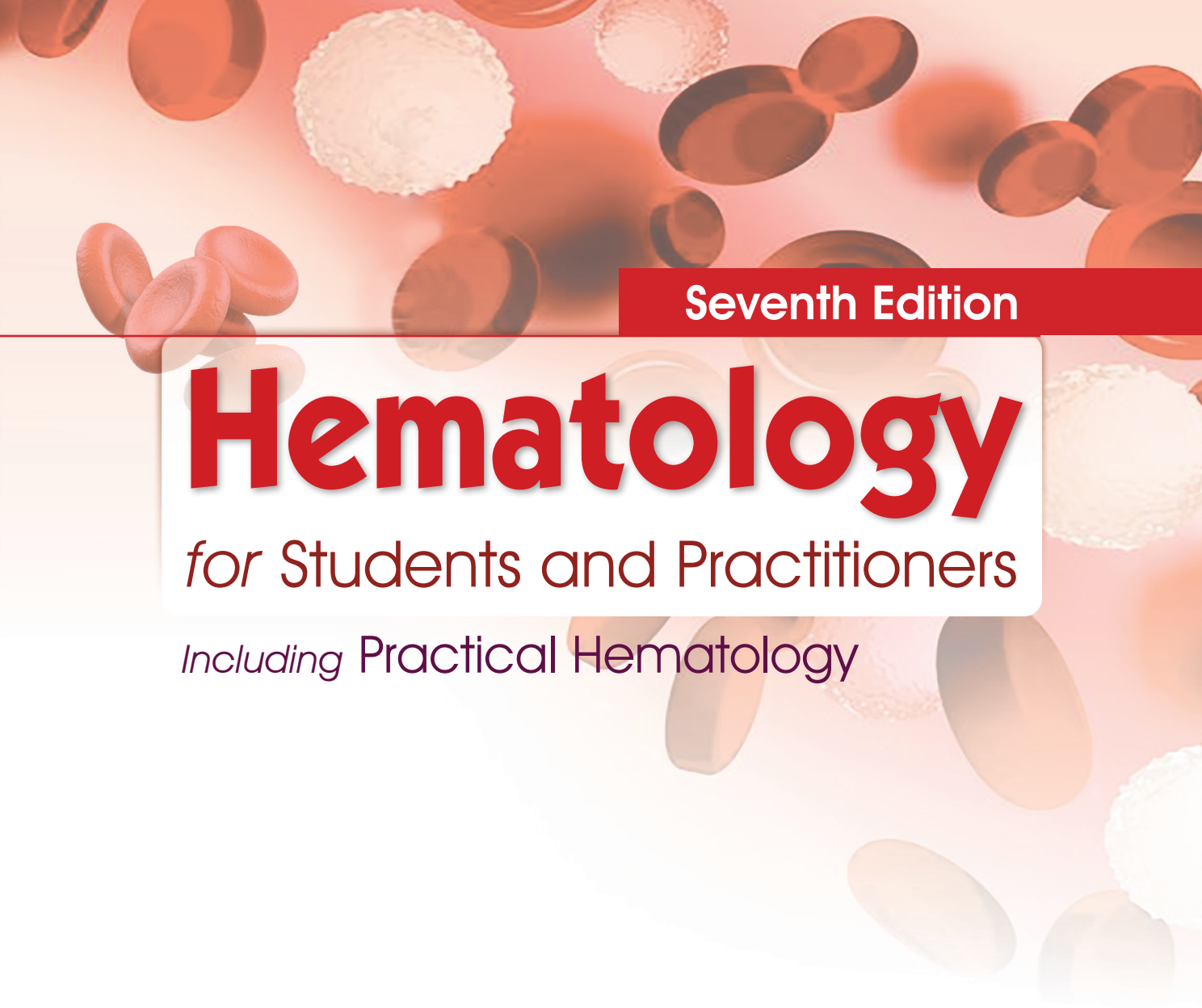

Seventh Edition

Hematology

for Students and Practitioners

Including Practical Hematology

CHAPTER

22

Bone Marrow in Nonhemopoietic Disease

The bone marrow may be involved in a number of disorders which are not primary diseases of the hemopoietic system. Aspirates or trephine biopsies may be used to assess bone marrow involvement after primary diagnosis based on material from other sites, or may be responsible for the primary diagnosis itself.

