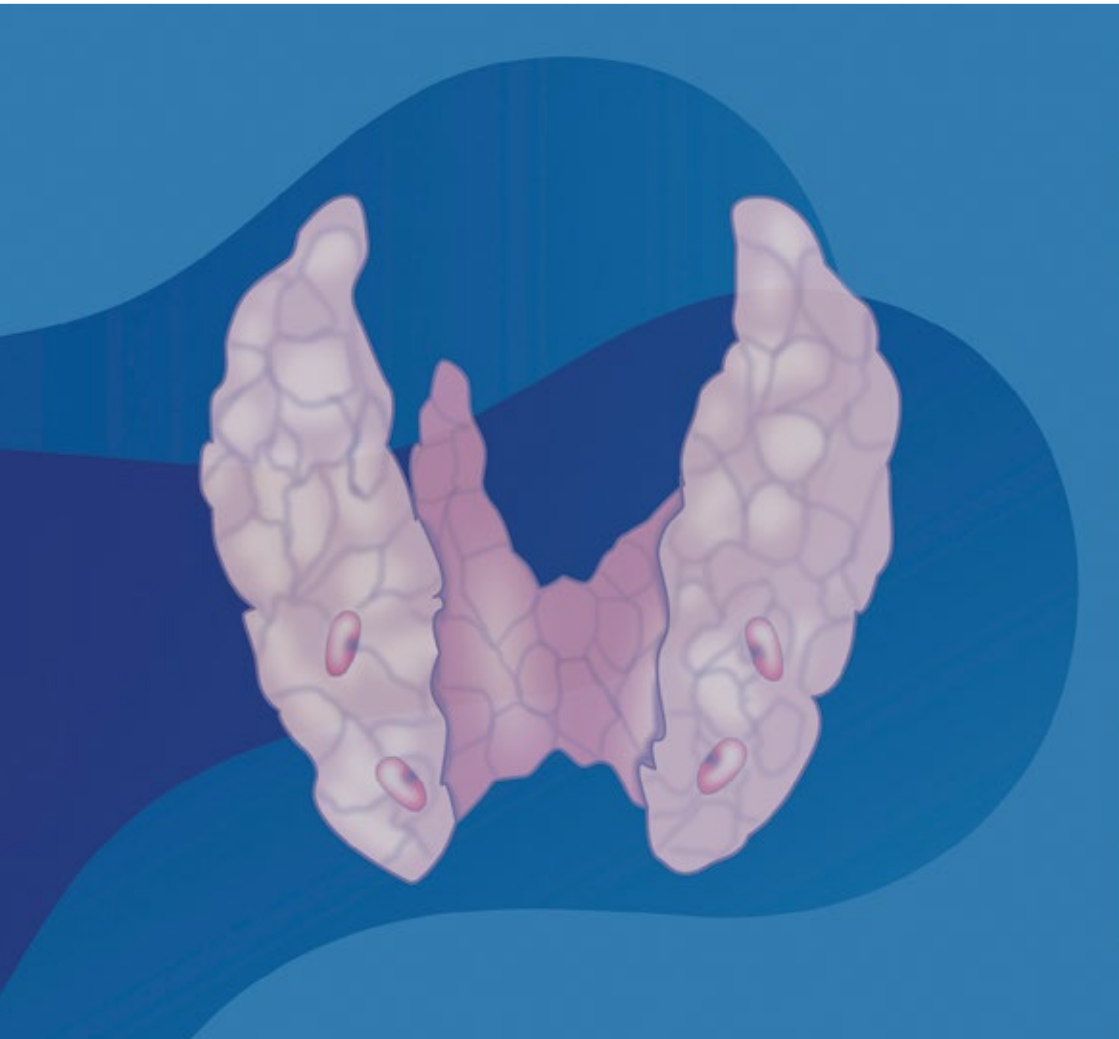
I.V. Sleptsov

PRIMARY HYPERPARATHYROIDISM

DIAGNOSTICS AND TREATMENT



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Preface

In a human body there is a tiny organ. Or rather, there are as many as four organs, each of them the size of a rice grain. Despite being small, these organs have great and very diverse influences on human life. These organs are called **parathyroid glands**. They are located on the neck next to the well-known thyroid gland, one of the main endocrine glands in a human being. It could be said that parathyroid glands are «in the shadow» of their famous neighbor. Everyone has heard something about thyroid disease, but very few people know that parathyroid glands are also vulnerable to diseases. The consequences of these diseases can be very serious.

In Latin, the parathyroid gland is called glandula parathyreoidea from «para» – «next to something» and «thyreoidea» – «thyroid». In Russian, these glands are called паращитовидные, parathyroid, which is not entirely correct as it is believed that a Russian word should not be combined with a foreign root.

> **The most common parathyroid gland disease, primary hyperparathyroidism, is caused by a parathyroid hormone that is produced by one or more tumors located in the glands.**

An excessive amount of parathyroid hormone in the blood flow can cause multiple and very severe metabolic changes. This significantly shortens life expectancy and a decline in quality of life.

