

Various local factors contribute considerably to the maintenance of the tender balance in activities of single types of bone cells. Topically produced prostaglandins e.g. PGE₂ may directly act on the bone metabolism by stimulation of osteolytic processes or by inducing synthesis of further local factors (epidermal growth factor, platelet-derived growth factor). Interleukin-1 is a very effective substance stimulating the bone resorption. Similar to the interleukins is the osteoclast activating factor. Further cytokines e.g. the gamma interferon exert also topical regulative effects on bone tissue. By osteoblasts produced TGF beta (transforming factor beta) stimulates the mitogenesis and collagen synthesis. The majority of these factors is involved also in the healing and reparation of microfractures. Besides the hormones and topically acting factors the trophic influence of nervous system has a substantial importance in bone metabolism regulation. When the nervous system is excluded the bone formation is reduced and bone resorption enhanced (bone atrophy).

8.2 Generalized skeleton disorders

By evaluation the bone diseases the fact should be taken into consideration that in bones a continuous process of remodelling takes place. The bone remodelling does not occur however at identical velocity in all parts of skeleton. Therefore the disorder becomes manifest first in those parts of skeleton where the metabolic turnover is maximal. Intensity of remodelling has a declining tendency: mostly affected is the vertebral column, afterwards pelvis, ribs, lower extremities, shoulder girdle, upper extremities and at least the skull. Generalized process with identical manifestations in all parts of skeleton does not exist. The term – generalized process – indicates a biological process occurring at the molecular level, it does not indicate clinical manifestations. A metabolic disturbance induced mostly by hormonal or nutrition disorders is always involved. Specification as a process at molecular level is important because the bone affection assessed in clinical, radiological and even his-

tological examinations can be manifest only at one or more sites of the skeleton. Thus, the vertebral column alterations might have the look of local lesions, they however are indicative of generalized skeleton disease. The genuine real local disorders are caused by:

1. immobilization of one part of the skeleton leads to local atrophy developing the sooner the higher is the metabolic turnover in affected bone
2. disorder of circulation (local obliteration or obturation of blood vessel, or A-V anastomosis lead to trophic disorders of bone)
3. tumours of bones (every tumour of bone including the cyst whether it originates in bone or has been metastasized is substantially of local character, even if a multiple dispersion is involved because the bone among the metastases is normal).

8.2.1 Skeleton balance disorders

8.2.1.1 Negative balance of skeleton

Osteoporosis The term osteoporosis is reserved for bone mass loss per bone volume unit. The composition of bone remains however normal as show the histological and biochemical findings.

The bone mass quantity is determined by mutual proportion of bone formation and resorption processes. Positive, neutral or negative bone balance are observed in various periods of life. In childhood and adolescence the bone formation preponderates evidently over the bone resorption. In adults are both processes in equilibrium (remodelling). The peak bone mass is attained in age of 30 to 35 years. In men are the peak values substantially higher than in women, so they are in black population in comparison to the white people. Genetic factors however predetermine the peak bone mass in every individual. Following five to ten years a slow decline in total bone mass begins. At the beginning the velocity of the decrease is identical in both sexes. Subsequent bone loss in women is during the menopause significantly accelerated. In advanced age is the rate of bone loss again identical in both sexes. The less the attained peak bone mass the sooner osteoporosis will develop. Therefore are the white postmenopausal women at greatest disadvantage.

