

the thyroid gland of individuals with familial form of medullary thyroid carcinoma. Infusions of pentagastrin or calcium (and also having drunk alcohol) elicit secretion of calcitonin and successively increase calcitonin concentration in circulating blood. This is considered as **an early biochemical signal** of starting medullary thyroid carcinoma.

With time, premalignant hyperplasia of the C cells is followed by progression to nodular hyperplasia, microscopic medullary carcinoma, and finally frank medullary thyroid carcinoma. Basal plasma calcitonin concentration is elevated in about two thirds of patients with clinically developed medullary carcinoma. In these patients, however, hypercalcemia is usually not present.

In patients with the familial form of medullary thyroid carcinoma, there is often clinical or laboratory evidence of hyperparathyroidism and pheochromocytoma (MEN 2A, Sipple syndrome). Hyperparathyroidism is most commonly due to parathyroid hyperplasia, rather than adenoma. Pheochromocytomas are often bilateral. This **variant of the MEN 2A syndrome** is one in which medullary thyroid carcinoma, pheochromocytoma, and possibly parathyroid hyperplasia are associated with ganglioneuromas. If there are a marfanoid habitus, thickened corneal nerves, multiple mucosal neuromas, and typical facies simultaneously present in the patient, this disease is denoted as **the variant of the MEN 2B syndrome**. Mucosal neuromas may occur on the distal portion of the tongue, on the buccal mucosa, on the lips (thick bumpy lips), in subconjunctival areas (thickened and friable eyelids-margin), and throughout the gastrointestinal tract (ganglioneuromatosis of the GIT). In the patients with the variant of the MEN 2B syndrome tumors originate at younger age and metastasize more frequently than in those with the variant of the MEN 2A syndrome.

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## 5.5 Pathophysiology of parathyroid glands

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Primary disorders of hormonal activity of the parathyroid glands are rare. The pathophysiological

state resulting from undersecretion of parathyroid hormone (PTH) is denoted as **hypoparathyroidism**. The pathophysiological state resulting from oversecretion of PTH is called **hyperparathyroidism**. There is also a pathophysiological state similar to hypoparathyroidism in which secretion of PTH is normal. The disorder is on the level of target tissues, which are insensitive to PTH. It is in fact pseudohypofunctional endocrine disorder (pseudohypoparathyroidism) denoted as **pseudohypoparathyroidism**.

### 5.5.1 Hypoparathyroidism

It is a pathophysiological state when the parathyroid glands are not able to maintain normal calcium concentration in circulating blood (normocalcemia) and thereby its homeostasis in organism. Hypoparathyroidism is characterized by low plasma PTH concentration, hypocalcemia, hyperphosphatemia, and increased neuromuscular excitability.

**Etiology** of hypoparathyroidism is heterogeneous. Organic and functional causes participate in its origin.

**A. Organic causes.** The most frequent organic causes are various iatrogenic influences, mainly postsurgical injuries or inadvertent removal of all parathyroid glands, respectively impairment of their vascular supply during thyroidectomy or during radical dissection in the neck for some form of malignant disease. **Postoperative hypoparathyroidism** originates when during surgical intervention more than 50% of parenchyma of parathyroid glands is damaged. It occurs as a complication in about 1% of patients after the mentioned operations. The risk of the origin of permanent hypoparathyroidism exists also in the patients after therapeutic subtotal parathyroidectomy for parathyroid hyperplasia. Acquired hypoparathyroidism is an extremely rare complication of radioactive iodine therapy (**postradiation hyperparathyroidism**). Its onset is generally between 5 and 18 months after radiotherapy. Most cases are associated with large doses of radioiodine in the patients with Graves-Basedow disease rather than in those with thyroid carcinoma. In the latter hypoparathyroidism often originates after the therapy by external irradiation.

Spontaneous origin of hypoparathyroidism due to organic lesion is rare. It is denoted as **idiopathic**

**hypoparathyroidism.** It may occur sporadically or familiarly. **The familial form** is usually manifested already in early childhood and the mode of its inheritance is uncertain. Sporadic variety usually begins later. On histopathological examination lymphocyte infiltration and atrophy of parathyroid parenchyma with fatty replacement can be seen. In the sera of patients the presence of antibodies directed against parathyroid tissue (anti-endothelial cell antibodies) was found. These findings are the evidence of participation of autoimmunity in etiopathogenesis of this variety of hypoparathyroidism (autoimmune disease). This **autoimmune form** of hypoparathyroidism usually occurs as a part of the polyglandular-autoimmune syndrome. Therefore, in patients with this disease, or in their family members, Addison disease, Hashimoto thyroiditis, primary hypothyroidism, primary hypogonadism, and type 1 diabetes mellitus may also develop. Nonendocrine autoimmune diseases, such as alopecia areata, vitiligo (with antibodies directed against melanocytes), pernicious anemia, and recurrent or chronic mucocutaneous candidiasis (resulting from a defect in cellular immunity) may also occur in patients with idiopathic hypoparathyroidism and bolster the hypothesis on autoimmune etiopathogenesis of this disease.

Any process that replaces or destroys sufficient amount of normal tissue of the parathyroid glands may cause hypoparathyroidism. Iron storage disease (secondary to idiopathic hemochromatosis or hemosiderosis after repeated blood transfusion), Wilson disease (copper deposition in the parathyroids), metastases to the parathyroids (breast cancer is the most common primary tumor), or infiltration of the parathyroids in patients with sarcoidosis has been considered a rare organic cause of hypoparathyroidism.