Primary hyperparathyroidism is a common disease. According to recent studies, about 1% of the world's population suffers from it. Consider this; in Russia the number of patients exceeds one million people! Regardless of these facts, you do not hear much about primary hyperparathyroidism in everyday life. There are several reasons for this "silent conspiracy".

> **One of the reasons why this disease is underestimated is the lack of detection mechanisms.**

Usually diagnostics for primary hyperparathyroidism begins with the detection of elevated calcium in the blood. In Russia, the calcium level

is not routinely measured in hospitals and outpatient clinics. That is why the healthcare system misses diagnosing many patients, their calcium level has never been measured so they don't know they are sick.

> **The second reason is that for a long period of time the disease develops in the body asymptomatically.**

An increased calcium level causes discomfort, weakness, and signs of depression. These days who isn't suffering from these symptoms? High calcium causes gastritis and gastric ulcers, but isn't almost everybody suffering from gastritis? A patient can suffer from hypertension, have a heart attack or stroke and we blame it on the natural aging of the organism. Even bone deformities and fractures do not often result in evaluating calcium in the blood. These problems are also explained by aging. Only a diagnosis of urolithiasis, that often accompanies parathyroid gland disease, is it considered obligatory to check blood calcium levels. Although we have seen cases where patients with large recurrent kidney stones have spent years in therapy without a calcium test and, therefore, without an accurate diagnosis.

> **There is also a third reason for the lack of proper interest in primary hyperparathyroidism, doctors have a poor understanding of the way this disease usually develops.**

Many consider this a complicated disease. In reality, there are few diseases as logical and even mathematically clear as primary hyperparathyroidism. Diagnosing this disease is easy and its treatment is very effective. The treatment of primary hyperparathyroidism, if administered properly, can result in very positive changes in the life of a patient This confirms to both patient and doctor the therapy choice.

Our clinic, the St. Petersburg Northwestern Center of Endocrinology and Endocrine Surgery, has more than 20 years of experience in the treatment of primary hyperparathyroidism. We have performed more surgeries for this disease than anywhere else in Russia and Europe. Every year we provide treatment to more than 800 hyperparathyroidism patients from all over Russia, as well as countries in the near and far abroad. It took some time before we accumulated significant experience in the treatment of this disease. Today, we have a clear understanding of the mechanism behind the development of hyperparathyroidism and we know how to treat it effectively.

In this book I share some of my knowledge and experience accumulated in the diagnosis and treatment of primary hyperparathyroidism. I understand this book should have been written earlier, but I didn't have time for it

as we perform approx. 6,000 surgeries on endocrine system organs a year. My hope is that now I complete the task I set for myself a long time ago.

This book is intended for patients interested in endocrine diseases but it can also be of use to doctors. At the very least, it will help us make sure we are on the same page when it comes to the diagnosis and treatment of parathyroid pathology.

> **For more information on how to visitour center, please visit www.endoinfo.ru. You can schedule an online consultation on the same website. To make an appointment for a consultation with one of our specialists, please call +7812-565-1112 (weekdays from 7 AM till 9 PM, weekends from 7 AM till 7 PM), to make an appointment for surgery, please call +7 812 980-77-21 on weekdays from 9 AM till 5 PM.**

Please, send your comments or suggestions to my email: **mail@islep.ru**. I will appreciate any feedback.

Sincerely,
I.V. Sleptsov

Chapter 1

Parathyroid Glands: Structure and Function or Small, but Very Important

Location of parathyroid glands

Parathyroid glands are located in the neck area in close proximity to the thyroid gland and in close connection to it and its vessels (Fig. 1). Typically a human has four parathyroid glands, but in some cases a larger number of glands is detected, 6 or even as many as 12. Parathyroid glands are not big. They look very much like rice grains with a length of about 4-6 mm, width and height range from 2 to 4 mm. It should be noted that no parathyroid gland has the same size. Their sizes vary in every person. Some people's parathyroid glands are only 1 cm but they function completely normally.