Osteoporosis is the most common bone disease. It develops in majority of cases (about 80 per cent) in consequence of progressive bone mass loss dependent on age. Moderate degree of bone atrophy is a physiological phenomenon and belongs to involutonal manifestations of aging. Only when the symptoms become intensified and the bone density falls by more than 25 per cent the condition is considered to be pathologic. It is reported that as much as 20 per cent of people more than 60 years old are affected by osteoporosis. The involutonal osteoporosis can be of type II – senile, and type I – postmenopausal. Both types of disease belong to important medical problems in advanced countries where owing to the higher age achievement higher percentage of population is affected by osteoporosis. Clinical manifestation appears frequently as late as the bone density is reduced to such a degree that the bones are extremely fragile and prone to spontaneous fractures. Because during the menopause the process of resorption attacks mainly the spongy bone tissue, typical for the postmenopausal osteoporosis is the fracture or osteoporotic break down of vertebra. Unlike to this situation in advanced age the bone loss equally affects the spongy and the trabecular bone tissue hence typical for senile osteoporosis is the fracture of femur. The most frequent clinical manifestation of osteoporosis is pain behind which a fracture or infraction of a brittle bone are hidden. Long-term and repeated fractures of vertebrae result in spinal column deformities (characteristic are outstanding loss of body height and severe kyphosis).

Osteoporosis originates either from reduced bone formation or increased bone resorption.

In the age-related **bone osteoporosis** is the bone new formation reduced. The osteoblasts and osteoclasts become less active. Reduced renal functions occurring in aged people participate to a certain degree in the pathogenesis of osteoporosis of type II. The mechanism is indirect: by influencing the vitamin D metabolism in kidney is the calcium absorption through the wall of intestine impaired. In elderly is also the intake of calcium in food insufficient and the occurrence of further deficiency states is more frequent. In bones the circulatory and neurotrophic disturbance arise and in bone collagen structural alterations typical of old age may be seen.

The **postmenopausal osteoporosis** is characterized by high metabolic turnover in bones and increased

bone resorption. The number and activity of osteoclasts rises. The major etiologic factor of these alterations is the postmenopausal decrease in estrogen level. Physiological estrogen level before the menopause exert by direct or indirect influence on other hormones an inhibitory effect on bone resorption. Estrogen deficiency or complete loss enhances the bone responsiveness to PTH effect causing the bone resorption and probably negatively influences the calcitriol synthesis in kidney.

Other types of osteoporosis are less frequent, nevertheless not less severe. The **juvenile osteoporosis** may arise reversibly in young people during the period of accelerated growth. Its cessation is spontaneous, nevertheless during the active phase fractures may occur. **Osteoporosis due to inactivity** develops during complete immobilization. According to the intensity of bone metabolism in the given patient severe bone atrophy develops during weeks to months. Inactivity of muscles leads to vasodilatation in periost resulting in massive osteoclastic bone resorption as shown in animal experiments. The mechanical stimulus for compensatory bone new formation is lacking. This mechanism seems to be important in weightlessness as confirmed by rapidly developing osteoporosis frequently accompanied with fractures of collum femoris in astronauts. Hypogonadism leads to osteoporosis mainly in trabecular bones. Hypogonadism may originate in primary affection of gonades or in secondary disorders induced by deficiency of gonadotropins. It occurs frequently in women with hypothalamic amenorrhea. In sportswomen, the runners above all, having amenorrhea due to physical exertion in top performance, reduced mineral content in vertebral column was also found. Estrogen deficiency in them predominates obviously the positive effect of physical activity on the bone formation. Hypogonadism in men predispose them to osteoporosis. Major factor responsible for the reduced bone density in men is the testosterone deficiency.

Osteoporosis induced by glucocorticoid excess appears in Cushing's disease or during long term glucocorticoid administration in high doses (e.g. in severe bronchial asthma). In the first phase the excess of glucocorticoids increases the number and activity of osteoclasts accompanied with massive destruction of bone. Later follows the phase of reduced bone formation with depressed osteoblastic activity. This direct effect on bone is supported by further indirect