METASTATIC BONE TUMORS (Fig. 22.1)

The most common malignant tumors of bone are metastatic deposits from primary sites elsewhere in the body. Carcinomas of the breast, lung, kidney, thyroid and prostate are very likely to involve the marrow; stomach, pancreas, colon and rectum tumors involve the marrow less frequently but virtually any malignant tumor may reach the bone and the marrow therein.

In advanced disease, leukoerythroblastic changes may be found in the blood film: there may be evidence of bone marrow failure. The skeletal lesions are predominantly osteolytic, presenting as radiolucent areas or radiographic examination.

Extensive osteoclastic resorption of bone is often found in trephine biopsies. Almost all tumors provoke some bone healing and sometimes new bone deposition: osteoblastic activity is most pronounced in metastatic spread from carcinoma of the prostate.

Occasionally, fragments of epidermis are carried into the marrow cavity during trephine biopsy, but the well-differentiated nature of such fragments allows easy differentiation from metastatic carcinoma.

Involvement of bone marrow by tumors other than carcinomas also occurs, e.g. by melanoma, neuroblastoma and medulloblastoma. Bone marrow involvement due to

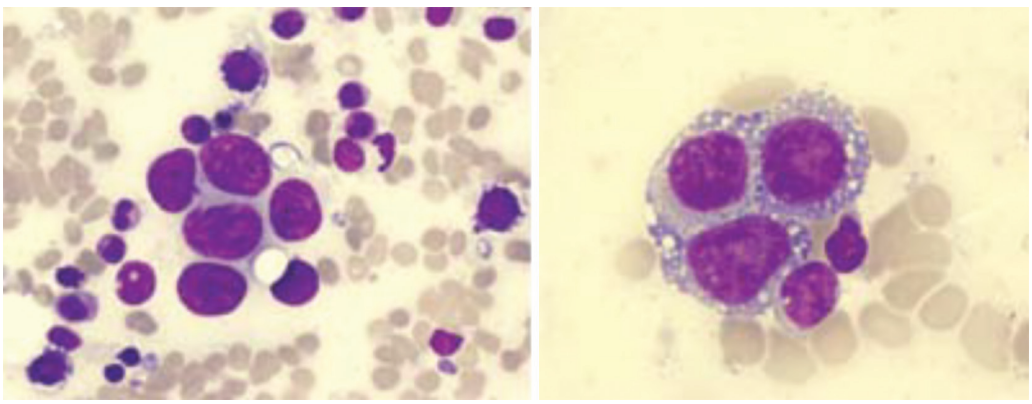

Fig. 22.1: Metastatic carcinoma to bone marrow

malignant lymphomas and histocytic proliferative disorders has already been discussed earlier. Although majority of primary bone tumors do not spread to parts of the skeleton but Ewing's sarcoma may sometimes metastasize to distant bones.

Metastatic tumors in the marrow may be detected using monoclonal antibodies and indirect immunofluorescence or alkaline techniques. Anti-milk fat globulin may detect breast carcinoma: anticytokeratin may detect epithelial carcinoma: and antidesmin (intermediate filaments) may detect mesenchymal tumors.

MAST CELL DISEASE (Fig. 22.2)

Systemic mastocytosis is a rare disease of adults in which a persistent and progressive cutaneous eruption is a characteristic presentation. Radiography reveals usually multiple, regularly rounded, lytic lesions or new bone formation in the skeleton. In severe cases there may be lymphadenopathy, hepatosplenomegaly and extensive infiltration of the bone marrow by mast cells. Evidence of disease may also be found in splenectomy. Disease confined to the skin and bone is frequently associated with prolonged survival; but patients who develop extensive reticuloendothelial involvement often die soon after diagnosis.