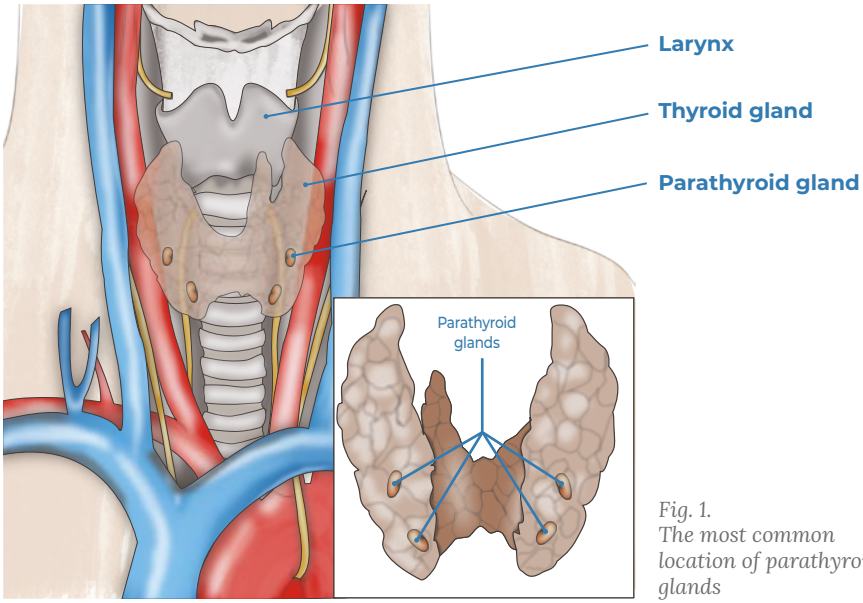

Fig. 1. The most common location of parathyroid glands

Location distinguishes parathyroid glands as upper and lower although this division is relative. In some people, «upper» glands are below «lower glands». In surgical practice, this classification of parathyroid glands into upper and lower is not primarily based not on the height of their actual location, but on the structure of vessels that supply these glands with blood.

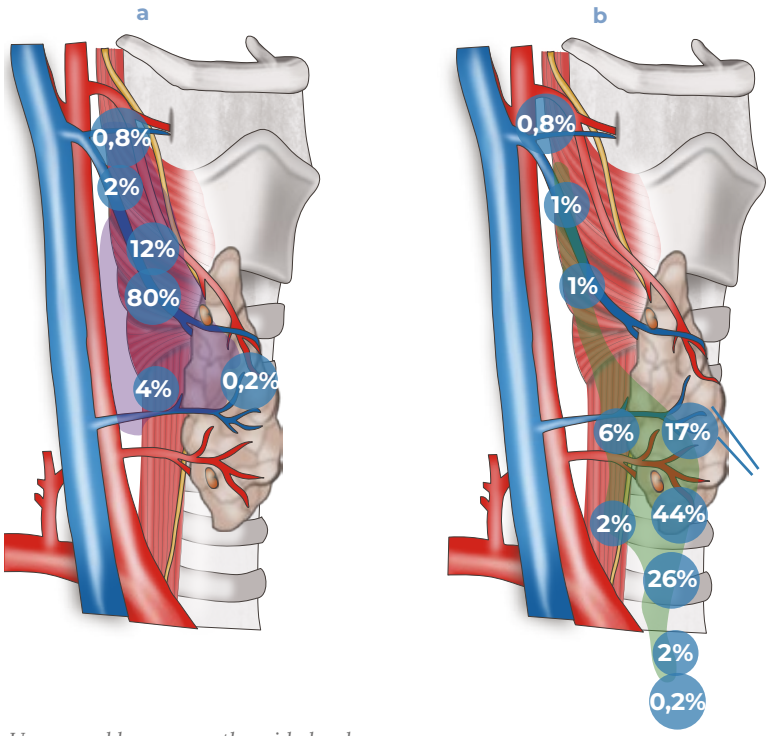

Fig. 2. Upper and lower parathyroid glands
a) common locations of upper parathyroid gland
b) common locations of lower parathyroid gland (after K.Y. Novokshonov)

Parathyroid glands are located either directly on the surface of the thyroid gland or very close to it. Parathyroids are fed by the same vessels that feed the thyroid. That is why in surgery it is important to protect the vessels that supply parathyroid glands with blood. If we don't, a patient can develop hypoparathyroidism (parathyroid insufficiency) with its severe effects including convulsions and death.

The location of parathyroid glands can vary greatly from one person to another. (Fig. 3). Numerous possible parathyroid gland locations are de-

scribed in the literature, but all of them fit into a specific logical scheme that is based on a single blood supply system. Any surgeon performing surgery for primary hyperparathyroidism must have a clear understanding of parathyroid gland anatomy and know how to locate them quickly in the neck without injuring the patient.

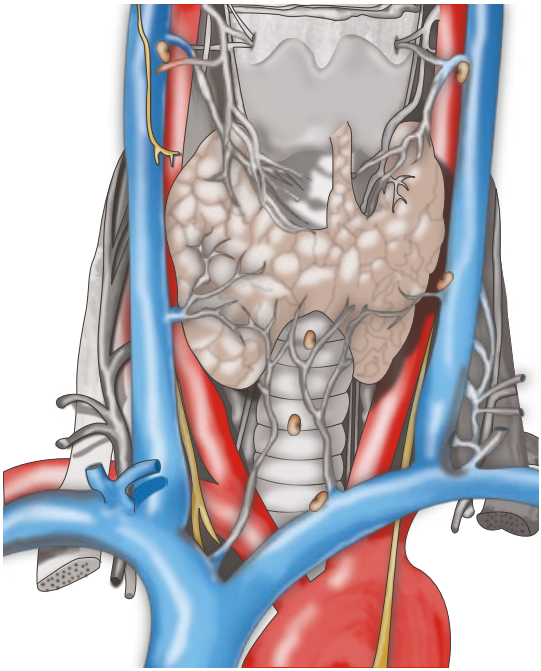

Fig. 3. Possible locations of parathyroid glands

Parathyroid glands are located in the area of the recurrent laryngeal nerve that transmits electrical pulses that cause the vocal cords in the larynx to contract (see Fig. 1). Therefore, parathyroid gland surgery requires good knowledge of neck anatomy since it is important to ensure the safety of the "vocal" nerves. Nerve injury can seriously deteriorate a patient's quality of life and even result in the loss of their profession. If the larynx nerve is injured on one side, one of the vocal folds loses its mobility which causes such symptoms as sudden weakening of the voice, hoarseness, and huski-

ness. If during the surgery the larynx nerves on both sides are damaged, the patient could lose their voice completely or develop respiratory failure including asphyxia (suffocation).