effects of glucocorticoids as: antianabolic effect on proteins, antagonism against the calcitriol formation in kidneys, and enhancement of calcium excretion. In **hyperthyroidism** osteoporosis occurs infrequently. Excess of thyroid hormones stimulates the bone metabolism. During this process the bone resorption is more effective than the bone formation. Long-lasting heparin administration leads to osteoporosis because according to the today's opinions heparin either depresses the collagen synthesis in bone or enhances its degradation. **Calcium deficiency** is an important factor in osteoporosis development. Bone atrophy can be induced in animal experiments by elimination of calcium from the food. The calcium absorption from intestine decreases with age. Uniformity of nutrition without sufficient participation of useful components in elderly may also lead to negative calcium balance. Lactose intolerance can be responsible sometimes for the negative calcium balance. Patients suffering from this disease are unable to utilize the calcium present in milk and milk products. It is because these patients have diarrhea after ingestion of milk or its products, thus this condition is associated with calcium malabsorption. The underlying cause of the lactose intolerance is the absence of lactase, an enzyme enabling the absorption of monosaccharides derived from di- or polysaccharides. In patient with atrophic gastritis or following gastrectomy osteoporosis occurrence is not seldom. It seems the cause might be the gastric acid deficiency and GIT motility disturbances. Deficiency of proteins and vitamins, vitamin C and D above all, contributes to the development of osteoporosis.

Regional osteoporosis arises most commonly owing to the extremity immobilization after fracture, tendon injury, arthritis etc. The underlying cause of osteoporosis in immobilized region is mainly the reduced afferent signalization arising from various receptors i.e. the decrease in trophic influence of NS. Significant symptoms of osteoporosis may appear in about 8 weeks in patients 20 to 50 years old but they can develop sooner. The reduced or interrupted trophic effect of nervous system is also the cause of bone atrophy following dissection of peripheral nerves (postdenervation atrophy). Regional osteoporosis may be due to inadequate number of osteoblasts and osteoclasts in a certain bone region since the complete remodelling cycle requires continuous and sufficient supply of precursor cells from the

bone marrow. Any kind of the subtle bone vessel system damage can result in regional osteoporosis.

Osteitis fibrosa cystica is thanks to the present status of medical care an extremely rare bone disease appearing at advanced stage of primary or infrequently secondary hyperparathyroidism. The metabolic turnover in bones is enhanced by influence of long-term continual PTH hypersecretion. The bone resorption prevails due to considerable increase in osteoclastic activity. The endosteum and the trabecular bone tissue are the most responsive sites to the excess of PTH. Increased number of trabecular surfaces exhibit resorption and their density progressively declines. Conglomerations of osteoclasts produce cysts and cyst-like formations (so called brown tumours). The bone cysts are filled with fluid and bordered by fibrous tissue. They occur mainly in subperiosteal region. Brown tumours form a solid non calcifying tissue mass consisting mainly of polynuclear osteoclasts. Proliferation of osteoclasts and fibroblasts is evident also in bone marrow cavities. PTH leads also to enhancement of osteocytic osteolysis enlarging the lacunae around the osteocytes. Thus, the resulting manifestation of osteitis fibrosa cystica is the generalized osteopenia and increased bone resorption with occurrence of cysts and so called brown tumours.

8.2.1.2 Positive balance of skeleton

Osteopetroses (osteoscleroses) Osteopetroses are very seldom bone diseases characterized by excessive bone tissue formation. In contrast to the osteoporosis the bone formation predominates the bone resorption, thus by positive bone balance the bone mass becomes excessive. Positive bone balance can be induced by several mechanisms.

Albers-Schönberg disease (so called marble bone disease) results from failure of normal coupling between bone formation and resorption. The bone density is greater with occurrence of sclerotic foci. Impairment of physiological function of osteoclasts leads to defective modelling and remodelling processes. Numerous osteoclasts are present on the bone surface, nevertheless without signs of activity. The mechanism of osteoclast activity disorder at the molecular level is not known till now. It was found, however, that the transfusion of healthy haematopoietic stem cells to mice with osteopetrosis leads to

healing, and on the contrary, the transplantation of bone marrow from mice with osteopetrosis to healthy mice results in osteopetrosis. Definitive evidence of "inoculation" has been referred by Coccia et al. in the case of an affected girl after transplantation of bone marrow from her HLA-identical brother. In osteoclasts in girls' bones chromosome Y was present (confirming their origin), while in osteoblasts it was not present. The Albers-Schönberg disease has several types:

- **Infantile osteopetrosis (lethal).** It is an extremely rare disease with autosomal recessive inheritance which begins to develop immediately after the birth. Generalized osteosclerosis leads rapidly to obliteration of bone marrow spaces and to aplastic anaemia and excessive compensatory hematopoiesis associated with hepatosplenomegaly. The epiphyseal growth plates become calcified. Increased density of cranial bones narrows down the foramina for cranial nerves what may lead to blindness, deafness, paresis n. facialis, hydrocephaly etc. Increased fragility of bones may result in pathologic fractures. Disease ends with death within the first decade of life.
- **Osteopetroses with early onset (non lethal).** On the contrary to the severe autosomal recessive form these types of osteopetroses in childhood are not lethal. Because of positive bone balance and moderately reduced bone marrow spaces only mild anaemia and rare pathological fractures are associated with this condition. Complete absence of carbonic anhydrase II in erythrocytes has been found in many patients. Besides, this form of osteopetrosis is frequently accompanied with renal tubular acidosis and similar defect of carbonic anhydrase II. It seems therefore possible that in osteoclastic bone resorption even the carbonic anhydrase II plays an important role. Chronic acidosis reduces the manifestations of osteopetrosis because it supports conditions for continual osteolysis.
- **Osteopetrosis with late onset** is more frequent but less severe condition with autosomal dominant inheritance in comparison with the above mentioned infantile form. It remains long time hidden or becomes manifest by moderate anaemia and by pathological fractures.

Fluorosis In endemic regions with high content of fluoride (in water or soil) is the occurrence of fluorosis already many years known. On the basis of experimental results it is supposed that fluoride replaces the hydroxyl ions in the deposition into the apatite crystals causing their enlargement and reduced solubility. Long-term observations in people showed that fluoride in high doses stimulates the osteoblasts. Calcium balance becomes positive, new trabeculae of osteoid are formed and calcified in dependence on fluoride dosis.

Acromegaly The growth hormone is the single hormone which induces new formation in adult skeleton. This effect is probably mediated by somatomedins (IGF-1, IGF-2). Acromegaly is associated with enhanced bone metabolism leading to rise in bone density. The consequence of STH overproduction in adulthood is the enlargement and thickening of acral parts of skeleton. At least in 30 per cent of ill persons suffering from acromegaly the syndrome of carpal tunnel develops with compression of nervus medianus by hypertrophic bones and soft tissue of the forearm distal part. Enlargement in height and width of vertebrae by periosteal bone apposition is sometimes observed. These alterations may cause compression of spinal nerve roots in foramina vertebrales and stenosis of spinal canal.

8.2.2 Disorders of ground substance

Seldom conditions, in majority of genetic origin, are included in this group of diseases. Not only the growth and the bone composition irregularities are involved but more often outstanding disorders of other tissues and organs.

Disturbances in acidic mucopolysaccharid metabolism occur in hereditary disorders of acidic mucopolysaccharide degradation. In all eight till now recognized types of mucopolysaccharidoses the affection of the skeleton (dysostosis multiplex) being the consequence of defective composition of ground substance is combined with mucopolysaccharide deposition into various extrasketal sites. These alterations can lead to e.g. pseudoatherosclerosis due to involvement of blood vessel tunica intima, to valvular heart diseases, thickening of articular capsulae and ligamenta, splenomegaly etc. Clinical manifestations of skeleton involvement depend on type of disease. In general, disorders of ossification are included accompanied with retardation or cessation of growth, kyphoses caused

by vertebral deformities, thicker and shorter diaphyses of long bones, and chest deformities. Similar alterations can be observed in some types of hereditary disturbances in **glycoprotein** degradation (e.g. mucopolipidosis I, II, III, aspartylglucosaminuria, mannosidosis).