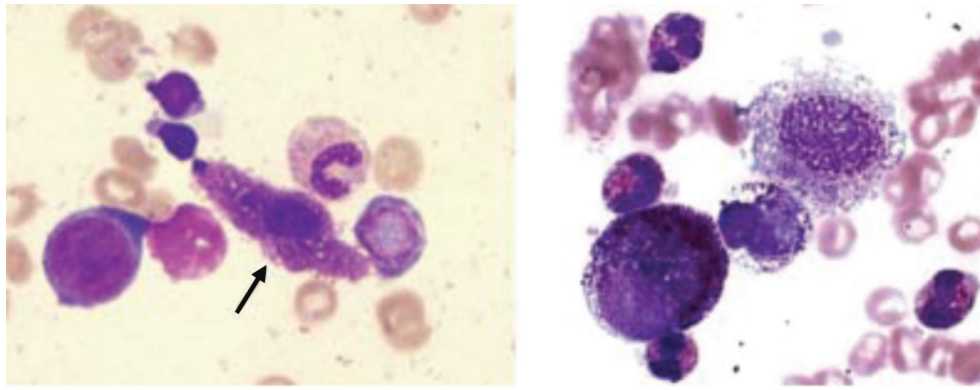

Fig. 22.2: Mast cells in the marrow

GRANULOMATOUS DISEASE

TUBERCULOSIS (Fig. 22.3)

Hematogenous spread of tubercle bacilli may bring them to bone marrow; aspirates from patients with suspected miliary or other typical hematogenous form of tuberculosis may show characteristic epithelioid granulomas. If left untreated, the disease becomes extensive, particularly in the anterior aspects of the vertebral bodies and in the metaphyseal areas of long bones. The tubercular foci may progress, producing cystic areas of osteomyelitis which erode the end plates and involve the nearby joint spaces. Tuberculous spondylitis (Pott's disease) involves the anterior aspects of vertebral bodies with subsequent wedging and eventual collapse.

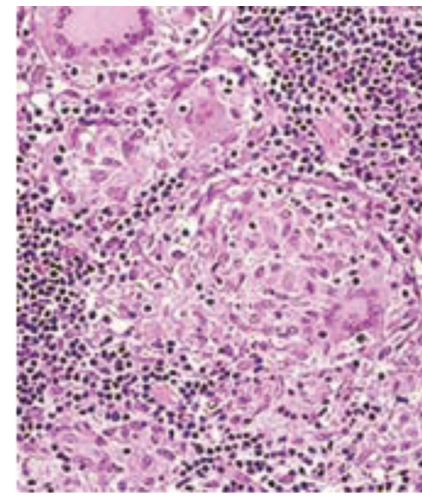

Fig. 22.3: Granuloma in the marrow

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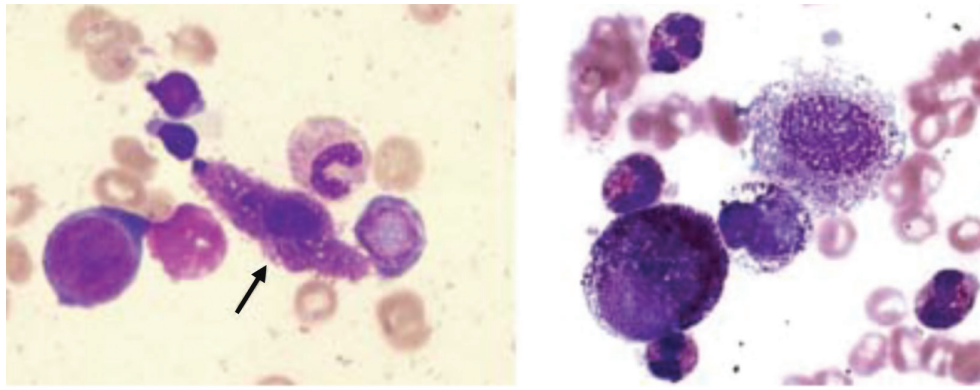