> **There is one indisputable law – the location of parathyroid glands in the neck follow specific rules.**

Under no circumstances during the operation should the surgeon look for parathyroid glands randomly by "searching through" the tissues hoping a parathyroid gland will appear. This approach causes injury of the surround ding tissues and is never successful. After looking at a patient's thyroid vascular system structure, an experienced surgeon first determines the location of the parathyroid glands in his mind and only after that quickly identifies the actual location of the glands. Many textbooks describe the detection of parathyroid glands as a very difficult process. In reality, this is a myth that comes from lack of experience in this field of surgery.

Structure of the parathyroid glands

There are two types of cells that make up parathyroid glands, the chief and oxyphilic. The chief cells produce the parathyroid hormone. The function of oxyphilic cells is still not entirely clear. However, their quantity and activity define, to a large extent, the ability of the parathyroid glands to accumulate technetril. This is an isotope doctors use to visualize parathyroids during an examination. The more oxyphilic cells there are in the parathyroid glands, the better it is at accumulating this isotope and the better its visibility with scintigraphy.

Function of the parathyroid glands

The main function of parathyroid glands is the production of parathormone, the hormone that controls calcium exchange in the body. There are several ways parathormone keeps the blood calcium concentration at the necessary level (Fig. 4). First, parathormone reduces calcium excretion with urine that reduces calcium loss. Secondly, parathormone increases calcium absorption from food. This effect is achieved through the activation of vitamin D that is why an increase in calcium absorption is impossible if vitamin D is deficient. Thirdly, parathormone activates special cells, osteoclasts, that take calcium from its deposits in the bones, converts it into a soluble state, and delivers it into the blood. Through all of these effects, reduction of cal-

cium loss, increased absorption of calcium from food, and extraction of calcium from bones, parathormone elevates the calcium levels in the blood. In summary, parathormone is needed to ensure there is calcium in human blood. This ion is needed for various processes from muscle contraction to the transmission of nerve signals and coagulation.

If for some reason calcium concentration in the blood drops below a certain level, a patient may die. That is why the parathyroid hormone is so important, it serves the function of preserving a normal concentration of calcium in the blood.