A very rare form of hypoparathyroidism is due to congenital aplasia of the parathyroid glands which is manifested shortly after birth. There is a linkage between defective development of the thymus (thymic aplasia with resulting T cell abnormalities) and the parathyroid glands. This disorder is termed **the Di-George syndrome**, and is associated with congenital cardiovascular malformations (mainly anomalies of aortic arch) and other developmental defects.

**B. Functional causes.** Functional hypoparathyroidism is rarer than organic ones. It includes **transient hypoparathyroidism** following surgical re-

moval of a parathyroid adenoma. It originates because the remainder of the parathyroids is suppressed by preceding long-term hypercalcemia and its recovery is slow, usually occurs months after the surgery. Hypoparathyroidism of newborns (**neonatal hypoparathyroidism**) may originate by an analogous mechanism. It occurs in newborns of hypercalcemic mothers or of those with mild secondary hyperparathyroidism. These disorders in mother may result in suppression of the parathyroid activity of fetus. However, the parathyroid glands of newborns recover their function quickly, generally within one week.

Functional hypoparathyroidism may be induced also by **hypomagnesemia**. The major effect of hypomagnesemia is probably impaired PTH release (not its synthesis). Reduced responsiveness to PTH may also contribute to hypocalcemia in patients with hypomagnesemia. The possibility of secretion of **biologically inactive PTH** in the origin of hypoparathyroidism is admitted.

Clinical picture of hypoparathyroidism depends on the length of duration of the disease. At the onset of hypoparathyroidism metabolic signs and symptoms of increased neuromuscular excitability are most evident. Besides increased neuromuscular excitability for chronic hypoparathyroidism the most characteristic are psychic and neurological signs, heterotopic calcifications, trophic changes of skin and its appendages, and dental abnormalities.

The most evident **metabolic manifestations** of hypoparathyroidism are hyperphosphatemia, hypophosphaturia, hypocalcemia, and hypocalciuria. The cause of their origin is inhibition of urinary phosphate excretion and decreased mobilization of calcium from bones due to PTH deficiency.

**Increase of neuromuscular excitability** is related to the decrease of serum total calcium concentration and thereby also to the decrease of serum ionized calcium concentration. Ionized calcium covers about one half of the total calcium in circulating blood, respectively in extracellular fluid. Therefore, the decrease of its concentration causes the change of proportion of ions on outer and inner side of the cell membrane, which leads to the decrease of threshold of excitability, respectively to hyperexcitability of nerve and muscle cells. Excitability of the whole **peripheral motor neuron**, respectively neuromuscular unit, is being increased. It is derived from the fol-

lowing simple relationship of **Szent-György formula**:

$$\text{Excitability} = \frac{[\text{Na}^+] + [\text{K}^+]}{[\text{Ca}^{2+}] + [\text{Mg}^{2+}] + [\text{H}^+]}$$

According to this formula neuromuscular excitability is indirect proportional to concentrations of calcium, magnesium, and hydrogen ions. If concentrations of these ions in extracellular fluid decrease, neuromuscular excitability increases. The increase of neuromuscular excitability is manifested by spontaneous or poststimulative attacks of painful tonic contractions (convulsions) of certain groups of muscles which are termed **tetany**. The signs of increased excitability of **peripheral sensitive neuron** (an origin of paresthesia, e.g., formication or numbness) and of **vegetative nerve** (visceral tetany) may be simultaneously observed.

Tetany is a clinical manifestation of increased neuromuscular excitability. Tetany due to hypoparathyroidism is termed **parathyroprivic tetany** which is one of the types of hypocalcemic tetany. The clinical syndrome of tetany is manifested either by increased readiness to tetanic convulsions (latent tetany) or by spontaneous origin of tetanic convulsions (manifest tetany).

**A. Latent tetany.** In patients with increased readiness to tetanic convulsions, tetanic attack may be evoked by application of certain diagnostic methods. This subclinical degree of increased neuromuscular excitability is termed latent tetany. It originates when calcemia is between 1.75 and 2.0 mmol/L (the normal range of calcemia is 2.25–2.75 mmol/L).

The increased readiness to the origin of tetanic cramps may be objectively proved by gentle tapping over the facial nerve in front meatus acusticus externus, which induces twitching of the muscles of the eye, nose, and mouth on the same side of the face (**Chvostek sign**). Alternatively, occluding the arterial blood supply to the forearm and hand by inflating a sphygmomanometer cuff (above blood pressure) about the arm for less than for 3 minutes induces carpal spasm (**Trousseau sign**), which disappears as soon as the cuff is deflated. Due to irritation of peripheral nerve (median or ulnar nerve) by galvanic current of less intensity than 5 mA, tetanic convulsion of competent group of muscles originates (**Erb sign**).

Latent tetany may be also manifested by **subjective symptoms**, such as paresthesias (circumoral tingling and numbness, "needles and pins" feeling in hands and feet), evident weakness, tensions even spasms of muscles when writing or walking.

**B. Manifest tetany.** Spontaneous tetanic cramps originate due to rapid fall of calcemia below the level of 1.75 mmol/L, and usually occur in attacks. This degree of increased neuromuscular excitability is denoted as manifest tetany. In the period between single attacks the presence of latent tetany may be proved. If the value of calcemia rapidly falls to the level of 1.25 mmol/L, the tetanic attack is usually fatal.

Spontaneous tetany attack starts either without evident cause or after emotional stress, physical work, or after other activity associated with hyperventilation (respiratory alkalosis due to overbreathing leads to depression of serum ionized calcium concentration). Before its origin **prodromal symptoms** may sometimes appear, e.g., paresthesias of lips, tongue, and fingers and toes, feeling of tension and stiffening of some groups of muscles, limitation of voluntary movements, muscle pain, or even slight muscle twitches.