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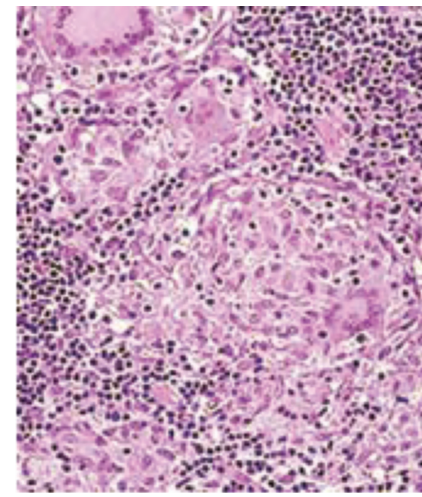

Fig. 22.3: Granuloma in the marrow

SARCOIDOSIS

Of unknown etiology, this granulomatous disorder most frequently affects the middle-aged. It is characterized by widespread epithelioid cell granulomas, depression of delayed hypersensitivity and lymphoproliferation. Multisystem involvement is characteristic with intrathoracic disease affecting 90% of patients, occular and stem involvement in about 25% each, and erythema nodosum in up to a third of cases. Evidence of disease may be found during bone marrow examination or at splenectomy.

OTHER GRANULOMAS

Brucellosis or foreign body granulomas may be found rarely during routine examination of trephine biopsies.

KALA-AZAR (VISCERAL LEISHMANIASIS) (Fig. 22.4)

Common in eastern Uttar Pradesh and Bihar. The causal organism, *Leishmania donovani*, is transmitted by the bite of sandflies of the genus.

Phlebotomus: The nonflagellated amastigote forms of the organism are distributed widely through reticuloendothelial macrophages in the bone marrow: spleen and liver. Diagnosis is usually made by examining bone marrow splenic aspirates or biopsy specimens. Clinical features include prolonged fever, lassitude, weight loss, splenomegaly, hepatomegaly, anemia, leukopenia and polyclonal increases in immunoglobulin.

OTHER INFECTIONS

Bone marrow examination has little significance in the diagnosis and management of osteomyelitis although, occasionally, initial evidence of a disseminated fungal infection may be uncovered. The bone marrow and spleen may be involved in cases of disseminated histoplasmosis. The *Histoplasma capsulatum* fungal organism may be seen inside macrophages in stained aspirates.

GAUCHER'S DISEASE (Fig. 22.5)

This relatively common familial disorder is characterized by the accumulation of glucocerebrosides (especially glycosyl-ceramide) in reticuloendothelial cells, which occurs because the enzyme β-glucocerebrosidase (glycosidase) is deficient. Three types occur: (i) chronic adult, (ii) acute infantile neuropathic, and (iii) subacute neuropathic with

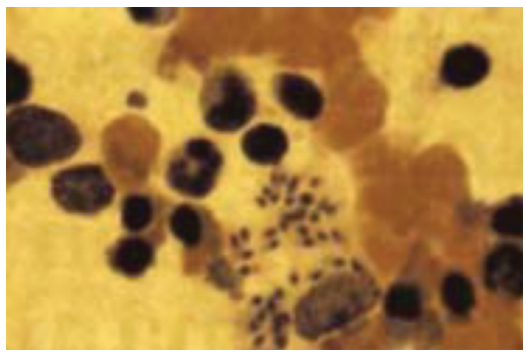

Fig. 22.4: Leishmania bodies in the marrow

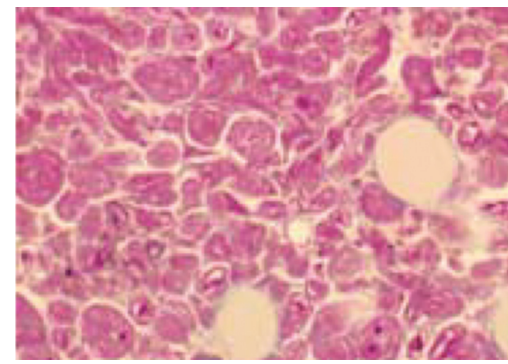

Fig. 22.5: Gaucher's cells in the bone marrow

onset in childhood or adolescence. The chronic adult non-neuropathic form of disease is accompanied by hepatosplenomegaly and bone lesions, and sometimes lymphadenopathy, skin pigmentation and pingueculae. The most acute neuropathic forms present in infancy and survival beyond the first three years of life is rare. A juvenile form may present in childhood with features of the chronic adult form as well as progressive neurological dysfunction.