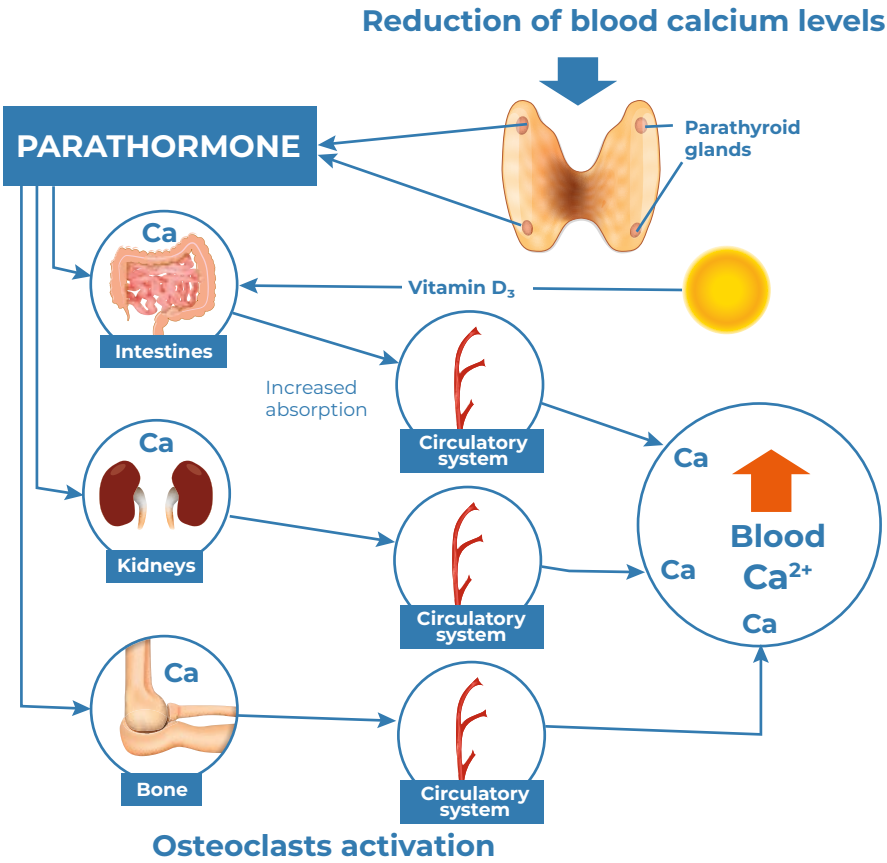

Fig. 4. Mechanism of action parathormone

How do parathyroid glands "understand" how much parathormone they need to produce? On the cell surface of parathyroid glands, there are special receptors that measure the concentration of calcium in the blood. When the blood calcium drops below a certain threshold (a specific level for every human that foreign colleagues call a "set point" that actually means "setup point"), parathyroid glands "turn on" and produce in the blood as much parathormone as needed to bring blood calcium back to acceptable limits. After the normal concentration of calcium in the blood is attained again, parathyroids "turn off" and stop secreting parathormone. I especially appreciate the fact that parathyroid glands "decide" when to "turn on" and "turn off" independently. Receptors that determine calcium concentration are located on the cells of parathyroid glands themselves and not on the cells of the pituitary gland. The latter is the main endocrine gland that manages all the other glands through the release of command hormones: TSH for thyroid, ACTH for adrenal glands, FSH for ovaries, etc. Thus, parathyroids have the ability to react very quickly to changes in blood calcium levels. They don't need to "wait" for any commands from senior organs. That is why the job of parathyroids is important, because calcium is crucial to the body.

Parathyroid glands have a very complex relationship with vitamin D.

Vitamin D enters the body in an inactive form but the vitamin can also be produced in human skin through sunlight. In order for inactive vitamin D to turn into an active form, it must undergo two enzyme-powered stages of activation in the kidneys and the liver. After that, vitamin D converts into calcitriol. This substance is a hormone with many functions that are important and useful for our body. One of the most well-known is ensuring calcium absorption in the intestine. The efficiency of the enzyme that activates vitamin D in the kidneys depends on the level of parathormone. The higher the level of parathormone, the more efficient the enzyme becomes in the kidneys and the more active vitamin D is produced. By enhancing the activation of vitamin D, parathormone increases calcium absorption from food. That is how parathormone "helps" vitamin D perform its function.

Vitamin D also affects the parathormone. When the concentration of active vitamin D in blood rises, it begins to influence special receptors that are located on the surface of parathyroid cells. When these receptors are activated, parathyroid glands inhibit the production of the parathyroid hormone. It appears this "feedback" was built in our body to prevent an excessive increase in calcium levels. Parathormone activates vitamin D, which in turn can "turn off" the production of the parathyroid hormone.

When talking about the relationship between parathormone and vitamin D, we have to mention one very important fact. Parathormone can influence activation of vitamin D, but it cannot influence the amount of the vitamin our body receives. The parathyroid hormone has no effect on the amount of vitamin from food or the amount produced in the skin. This means that if one doesn't spend enough time in the sun and doesn't take vitamin D supplements, its concentration will go down and the parathyroid hormone will have nothing to activate.

Chapter 2

Calcium Metabolism in Bone Tissue or Parathormone is the Staff of Life

Before I proceed with the story of primary hyperparathyroidism, I have to explain something about the structure of human bone tissue and the way it functions in the body.

There are four types of cells in bone tissue (Fig. 5):

- osteoblasts aka bricklayers, that take calcium from blood and deposit it in the bones to build new bone trabeculae and strengthen the bone;
- osteoclasts, aka miners, that destroy bone tissue taking calcium from it that is later released into the blood;
- osteocytes, mature bone tissue cells, are the foundation of bone trabeculae;
- osteogenic cells form osteoblasts and osteocytes.

Bone tissue only appears to be a non-living thing. In fact, processes for removing old bone trabeculae and constructing new ones are happening non-stop in the bones. Both destruction and construction processes are controlled by parathormone. One of the most interesting facts about parathormone is that its effect on bone tissue depends on how the hormone is released into the blood. If the parathyroids produce parathormone in an intermittent mode, they stimulate the work of osteoblasts, bricklayers, more calcium is deposited in the bone, and new bone tissue is formed. If the concentration of parathormone in the blood is constantly elevated, osteoclasts, miners, are activated and start to destroy the bone and take calcium from it.

Under normal conditions, the parathyroid gland can independently set the mode for parathormone release into the blood, depending on whether it needs to destroy bone tissue or build it up. If a tumor develops in the parathyroid gland, it is only capable of releasing parathormone in a continuous

