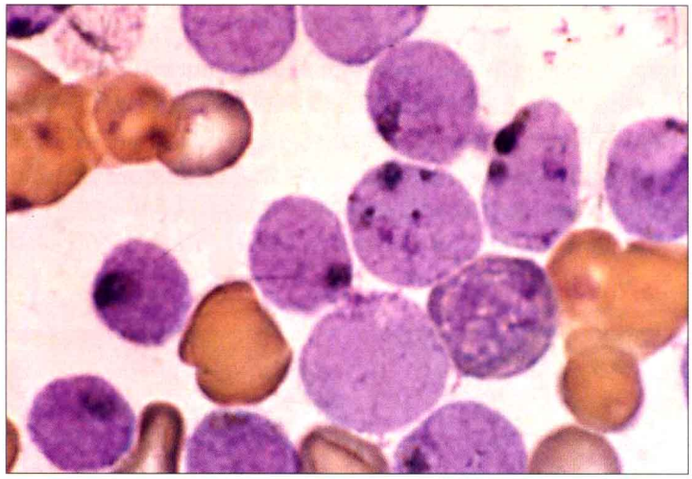


Figure 2.13 Bone marrow aspirate film from a patient with FAB M1 AML (same patient as **Figure 2.12**) showing Sudan black B activity that identifies the blast cells as myeloid. MGG, high power.

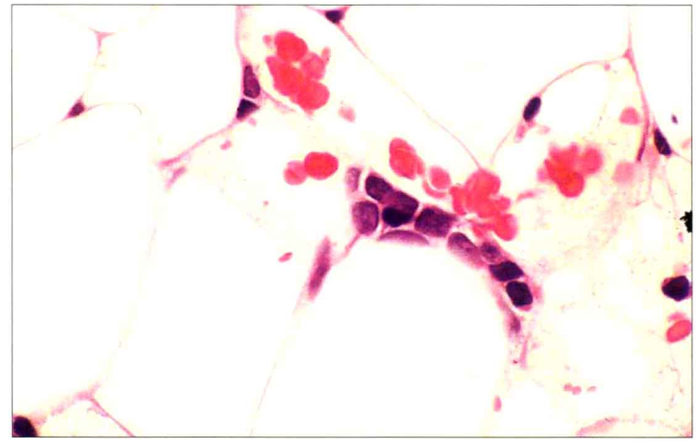


Figure 2.14 Bone marrow trephine biopsy section from a patient with hypoplastic AML of FAB M1 type showing a markedly hypocellular marrow in which most of the recognizable cells are blast cells. H&E, low power.

M2 AML

In FAB M2 AML (**Figures 2.15–2.19**) the bone marrow has at least 30% myeloblasts but more than 10% of cells are maturing cells of granulocyte lineage. These maturing cells are often dysplastic. Residual erythroid precursors and megakaryocytes may also be dysplastic. Usually myeloid cells are of neutrophil lineage, but sometimes they are of eosinophil lineage (**Figure 2.20**). Blast cells may contain Auer rods. Blasts and maturing cells are positive for SBB, MPO and CAE.

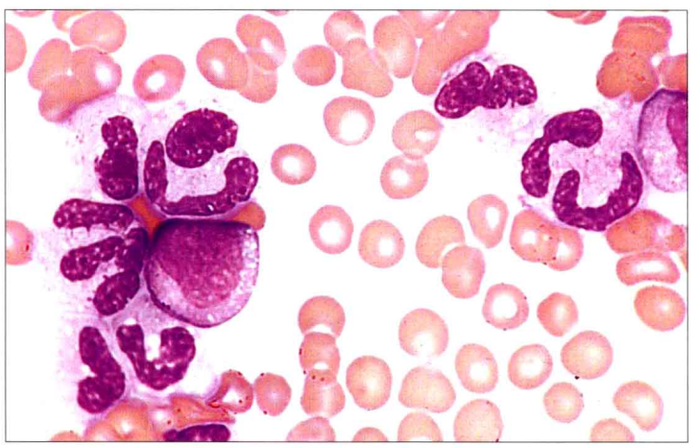


Figure 2.15 Peripheral blood film of a patient with FAB M2 AML showing very dysplastic neutrophils (hypogranular and often binucleated). MGG, high power.

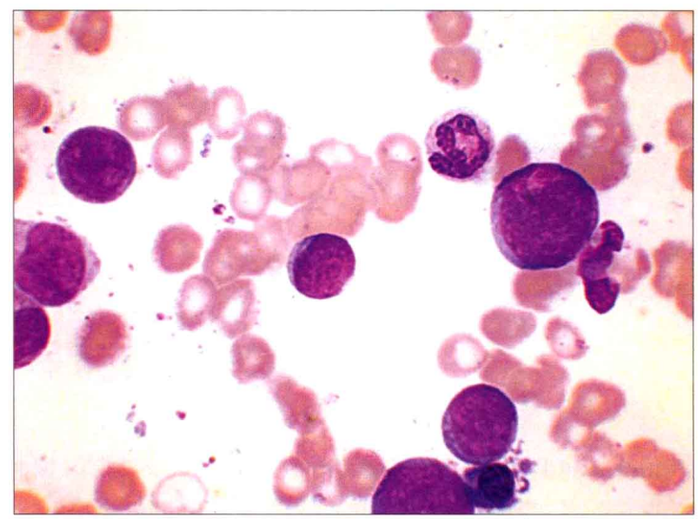


Figure 2.16 Bone marrow aspirate film from a patient with FAB M2 AML showing small to medium sized blast cells, a promyelocyte and a neutrophil. MGG, high power.