The **collagen anomalies** occur in several genetic diseases.

Osteogenesis imperfecta is a hereditary disease with mutations in one or two structural genes coding the protocollagen of type I. Presence of anomalous collagen III or V and alterations in cross bindings of collagen fibrils have been found in bones. Defective collagen synthesis leads to typical bone fragility (brittle bones) resulting in deformities and fractures. The extraskelatal manifestations include: blue sclerae, deafness, thin skin, valvular heart diseases, defective dentin. All these signs are manifestations of collagen synthesis disturbance. Further seldom genetic diseases involving the collagen anomalies are: Ehlers-Danlos syndrome characterized by loose and infirm network of collagen fibers (manifested by laxness of joints), Marfan's syndrome with characteristic phenotypic manifestation – a long and thin skeleton. Vitamin C deficiency (scurbut) leads in childhood to disorders in collagen synthesis with resulting bone atrophy. Ascorbic acid is probably required for collagen hydroxylation.

8.2.3 Disorders of mineralization

8.2.3.1 Insufficient osteoid mineralization

Osteomalacia (rachitis) The term osteomalacia expresses a condition characterized by defective osteoid mineralization. The remodelling cycle passes normally to the osteoid formation, nevertheless, the calcification and deposition of minerals is retarded. The bone size remains unchanged but the new bone consists of soft osteoid instead of firm, hard bone tissue. When this condition develops in childhood in the period of growth it is called rachitis (rickets). Many etiologic factors may participate in the development of osteomalacia, however, the most important is the vitamin D deficiency. Vitamin D supports the mineralization by stimulation of calcium and phosphate absorption from intestine. Deficiency of vitamin D in food is in our country infrequented. Frequent is, however, its insufficient resorption in syndromes of malabsorption (chronic diarrhea, steat-

orrhea, chronic disorders in bile secretion, in syndromes arising following gastrectomy, etc.). All these conditions may reduce considerably the absorption of vitamin D, calcium and less the phosphate from GIT. Decreased calcium level in serum leads to secondary hyperparathyroidism. Nevertheless, parathormone is not able to enhance the calcium absorption from intestine under these circumstances. By its effect on kidneys it aggravates even more the condition: the phosphate level becomes more reduced.

Further underlying causes of osteomalacia or rickets are disturbances of vitamin D transformation into calcitriol :

- 25-hydroxylation of vitamin D₃ in the liver is retarded in hepatocellular diseases
- 1-alpha-hydroxylation of 25-hydroxy-vitamin D₃ in kidneys is significantly reduced mainly during chronic renal failure.

Osteomalacia belongs to the uraemic bone syndrome and is associated mostly with further metabolic osteopathies (see later). 1-alpha hydroxylation is reduced also in parathyroid hormone deficiency. Another very infrequent cause is the inherited disorder of 1-hydroxylase (vitamin-D dependent rachitis of type I).

Anomalies of receptors for calcitriol in target tissues occur rarely, if present they cause the vitamin-dependent rachitis of type II.

Hypophosphataemic osteomalacia develops when reduced capacity of tubular phosphate reabsorption is present e.g. in inherited tubular disorders, or in Fanconi's syndrome. Excessive and long-lasting ingestion of antacids reducing the phosphate reabsorption in gut may be a further cause of hypophosphataemia. In these cases the organism is lacking for phosphorus a very important "building stone" of osteoid mineralization. In addition the already completely formed bone begins to demineralize. Calcium is released from the skeleton in order to maintain calcium-phosphate equilibrium in extracellular fluid.

Every metabolic acidosis of long duration contributes at last to the bone demineralization. The most typical example is the so called renal tubular acidosis persisting during the life of the patient. Mineralization disorder occurs either because of calcium deficiency due to defective vitamin D metabolism or because the bones compensate constantly the acidosis (phosphate anions exchange the Ca²⁺ for H⁺).