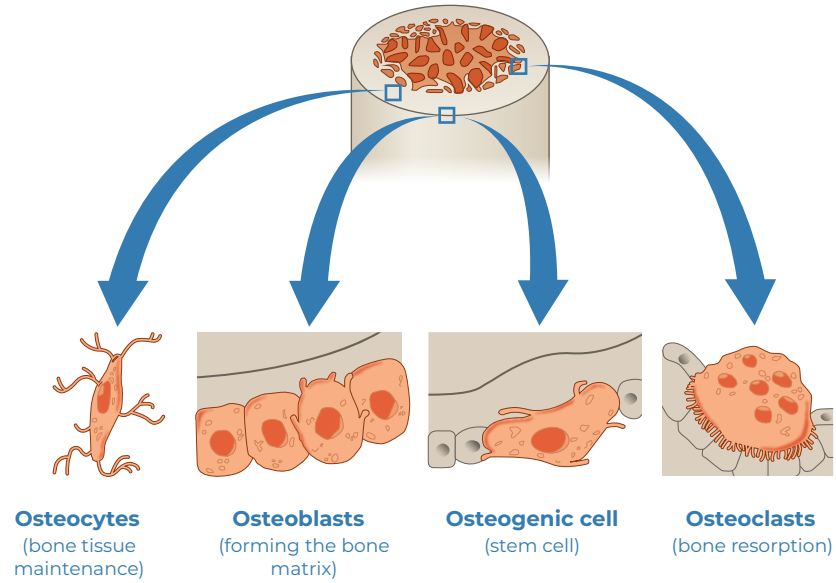

Fig. 5. Bone tissue cells

mode. This causes greater destruction of the bone tissue and is why reduced bone density (osteoporosis) and bone fractures are one of the main symptoms of hyperparathyroidism.

In books, one can often find a mention of calcitonin as a parathyroid hormone antagonist. It is a thyroid hormone and its main action is promoting calcium deposits in the bone. Calcitonin can stimulate the formation of bone tissue; however its effect is very weak and in no way can be compared to the effect of parathormone.

Many other factors influence the formation of bone tissue. For example, in women, the formation of bone tissue largely depends on the level of female hormone estrogen. Post-menopausal decrease in estrogen levels can cause, among other things, the gradual development of osteoporosis (reduced bone density).

Chapter 3

What is Primary Hyperparathyroidism or What? In who? How often?

In primary hyperparathyroidism, a tumor actively producing parathormone develops in one or more parathyroid gland. A benign tumor is called adenoma, a malignant one is called carcinoma. Carcinomas can expand into surrounding organs and tissues. They can also metastasize; develop new tumors in other parts of the human body. The good news is that parathyroid carcinomas are rare and diagnosed in only 1% of cases.

Some patients (5-15%) develop tumors in two or more parathyroid glands at once. Cases when all the parathyroids are affected are rare, but finding two tumors in in the same patient is common. Because of that, when a surgeon is operating on a patient with primary hyperparathyroidism, the goal is not only to find the tumor affected gland, but to confirm that this is the only tumor. If it isn't, the surgeon must find and resect the second tumor.

There are many theories that explain what causes primary hyperparathyroidism. One of the most proven is the theory of a long-lasting vitamin D deficiency causing the development of the disease.

When nature was coming up with a way to control the calcium metabolism, it gave humans the ability to produce the most important substance responsible for the absorption of calcium from food. We can generate vitamin D in our skin through sunlight but nature couldn't imagine a time when people would always wear clothes and move to apartments and houses so that most of the time no sunlight falls on their skin . Today, changes in lifestyle, as well as the relocation to northern regions of the planet, have caused a universal vitamin D deficit in people. Our body needs vitamin D in order to be able to absorb calcium from food. It is normal these days to take it as a medical supplement since most of the year we don't have time for sunbathing and producing vitamin D in the skin. Despite all of that, it's safe to say there are very few people who regularly take vitamin D and those who don't suffer from a significant reduction in vitamin D levels.

If one doesn't get vitamin D for a long time, its concentration in the blood drops to a deficit level, that is below 20 ng/ml. Consequently, the body can't absorb the required calcium volumes from food and the calcium concentration in the blood begins to decrease. In response to decreasing calcium levels, parathyroid glands activate and start secreting parathormone. The parathormone has only one goal, to bring calcium concentration back up to the levels required by the organism. Given there is not enough vitamin D in the blood, there is no way to make the body absorb more calcium from food. Even though the parathyroid hormone can activate vitamin D molecules, if there are no such molecules in the blood, there is nothing to activate. When this happens, parathormone affects kidneys (reducing excretion of calcium through urine) and bones (promoting the destruction of bone tissue that is needed to "extract" precious calcium). Thus, Calcium deficit is no longer a problem but it comes largely at the cost of removing calcium deposits from the bones.

> **A long-lasting vitamin D deficit "makes" the parathyroid glands always do the heavy lifting. Over time, this can cause a "breakdown" of the mechanism that inhibits cell division and the development of a parathyroid gland tumor. This cascade of events is probably the main reason for the development of primary hyperparathyroidism.**

In some patients, hyperparathyroidism can have hereditary causes, especially if there is not one, but several parathyroid gland tumors. In hereditary cases, hyperparathyroidism is often transmitted from one generation to another with a whole "set" of tumors on other endocrine organs. This disease is called multiple endocrine neoplasia syndrome (MEN). For example, in MEN type I hyperparathyroidism is inherited together with pituitary glands and neuro-endocrine tumors of the pancreas or other organs. In MEN type II hyperparathyroidism is inherited together with medullar thyroid cancer and pheochromocytoma, an adrenal gland tumor that produces adrenalin and causes a hypertension crisis.

Primary hyperparathyroidism is most often diagnosed in female patients over the age of 50. However, one should keep in mind that this disease can occur in children and young people. If primary hyperparathyroidism is diagnosed in an "atypical" patient (for example, in a young man aged 25), it is imperative to examine this patient for the hereditary nature of the tumor.