Spontaneous tetany attack may be manifested as convulsions of only some groups of muscles or as generalized tonic cramps. Sometimes tonic-clonic cramps may appear. The most frequent form of the tetany attack is a **carpal spasm**, which affects both upper limbs. So-called obstetrical hand (main d'accoucheur) due to the carpal spasm is characterized by adduction and opposition of the thumb (its relation to the other fingers when it is moved towards the palm), extension in interphalangeal joints, flexion in metacarpophalangeal joints, and flexion in the wrist. The cramp may affect arm muscles, too, resulting in flexion in elbows. In the lower extremities tetany attack is manifested by the total extension of the limbs with extreme plantar flexion of the foot and toes (**a pedal spasm**). The simultaneous affection of upper and lower extremities is common. This form of spontaneous tetany attack is denoted as a **carpopedal spasm**.

Tonic cramps may affect also other muscle groups. Tonic spasm of the upper lip causes pursy mouth (fish mouth). Tonic cramps of other mimic facial muscles may also appear at the same time (facial grimacing). Spasm of laryngeal muscles (**laryngospasm**) and spasm of respiratory muscles are most dangerous.

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ous. They are manifested by inspiratory stridor, dyspnea, and cyanosis. In severe cases they may lead to death by asphyxiation.

Spasm of smooth muscles causes the origin of symptoms of **the visceral tetany**. It is manifested by cardiospasm with dysphagia, pylorospasm, spastic constipation, biliary colic, bronchospasm, dysuria, or arteriolar spasm. Arteriolar spasm causes the origin of Raynaud syndrome or migraine. Long-lasting bronchospasm may cause death by asphyxiation.

**Generalized convulsions** (tonic or tonic-clonic) may be the result of extremely severe cases of tetany attack. The consciousness of the patient is not usually changed in the course of the attack. If the generalized convulsions are exceptionally associated with a loss of consciousness (especially in children) they may remind of the epileptic seizure of grand mal type.

Spontaneous tetany attack may last several seconds, minutes, or even hours. Remissions between single attacks are of various duration. The attack may withdraw spontaneously (in spastic muscles pH decreases, and thereby concentration of ionized calcium increases), or it may withdraw after therapy. Possibility of repeating of tetany attack depends on removal of the cause of its origin, respectively on proper treatment. If hypocalcemia continues, the signs of latent tetany are observed in the periods between the tetany attacks.

On **the electrocardiogram** persisting hypocalcemia is manifested by prolongation of the Q-T interval and by peaking T wave, or by its inversion. The Q-T interval returns to normal rapidly after correction of hypocalcemia, but T wave abnormality may be slower to regress. On **the electromyogram** increased neuromuscular excitability induced by hypocalcemia is manifested by the presence of groups of two, three, or even more peaks (so-called duplets, triplets, or multiplets).

**Chronic hypoparathyroidism.** Besides increased neuromuscular excitability, long-lasting nontreated hypoparathyroidism, likewise chronic hypocalcemia of any other origin, is manifested by further characteristic clinical features. **Mental changes** and **neurological signs** are common. Anxiety, depression, emotional lability, irritability, and frank psychosis may be present in the patient. Sometimes a decrease of intellectual abilities may be observed, too. Severe headaches are quite common. Epileptic seizures of

various types may also occur. Papilledema, elevated cerebrospinal fluid pressure, and neurological signs mimicking a cerebral tumor may occur. **Intracranial calcifications** are visible on skull x-ray films in approximately 20% of patients. They are most frequently present in the basal ganglia accompanied by a parkinsonian-like syndrome. Intracranial calcifications are rather common in cerebellum, too.

In about 50% of patients with chronic hypoparathyroidism calcification of the lens can lead to **hypocalcemic cataract** formation. Cataract may also occur in children or young adults leading to severe disorders of vision. Correction of hypocalcemia by pharmacotherapy may stop its development, however, it does not lead to regression of cataracts once formed. Development of calcified basal ganglia and cataract is probably a function of the duration of the hypoparathyroid state and is more common in idiopathic hypoparathyroidism than in postsurgical hypoparathyroidism. The pathogenesis of heterotopic calcifications in patients with permanent hypocalcemia is not menwhile known.

In many patients with chronic hypoparathyroidism **trophic changes of skin and its appendages** originate. Skin is dry with eczematoid changes, hair grows slowly and tends to fall out, and even alopecia may originate. Eyebrows, eyelashes, and other body hair are sparse. Uneven horizontal ridges on the nails and white discoloration of the nails (leuconychia) appear. The nails are thin, brittle, and fragile.

**Dental abnormalities** occur frequently in the patients with chronic hypoparathyroidism. Depending on the age at the onset of the disease, one may find enamel hypoplasia, dental hypoplasia, defective root formation, and failure of adult teeth to erupt.

### 5.5.2 Pseudohypoparathyroidism

Pseudohypoparathyroidism (a syndrome of end-organ resistance to parathyroid hormone) is a rare hereditary disorder. Manifestations of hypoparathyroidism are not due to PTH deficiency, but they are due to target organ **unresponsiveness to PTH**, especially kidneys. There is no direct evidence of skeletal resistance to PTH in patients with pseudohypoparathyroidism. Serum PTH concentration is increased. Excessive secretion of PTH is the consequence of hyperplasia of the parathyroids, a response to the resistance to hormone action.

From the point of view of **pathogenesis**, resistance to PTH might reflect defect at any multiple sites:

- a) circulating antagonist of PTH action, which prevents its binding to receptor of target organ;
- b) abnormal PTH receptor;
- c) abnormal adenylate cyclase component;
- d) abnormal cAMP-dependent protein kinase;
- e) defective protein substrate of the kinase.