A presumptive diagnosis of Gaucher's disease may be made when Gaucher's cells are detected in marrow aspirates and trephine biopsies. Diagnosis can be confirmed by demonstration of absence or severe deficiency of the enzyme glucosyl ceramide β-glucosidase in fibroblast cultures. Gaucher's cells are also found in the liver and spleen. Most patients with this condition have elevated plasma acid phosphatase activity (which is not inhibited by L-tartarate). Over 50% of adult patients usually have asymptomatic radiographic changes, such as cortical expansion of the characteristic radiolucent area.

NIEMANN-PICK DISEASE (Fig. 22.6)

Niemann-Pick disease is a sphingomyelin lipidosis, rarer then Gaucher's disease, and characterized by extensive tissue storage of sphingomyelin, hepatic and splenic enlargement, and large lipid-filled macrophages in the bone inarrow. In its best defined forms there is an inherited deficiency of the enzyme sphingomyelinase, and sphingomyelin concentration in the tissues is up to a hundred times higher than normal. As is Gaucher's disease, there are acute neuropathic and chronic non-neuropathic forms.

The disease is suspected in young children with hepatosplenomegaly when bone marrow aspirates show the presence of foam cells. Confirmation is by showing low levels of sphingomyelinase in fibroblast cultured from strain of bone marrow. In less severe adult forms of the disease, large numbers of sea blue histiocytes may be found in bone marrow aspirates in addition to classic foam cells.

SEA-BLUE HISTIOCYTE SYNDROME (Fig. 22.7)

Patients with the rare syndrome usually present with splenomegaly and thrombocytopenic purpura. In some cases there is associated hepatic cirrhosis. The inheritance pattern is autosomal recessive. Bone marrow aspirates contain large numbers of 'sea-blue' histiocytes. There is tissue accumulation of phospholipids and sphingomyelin and reduced levels of cellular sphingomyelinase activity have been reported. It appears that the syndrome is a variant of Niemann–Pick disease.

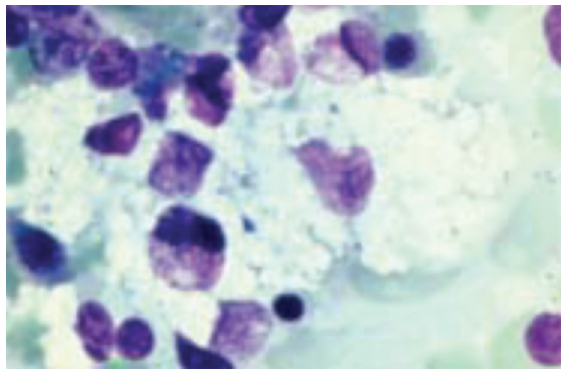

Fig. 22.6: Niemann–Pick disease, marrow

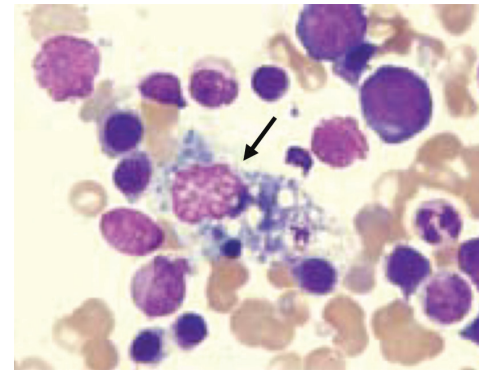

Fig. 22.7: Sea-blue histiocyte disease, bone marrow

CAUSES OF SEA-BLUE HISTIOCYTES

Large Numbers

- Sea-blue histocyte syndrome
- Niemann–Pick disease

Occasional or Moderate Numbers

- Hyperlipoproteinemia
- Hereditary acyltransferase deficiency
- Wolman's disease
- Other lipid storage disorders
- Chronic myeloid leukemia
- Polycythemia vera
- Chronic immune thrombocytopenia (ITP)
- Thalassemia
- Sickle cell disease
- Sarcoidosis
- Chronic granulomatous disease.