Usually parathyroid adenomas are not very big, from 1 to 4-5 centimeters. The longer the patient had an adenoma, the larger it may become and the more expressed the symptoms of hyperparathyroidism can be.

The larger the tumor, the higher the chances it is malignant. The earlier primary hyperparathyroidism is diagnosed and the treatment is provided, the safer it is for the patient.

Chapter 4

Symptoms of Primary Hyperparathyroidism or You Think You Are Fine

As I noted in the preface to this book, hyperparathyroidism is one of the most frequent endocrine system diseases. It can be detected in about 1% of the world's population so there are millions of patients with this disease. However, most people have never heard of parathyroid gland tumors. This is primarily because in many patients primary hyperparathyroidism is asymptomatic and thus, invisible.

We should remember that this disease always damages a patient's health and the absence of symptoms does not mean that a patient with a parathyroid tumor is doing fine. Hyperparathyroidism is one of those diseases in which even a minor lab change in blood composition can cause devastating and very serious consequences in many organs and systems of the body. In terms of the impact on the human body, perhaps only diabetes mellitus can compare with hyperparathyroidism. The difference is that in diabetes mellitus, it is the increased glucose level that damages the body and in hyperparathyroidism it is elevated blood calcium.

> **The most common and most underestimated symptoms of hyperparathyroidism by both patients and doctors are weakness, fatigue, depression, problems with memory, and focus. All of the above can be summarized as "deterioration of vitality and mental capacity".**

In a study that analyzed the treatment of more than 20,000 patients with primary hyperparathyroidism, these changes were detected in more than 70% of the population. Unfortunately, most of the time these symptoms are ignored even though they are particularly bad for the quality of life. In severe cases, when blood calcium is very high, mental capacity can be so constrained that it can even reach the level of a coma (we've dealt with such cases). Fortunately, after successful hyperparathyroidism treatment, a patient's vitality improves over time and the colors of daily life return (this usually happens after 3 or 4 weeks).

The second most common symptom of primary hyperparathyroidism is arterial hypertension (increased arterial pressure), detected in about half of all patients.

An excessive amount of calcium is inevitably deposited on the walls of blood vessels that makes them denser and less elastic. When the heart contracts, the vessels can no longer stretch enough to take in all the blood and pressure in the vessels increases. Increased pressure is the main reason for frequent strokes and heart attacks in patients with primary hyperparathyroidism. We should remember that heart attacks and strokes are the main cause of death for patients with this disease. The earlier hyperparathyroidism is treated, the less damage will be done to vessels and the lesser the risk of cardiovascular complications.

Bone changes are another frequent manifestation of hyperparathyroidism. As the osteoclast cells actively destroy bone tissue, more calcium is eliminated from bones to the blood and the density and strength of bone tissue deteriorates.

Patients experience pain in the bones that can get deformed or fractured sometimes even without any serious stress on the bone. I had a case when a patient broke her arm on the corner of a table. She just sat and leaned against the table, but her bones were so fragile that it was enough for a fracture. A very frequent symptom is height reduction caused by the compression of vertebrae under the weight of a patient's body (internal fractures occur in the vertebrae resulting in their flattening and becoming smaller in height). Bone changes can be detected during osteodensitometry, a study to assess the density of human bone tissue.

Urolithiasis (stones or "sand" in the urinary tract, renal pelvis, ureters, and bladder) is often mentioned in stories about primary hyperparathyroidism but this symptom is only detected in 20-30% of patients. If a patient suffers from urolithiasis, even repeated surgeries for lithotripsy or removal of stones will never result in full recovery until we deal with the root cause and normalize blood calcium levels.

Quite often, in every third patient, the disease is accompanied with lesions of the mucous membrane in the stomach or duodenum from gastritis up to erosions and peptic ulcer disease. Increased blood calcium boosts the production of gastrin, a hormone that acts on the stomach releasing hydrochloric acid that damages the mucous membrane.

The list of other serious consequences of hyperparathyroidism includes muscle weakness. Together with depressed senses and bone pain, it reduces the quality of life even further. The patient tries to move less and doesn't exercise.

> **The higher the blood calcium level, the more expressed are the symptoms of the disease.**

In severe cases a patient can become completely disabled, suffer from multiple fractures, lose the ability to walk and even this doesn't mean there won't be new fractures because they can now happen even when there is complete bed rest. Multiple stones in the urinary tract block the urine outflow that causes the development of bacterial complications: chronic inflammation of kidney tissues with gradual development of renal failure. Consciousness progressively deteriorates until the patient lapses into a coma.

Unfortunately, even in the most severe cases doctors do not always make a correct diagnosis. We have dealt with patients that underwent multiple bone surgeries for fractures and repeated lithotripsies in the kidneys and ureters and the doctors still didn't identify the reason for all of these problems. This is because during the years of treatment, blood calcium was never measured. I always feel bad for these patients because the diagnosis in these cases is obvious and the treatment should not target the complications, but the main cause of their development and that is primary hyperparathyroidism. Effective treatment is impossible without dealing with the root cause since both fractures and urinary tract stones will keep happening repeatedly.