Defects at c, d, and e sites are on the level of postreceptor mechanism.

Resistance of renal tubules to PTH results in hypophosphaturia, hyperphosphatemia, hypocalcemia, and hypocalciuria secondary to hypocalcemia. These metabolic changes are the same as those due to hypoparathyroidism. Along with reduced urinary excretion of phosphate also insufficient hydroxylation of vitamin D in kidneys participates in the origin of hypocalcemia. The cause of insufficient renal hydroxylation of vitamin D is hyperphosphatemia, which is associated with inhibition of renal 1- $\alpha$ -hydroxylase. This renal enzyme is necessary to conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which is the most active form of vitamin D. This tends to depress serum calcium concentration further by reducing intestinal absorption of calcium secondary to low serum 1,25-dihydroxycholecalciferol level.

Hypocalcemia is clinically manifested by latent or manifest tetany, which is persisting since the early childhood. Heterotopic calcifications (mainly in the basal ganglia, subcutaneous tissue, and lens) are rather common. In these patients intellectual impairment is quite frequent. Some patients have radiographic evidence of excessive parathyroid action on bones, i.e., osteitis fibrosa cystica.

At present time **four types of pseudohypoparathyroidism** are known:

1. Pseudohypoparathyroidism type Ia
2. Pseudohypoparathyroidism type Ib
3. Pseudohypoparathyroidism type II
4. Pseudopseudohypoparathyroidism

Individuals with pseudohypoparathyroidism types Ia and Ib, the most common of the disorders, show a deficient response in urinary cyclic AMP (lack of the normal brisk rise in urinary cAMP excretion) following administration of exogenous PTH. This observation implies that hormone resistance in type I is due to a proximal defect in hormone action, presumably in the receptor-adenylate cyclase complex. Patients with pseudohypoparathyroidism type II have a normal urinary cAMP response to exogenous PTH. Therefore, the defect in the renal tubules appears to be distal to cAMP formation. It was suggested that a defective cAMP-dependent protein kinase could be responsible, but there are no direct data on this point.

Clinical picture of pseudohypoparathyroidism depends on the type of combination of the following **four groups of symptoms**:

- A. Symptoms due to resistance of renal tubules to PTH;
- B. Somatic anomalies of type of Albright hereditary osteodystrophy;
- C. Other skeletal changes;
- D. Presence of other endocrine anomalies.

#### 1. Pseudohypoparathyroidism type Ia.

Essentially all subjects with this form of the disorder show the somatic features of Albright hereditary osteodystrophy, such as short stature, round face, short thick neck, obesity, and shortening of the metacarpals and metatarsals. The most characteristic is shortening of fourth and fifth metacarpals (brachydactyly). The defects are usually bilateral. Reduced intelligence and subcutaneous calcifications are also present. Associated endocrine abnormalities are common. Some, such as primary hypothyroidism and primary hypogonadism, are usually clinically manifested. They probably originate due to primary resistance of the thyroid gland and gonades to adequate pituitary hormones, i.e., TSH and GTHs. It is an inborn resistance to several hormones (multi-hormonal resistance), which is due to defective G-protein. Abnormalities of other hormones are more subtle and evident only upon provocative testing. Pseudohypoparathyroidism type Ia is a familial disease with an X-linked inheritance, but also the existence of either autosomal dominant or autosomal recessive inheritance patterns have been identified.

## 2. Pseudohypoparathyroidism type Ib.

Patients with this type of pseudohypoparathyroidism have a normal phenotype without the Albright hereditary osteodystrophy syndrome. Hypocalcemia, hyperphosphatemia, and high serum PTH level are present. Administration of exogenous PTH detects the blunted urinary cAMP response. Detailed endocrine testing has generally disclosed no abnormality other than PTH resistance.

## 3. Pseudohypoparathyroidism type II.

There are only few patients with this type of disorder. They manifest hypocalcemia, hyperphosphatemia, elevated serum PTH concentration, normal urinary cAMP level, but subnormal phosphaturic response to PTH. These patients are normal in appearance, they do not have phenotypic abnormalities of Albright hereditary osteodystrophy.

## 4. Pseudopseudohypoparathyroidism.

It is a hereditary disorder, which is incomplete form of pseudohypoparathyroidism type Ia. These individuals are usually first-degree relatives of patients with pseudohypoparathyroidism type Ia (pseudohypoparathyroidism type Ia is usually present in the mother of the patient). Patients with pseudopseudohypoparathyroidism have the phenotypic features of Albright hereditary osteodystrophy but without demonstrable metabolic abnormalities. These patients have normal serum calcium concentration, normal serum PTH concentration, and normal response of urinary cAMP to exogenous PTH. For the present time it seems that the term pseudopseudohypoparathyroidism should be reserved for patients meeting the following criteria:

- (a) clear cut phenotypic features of Albright hereditary osteodystrophy;
- (b) first-degree relative with pseudohypoparathyroidism type Ia;
- (c) relatively normal urinary cAMP response to exogenous PTH.

### 5.5.3 Hyperparathyroidism

Hyperparathyroidism is a pathophysiological state resulting from oversecretion of PTH. According to the mechanism of its origin primary, secondary, and

tertiary hyperparathyroidism are distinguished. Hypersecretion of PTH with **primary hyperparathyroidism** does not depend on the needs of organism, but production of PTH by the parathyroid glands is autonomous. The cause of its origin is within the parathyroid glands themselves. Oversecretion of PTH with **secondary hyperparathyroidism** is a compensatory response to the increased needs of PTH due to any condition in which there is a tendency toward hypocalcemia and to calcium deficiency in organism. During long-standing secondary hyperparathyroidism (most often in renal failure) some part of hyperplastic parenchyma of parathyroid glands may gradually escape the influence of homeostatic regulation by calcemia, and, therefore, secretion of PTH by this part of hyperplastic parenchyma becomes autonomous. It may in time convert into autonomous adenoma formation, usually referred to as **tertiary hyperparathyroidism**.