CYSTINOSIS

In this recessively inherited disease there is deposition of cystine crystals in the reticuloendothelial and corneal tissues. In its more severe form (cystinosis with Fanconi's syndrome or the de Tori–Fanconi–Lignac syndrome) there is progressive renal degeneration which is fatal during early childhood. Children with this syndrome usually present with anorexia, thirst, polyuria, failure to thrive, rickets or photophobia. Laboratory tests reveal glycosuria, proteinuria, low serum bicarbonate, hypokalemia or hypophosphatemia. The diagnosis is based upon demonstration of cystine crystals in macrophages in bone marrow aspirates.

OSTEOPETROSIS (ALBERS-SCHÖNBERG'S DISEASE OR MARBLE BONE DISEASE)

This rare familial disorder is characterized by an increase in density of all bones due to a functional defect in osteoclasts, with failure of bone resorption and remodeling. Severe forms of the disease present in infancy with anemia and hepatosplenomegaly. These children have little or no bone marrow, hemopoiesis is chiefly extramedullary and blood transfusions are required to sustain life. Peripheral blood shows leukoerythroblastic changes.

Failure to resorb bone results in optic atrophy, deafness and hydrocephalus. Milder cases may present in later childhood or in adult life with retarded growth, anemia and splenomegaly.

AMYLOIDOSIS

CLASSIFICATION OF AMYLOIDOSIS

In some patients, particularly those with reactive systemic amyloidosis, a trephine bone marrow biopsy may reveal the first evidence of amyloidosis.

Type	*Chemical nature*	*Organs involved*
lmmunocyte-related myeloma	Ig light chains and/or parts or their variable regions (AL)	Tongue, skin, heart, nerves, connective tissue, kidneys, liver, spleen
Waldenstrom's macroglobulinemia, heavy chain disease, etc.		
Primary amyloidosis, Reactive systemic Rheumatoid arthritis Tuberculosis Bronchiectasis Hodgkin's disease Mediterranean fever, etc. also familial	Protein A (acute reactive; AA)	Liver, spleen, kidneys, bone marrow
Localized Tumors old age (Aizhelmer's disease) Also in skin	Hormones, protein A with other constituents	Around endocrine tumors, skin, CNS.

RENAL OSTEODYSTROPHY AND OSTEOMALACIA

In uremia, there is resistance to the action of vitamin D and a compensatory parathyroid hyperplasia. Characteristic changes are found in bony architecture on trephine biopsy examination. In mild disease the lesions are predominantly osteomalacic. Microscopically, the trabeculae are increased in thickness and number, and the osteoid seams have defective mineralization. A similar picture is seen in dietary vitamin D deficiency. In severe disease there is also evidence of osteitis fibrosa.

PAGET'S DISEASE OF BONE (OSTEITIS DEFORMANS)

In this disease of unknown etiology. There Is rapid bone formation and resorption in the involved regions of the skeleton. The lesions are essentially local and asymmetrical in early stages and frequently involve the weight-bearing bones especially the sacrum and pelvis. Unsuspected disease may be found during trephine bone marrow biopsy examination. The plasma calcium and phosphorus levels are usually normal, while the alkaline phosphatase level is invariably high. Where there is extremely rapid absorption, areas of fibrosis and intensive osteoclastic activity may resemble the microscopical appearance of osteitis fibrosa.

ANOREXIA NERVOSA

These patients suffer from severe deficiency of carbohydrates, fats and calories but little protein deficiency. The peripheral blood may reveal mild anemia and thrombocytopenia with acanthocytes; the marrow is hypocellular, with fat cells replaced by acid mucopolysaccharides appearing as pink-staining extracellular material.

PRIMARY OXALURIA

In this fatal autosomal recessive metabolic disorder, there is widespread deposition of calcium oxalate crystals in the kidneys and elsewhere in the body. Including the liver, spleen and bone marrow. A number of different enzyme deficiencies have been implicated as causal factors.