Clinical symptoms of osteomalacia and rickets can be deduced from the pathogenesis of these diseases. The soft bone does not break but it is bending under the action of minimal load. This leads to stretching or even to disrupting of periost associated with severe pain. At advanced stage of the disease the pains are present in the whole skeleton. Deformations sometimes of bizarre even grotesque forms occur owing to the pathologic flexibility of bones. On the sites of maximal load action and thus of relatively most intense bone metabolism pseudofractures occur. They appear in form of fatigue fractures (the callus during the healing process never calcifies) or in form of permanent fractures induced by pulsation of adjacent artery.

8.2.3.2 Excessive mineralization of osteoid

This term has theoretical meaning and is mentioned only to complete the scheme of classification concerning the logical and didactic approaches. Excessive mineralization leading to osteosclerosis develops namely only when there has been previously too much osteoid formed. Hence, the item of overmineralization is included into the item of positive balance of skeleton (see part 8.2.1.2).

8.2.4 Renal osteodystrophy – a combined disturbance of mineral metabolism

One of the most complicated bone diseases arises as a result of long-term renal failure. It is observed in patients who are regularly dialyzed. Since in these cases heterogeneous (mixed) histological findings are observed the most convenient terms are: renal osteodystrophy or renal bone syndrome. Renal osteodystrophy occurs in uraemic patients and includes: essential disturbances in metabolism of divalent ions, metabolic bone disorders (osteitis fibrosa cystica, osteomalacia, and osteosclerosis), hyperplasia of parathyroid glands, and calcifications in tissues.

The pathogenesis of renal dystrophy is complex. Many factors are involved, the most important being:

- the retention of phosphates
- reduced 1,25 dihydroxy vitamin D₃ synthesis in kidneys

The first step in the pathogenic process is probably the retention of phosphates due to reduced glomerular filtration. High plasmatic level of phosphates causes a reciprocal decrease in calcium level in order to maintain the product $Ca \cdot P$ unchanged. Decreased calcium level leads to enhanced secretion of PTH by feedback mechanism. PTH stimulates the phosphate excretion via kidneys and thus restores the $Ca \cdot P$ product to normal value. Always when a further decrease in glomerular filtration occurs a new equilibrium is established but only if the secondary parathyroidism is present. By these processes is the organism able to sustain the phosphate balance as late as the glomerular filtration falls to about 25 ml per minute. The price of this compensation, however, is the progressive bone resorption induced by PTH – the **osteitis fibrosa cystica**. With progressing renal failure further nephrons disappear and the remaining nephrons are not able to excrete sufficient amount of phosphates in spite of stimulating PTH effect. Plasmatic phosphates begin to rise again and the calcium level falls again. Calcium malabsorption makes the hypocalcaemia significantly worse. It appears when the renal failure progresses to a degree when the 1-alpha-hydroxylation of vitamin D is significantly reduced. This is caused partially by the renal parenchyma loss (including the loss of cells containing the 1-alpha-hydroxylase) and partially by the suppressive effect of hyperphosphataemia on 1-alpha-hydroxylation. Deficiency of calcitriol and azotaemia too, decrease the calcium absorption from GIT. Owing to this in some uraemic patients decreased osteoid calcification appears and **osteomalacia** develops. It is not proven if it is a direct consequence of calcitriol deficiency, or it reflects the defective collagen synthesis. It can result also from by uraemia induced disturbances in calciumphosphate transformation to hydroxyapatite. Aluminium present in solution used for dialysis accumulating in bones contributes considerably to the development of osteomalacia.

In about 10 per cent of patients the regional osteosclerosis can be observed mainly in vertebral column trabecular bones. It is probably the consequence of temporary, transient interruption of 1-alpha-hydroxylation inhibition in kidneys.

The progress of renal osteodystrophy is accelerated by metabolic acidosis if it is prolonged.