#### 5.5.3.1 Primary hyperparathyroidism

Primary hyperparathyroidism is a pathophysiological state manifesting permanent autonomous oversecretion of PTH by one or more parathyroid glands. It is characterized by hypercalcemia and by its consequences, as well as by combination of symptoms resulting from renal and skeletal disorders. Manifestation of the mentioned symptoms and signs in individual patients may be of various intensity.

The most common cause of its origin is **solitary adenoma** of single parathyroid gland while the remaining glands are normal. It occurs in about 80% of cases. Parathyroid adenoma is most commonly composed of the chief cells. **Double** or **multiple adenomas** occur in about 3–5% of patients. The second most common cause of primary hyperparathyroidism is **primary hyperplasia** (chief cell hyperplasia) of parenchyma of all parathyroid glands. It is revealed in about 10–15% of instances. Most, but not all, of cases of primary hyperplasia are hereditary and associated with other endocrine abnormalities. Hereditary primary parathyroid hyperplasia is a part of a multiglandular endocrinopathy. There are several distinct MEN syndromes. The MEN 1 type consists of hyperparathyroidism and tumors of the pituitary and pancreatic islet cells. Another distinct constellation of endocrinologic abnormalities consists of hyperparathyroidism associated with pheochromocytoma and medullary carcinoma of thy-

roid (MEN 2A). **Parathyroid carcinoma** accounts for about 1–2% of all cases of primary hyperparathyroidism though usually with severe hypercalcemia. In some patients with primary hyperparathyroidism anamnesis reveals irradiation of the neck area. The increase of PTH concentration in circulating blood may be the result of its production in some tumors of bronchi, breast, kidneys, and thymus. This ectopic PTH secretion is termed **ectopic hyperparathyroidism** (paraneoplastic hyperparathyroidism).

In the past primary hyperparathyroidism was considered a very rare disease. According to the present clinical experiences it is not such a rare disease as considered. **The prevalence** of this disease is approximately 1:1000. It is a prevalence approximately 10-fold that ascertained in early studies of hyperparathyroidism. The cause of this discrepancy is that during medical examination of patients with other diseases the possible presence of hyperparathyroidism was not often considered, and, therefore, necessary diagnostic tests were not realized (mainly hospital screening of hypercalcemia). It is also due to the fact that primary hyperparathyroidism is clinically manifested by apparently noncharacteristic symptoms resulting from disorders of distant organs. It is assumed that 5% of all cases of urolithiasis and 15–20% of bilateral recurrent cases of nephrolithiasis are caused by primary hyperparathyroidism. Therefore, this disease is often revealed accidentally or as late as the severe clinical symptoms suddenly appear. It is assumed that the number of diagnosed cases of primary hyperparathyroidism has been still lower than the real occurrence of this disease in population.

In childhood primary hyperparathyroidism is rare. The disease is most common in adults, with peak incidence between the fourth and sixth decades. It is more common in women (mainly after the age of 50) than in men (4:1).

Primary hyperparathyroidism is the disease with great variation in the clinical presentation. Patients commonly remain asymptomatic for a long period, and only the finding of a mild elevation of serum calcium may be present. Later, besides biochemical changes in blood and urine, skeletal, renal, gastrointestinal, neuropsychical, neuromuscular manifestations, and other associated abnormalities in various combinations may be present. However, manifestations of primary hyperparathyroidism involve primarily the kidneys and the skeletal system. Hy-

percalcemia is always present in patients with any combination of the above mentioned manifestations.

**Hypercalcemia** and **hypophosphatemia** are the laboratory hallmarks of primary hyperparathyroidism. Hypercalcemia is almost always present, either sustained or intermittent hypercalcemia. Hypophosphatemia does not have to be always present. The true hypophosphatemia is found in only about half of cases. Therefore, it is a less reliable biochemical parameter for diagnosis than hypercalcemia. These both mentioned biochemical changes in circulating blood are the consequences of the direct action of PTH on the skeleton and the kidneys. Due to the increased activity of osteoclasts, calcium and phosphorus are in a higher extent released from bones into extracellular fluid and circulating blood.

Reabsorption of phosphate in renal tubules is decreased and that of calcium is slightly increased. As a result of the mentioned changes in bones and renal tubules the increased serum concentration of PTH is manifested not only by hypercalcemia and hypophosphatemia, but also by **hyperphosphaturia**. The total excretion of cAMP in the urine is also increased. Besides the increased release of calcium from bones, also the increased calcium absorption from intestine, which is secondary to the enhanced rates of generation of 1,25-dihydroxycholecalciferol by the kidneys in response to increased serum PTH level, participates in the origin of hypercalcemia. In spite of slightly increased calcium reabsorption in renal tubules by PTH, the content of calcium in glomerular filtrate due to hypercalcemia is increased to such extent, that it results in its increased excretion into urine (**hypercalciuria**). However, urinary calcium is generally reduced relatively to serum calcium level. Hypercalciuria and hyperphosphaturia evoke **osmotic diuresis**.

Primary hyperparathyroidism is clinically manifested either only by some of the following syndromes, or by their variable combination. They are the following **clinical syndromes** of primary hyperparathyroidism:

1. Simple hypercalcemic syndrome
2. Skeletal syndrome
3. Renal syndrome
4. Gastrointestinal syndrome

## 5. Other associated manifestations and abnormalities

1. **Simple hypercalcemic syndrome** (chemical hypercalcemic syndrome). It is the set of signs and symptoms induced by hypercalcemia. The percentage of this form of primary hyperparathyroidism has been recently increasing. It is because of common examination of several biochemical parameters, including also serum calcium concentration, in all clinical patients, i.e., with any diagnosis.

If the serum calcium concentration is only slightly raised (value below 3.0 mmol/L), hypercalcemia is generally asymptomatic. If it is above 3.0 mmol/L, hypercalcemia evokes noncharacteristic symptoms resulting from decreased neuromuscular excitability and from osmotic diuresis. **Decreased neuromuscular excitability** results in hypotonia of skeletal muscles and atonic dysfunction of gastro-intestinal tract. It is manifested by generalized muscle weakness and hyporeflexia, increased tiredness, anorexia, nausea, vomiting, meteorism, and constipation. **Increased osmotic diuresis** is manifested by polyuria (up to 5 litres per day), dryness in mouth, feeling of intense thirst, and increased intake of fluid (polydipsia). The symptoms of hypercalcemic syndrome include also bradycardia, tendency to origin of arrhythmias, shortening Q-T interval, apathy, lethargy, depression, parosmias, and decrease of body weight.

In the course of primary hyperparathyroidism acute hyperparathyroidism (acute parathyrotoxicosis), which may result in hypercalcemic crisis, may originate. **Acute hyperparathyroidism** is manifested by sudden and expressive increase of calcium concentration in serum and by simultaneous increase of intensity of hypercalcemic syndrome symptoms. Evident muscle weakness, general muscle flaccidity even paralysis, expressive lethargy, depression, confusion, hallucinations, intense vomiting, evident polyuria, great thirst, and severe dehydration appear. Due to hypercalcemia between the levels 3.75–4.0 mmol/L **hypercalcemic crisis** originates. It is a life-threatening acute illness with 50 % mortality. It is usually evoked by bone fracture, surgical intervention, infectious disease, overdosage of vitamin D or calcium, over exposure to sun's rays, dehydration evoked by diuretics, bleeding to hyperfunctional parathyroid adenoma, or hypercalcemic pancreatitis. Its clinical picture is characterized by the origin of

acute renal insufficiency, evident mental deterioration, altered consciousness, and coma. If the value of hypercalcemia is above 4.0 mmol/L the patient is in danger of so-called "chemical death" due to asystole (the heart stops beating in systole).

2. **Skeletal syndrome.** The severe bone abnormalities characteristic for primary hyperparathyroidism are also termed generalized osteitis fibrosa cystica, or sometimes denoted as von Recklinghausen bone disease. It is the longest known syndrome of primary hyperparathyroidism. If the signs and symptoms of skeletal syndrome dominate the clinical picture, this disease is usually denoted also as osseous form of primary hyperparathyroidism. It originates in its later stage, when organ changes are already clinically manifested. Data on the presence of skeletal syndrome in patients with primary hyperparathyroidism rather differ. Some authors mention its 20 % occurrence, others affirm that skeletal syndrome is present even in 90 % of patients with this endocrinopathy. Data accuracy on its occurrence probably depends on experience and purposefulness of roentgenologist, as well as on applying other diagnostic methods.

The gist of skeletal syndrome origin is characterized partly by increased release of calcium and phosphorus from bones (bone demineralization) due to increased bone osteoclastic resorption (particularly at the subperiosteal surfaces), and partly by simultaneous fibrous rebuilding of bone structure and the origin of insufficiently calcificated osteoid tissue. **Generalized osteopenia** is being developed gradually.

On roentgenograms of long bones lamina corticalis is thinned and usually sharp cortical outline of the bone is replaced by an irregular outline (**subperiosteal resorption**). These subperiosteal resorptions (subperiosteal erosions, subperiosteal notching) are patognomonic for hyperparathyroidism, and they are more frequent and expressive in patients with primary than in those with secondary hyperparathyroidism. Bony trabeculae in the spongiosa are thick, their countours are not sharp, and they form irregular net. **Acroosteolysis** (resorption of bone epiphyses) may be also present. On radiographs it is manifested as disappearing of the phalangettes, proximal end of fibule and tibia, and lateral margins of clavicles. Bone ends are nibbled-like, their countours are slightly indented.

On roentgenograms of bones osteolytic foci are evident. They are manifested as resorption cyst,

or cyst-like formations, and are denoted as "**brown tumors**" (pseudotumors). They are multiple and are usually found as swellings on the epiphyseal-diaphyseal border of long bones, mainly in the areas of knee, elbow, and arms. They may be also found in the phalanges (especially of the hands), clavicles, skull, patellae, and ribs. Relatively characteristic findings are presence of "epulis" gigantocellularis of the jaw and presence of the resorption of the lamina dura of the teeth. Brown tumors are the areas in which quantities of osteoclasts (they are multinucleated giant cells, probably originating by transformation of tissue macrophages), osteoblasts and fibroblasts are gathered, and in which signs of bleeding are often present. The brown color of this reactive lesion is the result of the hemorrhage, hemosiderin deposition, and vascularity. Frequently these lesions undergo cystic degeneration.

Histologically, the pathognomonic features are a reduction in the number of trabeculae, an increase of numbers of the giant multinucleated osteoclasts, proliferation of osteoblasts and fibroblasts, and a replacement of the normal cellular and marrow elements by fibrous tissue. Bone resorption as well as formation is, therefore, increased. The increased bone formation is evidenced by increased osteoblast numbers and islands of newly formed bone tissue (unmineralized osteoid). Because osteoclast activity exceeds osteoblast activity, the net result is bone resorption. Histomorphometric analyses of biopsied bone reveal an abnormality in bone turnover in most patients, even in those who do not have a progressive loss of net bone mass. The progressive loss of bone mineral mass causes osteopenia.

In more advanced stage of the disease **pathological fractures** (spontaneous fractures) of bones may originate as a result of the changes associated with skeletal syndrome. The most frequent pathological fractures of neck of femur, some vertebrae, and some of pelvic bones may appear. **Bone deformations** are quite common because bones become softer due to production of insufficiently calcified osteoid tissue. Most often they appear on lower limbs, chest, and pelvic bones. Due to kyphoscoliosis the stature of the patient may shorten.

The mentioned skeletal changes are **subjectively** manifested by gradating diffuse bone pain, mainly in spine, sacral area (sacralgia), hip joint, symphysis, and lower extremities. The pain is more expressive

during some activities, e.g., climbing stairs, getting out of a chair, or getting into a bus or train.

**3. Renal syndrome.** It is the result of persisting hypercalciuria and hyperphosphaturia. If its signs and symptoms dominate the clinical picture, this disease is usually denoted also as renal form of primary hyperparathyroidism. Renal syndrome is characterized mainly by the presence of nephrolithiasis, nephrocalcinosis, and by their complications.

**Nephrolithiasis** is usually recurrent and occurs in about 60–80% of the patients with hyperparathyroidism, and it is bilateral in about 20% of them. There is usually a larger number of renal stones and they are usually composed of either calcium oxalate or calcium phosphate. Correlation has been reported between 1,25-dihydroxycholecalciferol concentrations in plasma and nephrolithiasis in patients with primary hyperparathyroidism. Renal colic is one of the most common symptoms of hyperparathyroidism, sometimes it may be the first symptom of hyperparathyroidism. Repeated episodes of renal colic or the formation of large calculi may lead to urinary tract infections (mainly pyelonephritis or interstitial nephritis), which usually appears recurrently.

**Nephrocalcinosis** due to primary hyperparathyroidism is not so common as nephrolithiasis. It occurs in about 7% of the patients. It originates by deposition of calcium salts in parenchyma of the kidneys (in distal tubules, renal papillae, and medullary pyramids). Nephrocalcinosis may be evident on x-ray films of the kidneys as multiple granular, lumpy, or cloud-like small shadows.

**4. Gastrointestinal syndrome.** It is characterized by symptoms of gastric or duodenal ulcer, acute or chronic pancreatitis, probably cholelithiasis as well. **Peptic ulcer** occurs in about 15% of patients with hyperparathyroidism. It is most frequently localized in the duodenum. It is 5 times more frequent in patients with hyperparathyroidism than in the rest of population. It is assumed that stimulation of gastrin secretion and an increase in gastric acid secretion participate in its origin. Symptoms of peptic ulcer in patients with hyperparathyroidism are severer than those in patients without hyperparathyroidism. Peptic ulcer in patients with hyperparathyroidism is more resistant to usual treatment and its recidivation is more frequent. **Pancreatitis** occurs in about 7–12% of patients with hyperparathyroidism and its

recidivation is also more frequent. The cause of its coincidence with hyperparathyroidism as well as its pathogenesis are unknown.

**5. Other associated manifestations and abnormalities.** Some of them are secondary to hypercalcemia itself, but pathogenesis of many of them is unknown. They are usually not pathognomonic for hyperparathyroidism.

**Psychical and neurological manifestations** include emotional lability, poor memory, slow mentation, apathy, somnolence, depression, paranoid features, and neuromuscular abnormalities. Intensity of the psychical disorder depends on the level of calcium in circulating blood. Neurological symptoms are also variable. The most evident of them are headache, somnopathies, parosmias, dysesthesias, and neuralgias. **Muscular symptoms** include easy fatigability, muscle weakness, muscle hypotony, myalgias, and postdenervational muscle atrophy which is due to neuropathy.

The best known of **cardiovascular symptoms** are bradycardia, arrhythmias, shortening of the Q-T interval on the electrocardiogram, arterial hypertension, and increase response of a heart to digitalis. **Hematological symptoms** include anemia and elevated erythrocyte sedimentation rate.

Long-lasting hypercalcemia is associated with the origin of **subconjunctival** and **corneal calcifications**. Corneal calcification is manifested as **band keratopathy**, which is recognized as opaque material in parallel lines within the limbus of the eyes. **Arthralgias** and **hypermobility** of the joints also have been described. Disorders of many organs resulting from long-standing hypercalcemia are also due to deposition of calcium into various tissues. These deposits of calcium are termed **ectopic calcifications**. They may appear mainly in lungs, kidneys, wall of arteries (especially in the media), pancreas, myocardium, gastric mucosa, subcutis of periarticular area, and skin. Microscopic deposits of calcium within the skin are presumably the cause of pruritus. Deposits of calcium in parenchyma of kidneys, cornea, and subconjunctival area are also considered as ectopic calcifications.

### 5.5.3.2 Secondary hyperparathyroidism

Secondary hyperparathyroidism is the state of **compensatory** hyperplasia of all four parathyroid glands

and of compensatory hypersecretion of PTH, which originates due to pathological state associated with long-lasting tendency to hypocalcemia. It is a regulatory response of the parathyroid glands to long-lasting negative balance of calcium in organism. Hyperplasia of the chief cells is diffuse and occurs in all parathyroid glands. The aim of secondary increased serum PTH concentration is to prevent the origin of hypocalcemia via the increased releasing of calcium from bones.

**Etiology and pathogenesis.** Long-lasting disorder of calcium and phosphorous homeostasis in organism, and thereby long-lasting tendency to the origin of hypocalcemia develops mainly due to the poor intestinal calcium absorption, phosphate retention induced by renal disorders, and increased urine excretion of calcium.

The most frequent cause of secondary hyperparathyroidism is **chronic renal failure**. Secondary hyperparathyroidism is rarely evoked by some **inborn tubulopathies** (renal tubular acidosis and Fanconi syndrome). Though in the patients with tubulopathy considerable demineralization of bones originates, hyperfunction of the parathyroid glands is of a milder degree. Overproduction of PTH due to renal disorders is termed renal form of secondary hyperparathyroidism.

Pathogenesis of PTH oversecretion in patients with chronic renal insufficiency is complex. Chronic renal failure results in phosphate retention and **hyperphosphatemia**. Phosphate retention is a consequence of the decreasing filtered load of phosphate as glomerular filtration rate falls. This causes a **reciprocal fall in plasma calcium** which, in turn, provokes increased release of PTH. The result is normalization of plasma calcium concentration and increased phosphaturia, such that plasma phosphate also returns to normal. Thus, with each decrement in glomerular filtration rate, a new steady state is reached with normal plasma concentration of calcium and phosphate, but only at the expense of secondary hyperparathyroidism. The parathyroids compensate so well for the alterations in calcium and phosphorous homeostasis as renal function declines, that overt hyperphosphatemia develops only when glomerular filtration rate falls to 25 ml/min. Hyperphosphatemia results in decreased activity of renal 1- $\alpha$ -hydroxylase, and thereby in **decreased production of 1,25-dihydroxycholecalciferol** (vitamin D<sub>3</sub>). Reduced for-

mation of 1,25-dihydroxycholecalciferol is also the result of damaged and shrunken parenchyma of the kidneys. Low serum 1,25-dihydroxycholecalciferol concentration leads to a reduction of intestinal absorption of calcium. Concentration of PTH in circulating blood increases also due to **decreased renal clearance of PTH**, which is caused by expressively decreased glomerular filtration rate. It is assumed that a further contributing factor to hypocalcemia is relative **skeletal resistance to PTH**.

Another, but less common cause of secondary hyperparathyroidism is **vitamin D deficiency**. Compensatory PTH oversecretion is due to hypocalcemia, which originates as a result of insufficient intestinal calcium absorption. This reduced calcium absorption is caused by undeproduction of its protein carrier in enterocytes. Decreased production of this high-affinity calcium-binding protein of intestinal mucosal epithelia is induced by vitamin D deficiency (its active hormonal form, i.e., 1,25-dihydroxycholecalciferol). By PTH oversecretion hypocalcemia is being normalized. By simultaneous decreased reabsorption of phosphates in renal tubules (due to increased serum PTH level) hyperphosphaturia and hypophosphatemia develop.

The third main cause of secondary hyperparathyroidism is **intestinal calcium malabsorption**. Most commonly it originates due to intestinal lipid malabsorption caused by pancreatic lipase and bile acid deficiency, celiac sprue (gluten-induced enteropathy), and tropical sprue. Nonabsorbed fatty acids together with calcium form insoluble calcium soaps, and, therefore, excessive intestinal calcium loss appears. Decreased intestinal calcium absorption is also induced by fat-soluble vitamin D deficiency which is in patients with intestinal fat malabsorption caused by its insufficient intestinal absorption.

**Clinical features.** The clinical features of secondary hyperparathyroidism are analogous to those of primary hyperparathyroidism, however, usually milder. Nephrolithiasis and nephrocalcinosis are less common in the patients with secondary hyperparathyroidism. Ectopic calcifications appear mainly in subcutis, tissues of periarticular area, and in the wall of arteries. Besides the symptoms resulting from PTH overproduction, also the symptoms of primary disease which gives rise to the disorder of calcium homeostasis may be observed. The symptoms of primary disease are the most evident

in the patients with chronic renal failure. Unlike the patients with primary hyperparathyroidism, in the patients with secondary hyperparathyroidism serum calcium concentration is slightly decreased, sometimes even normal, and serum phosphate concentration is increased. The symptoms of uremia are also present. The skeletal abnormalities include osteitis fibrosa cystica (caused by the excessive action of PTH on bones), osteomalacia (caused by impaired formation of 1,25-dihydroxycholecalciferol and by calcium deficiency), and generalized osteopenia. These bone abnormalities in patients with secondary hyperparathyroidism induced by chronic renal failure are usually termed **renal osteodystrophy**. Its expressive manifestations develop mainly in patients undergoing chronic hemodialysis. In this subjects generalized osteopenia may lead to a development of multiple pathological fractures. Any of the classic lesions of primary hyperparathyroidism can also occur, although bone cysts are less common. Clinically, osteodystrophy causes bone pain. In addition, proximal muscle weakness may be similar to that in primary hyperparathyroidism.

The clinical features of rickets develop with vitamin D deficiency in infancy or childhood. Vitamin D deficiency in the adults evokes the origin of the clinical features of osteomalacia.

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## 5.6 Pathophysiology of the adrenal glands

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The suprarenal glands are composed of two developmentally, morphologically, and functionally different parts, the cortex and the medulla. Cortical tissue is derived embryologically from the celomous mesoderm. Histologically it consists of three zones (zonae glomerulosa, fasciculata, and reticularis) and produces three kinds of functionally different corticosteroid hormones: glucocorticoids, mineralocorticoids, and androgens, and in small amounts also estrogen and progesterone. Medullary tissue is derived embryologically from neuroectoderm. Histologically it is rather homogenous and consists of chromaffin cells. The medulla produces catecholamines