There is another important fact I would like to mention. Even when there is only a slight change in the calcium level, there will still be negative consequences for the organs. Even a 0.01 mmol/l increase in the calcium level is significant for a human. For example, if the lab has set 1.31 mmol/l as an upper reference (as it is in our laboratory), then 1.32 mmol/l will already be a sign of disease. One should not think that a slight increase means the disease is less dangerous.

> **Research by J. Norman from the USA has shown that the duration of the disease is more important than its severity.**

The frequency of strokes depends largely on how long the patient lived with an increased calcium level than on how much the calcium was increased. This is very important so we have to be clear and very aware of this.

We often have to work with people who have been living with increased calcium levels for years without any treatment because it was “just a slight increase”. These patients have symptoms but they are either ignored or attributed to other causes. As a result, patients develop a whole complex of complications, life expectancy decreases, and quality of life deteriorates. All these negative manifestations are caused by a lack of a proper treatment. Primary hyperparathyroidism is never harmless. Whatever the increase in blood calcium level, the disease is dangerous and requires active intervention.

Chapter 5

Laboratory Diagnostics for Primary Hyperparathyroidism or Tests are the Backbone of the Diagnosis

Despite the abundance of symptoms, hyperparathyroidism is often not detected during an assessment of complaints but after a calcium blood test. It all starts when a patient undergoes a checkup that includes a test for calcium concentration in the blood. That is how the journey to the diagnosis of primary hyperparathyroidism beings, by detecting elevated blood calcium levels. You're lucky if a patient then goes to an endocrinologist who understands the problem. When visiting a doctor, people don't usually consider themselves sick. Only after close examination by the doctor, do they start to recognize that the symptoms that have been bothering them for a long time are actually signs of a serious disease and not just result of burnout or depression.

> **A "healthy" range of calcium in the blood is quite narrow. Any increase in blood calcium levels should be subject to a thoughtful analysis as it always indicates there is a disease.**

More than 90-95% of increased blood calcium cases are caused by the development of parathyroid adenomas. The remaining 5-10% are most often caused by malignant tumors, by some medication (vitamin D, lithium, diuretics) or systemic diseases of the connective tissue (sarcoidosis).

If a patient has an elevated blood calcium level, the doctor is obliged to refer him or her for a number of other tests to determine the cause of those laboratory results. The minimal set of examinations should include a blood test for parathormone and creatinine. A blood test for 25-hydroxyvitamin D can also be performed, but that one is quite expensive so it is not prescribed in all cases (especially since a correct diagnosis can be made without assessing vitamin D in the blood). It is mandatory to assess the level of calcium and creatinine in the daily urine (urine, collected during the day).

If a patient with elevated blood calcium has also elevated parathormone, primary hyperparathyroidism is confirmed. If both parathormone and calcium are increased, there is a 99.5% probability there is a tumor. The remaining 0.5% are cases of rare hereditary disease with a barely pronounceable name, **familiar hypocalciuric hypercalcemia**. This disease causes impairment to the sensitivity of the calcium receptor on the surface of parathyroid glands' cells and renal tubules cells. As a result, less calcium is excreted with urine and its concentration in the blood increases. In many cases, patients with this disease demonstrate a slight increase in parathormone, which makes it difficult to make a diagnosis. This disease can be easily distinguished from primary hyperparathyroidism because it inhibits calcium excretion with urine, while primary hyperparathyroidism elevates it. There is a special indicator, that can help the doctor determine what disease he is dealing with, the calcium-creatinine ratio. To calculate it one needs to know the levels of ionized calcium and creatinine in the blood, as well as calcium and creatinine in the daily urine.

If an "atypical" patient has elevated calcium (someone with an unusual age for primary hyperparathyroidism, e.g. a child or a young man or a woman), it is necessary to eliminate the possibility that hyperparathyroidism is hereditary. Young patients can develop different multiple endocrine neoplasia symptoms, including hyperthyroidism, as one of the disease components. However, there are other components that require special attention.

Patients with a suspected hereditary nature of the disease, should have their blood tested for calcitonin (to exclude medullary thyroid cancer), chromogranin A (to exclude neuroendocrine tumors), prolactin (to exclude pituitary tumors).

After a laboratory examination primary hyperparathyroidism is either confirmed or excluded. I would like to emphasize that the diagnosis is made only after all the tests are performed. At this stage of the journey no instrument exams are required, no ultrasound, no scans, no tomography. Data from the results of the analyses alone is enough for a doctor to confirm or exclude that the patient has a parathyroid tumor. It is the results of laboratory tests that answer the main question, "Does the patient have a parathyroid gland tumor or not?" Only after studying the analyses, can the doctor answer this question in the affirmative and it will be necessary to start looking for the tumor.

Quite often we have to deal with cases of inconsistent diagnostics, first a neoplasm in the neck (for example during ultrasound), something similar

to parathyroid adenoma, is discovered. Then additional tests are conducted, and only then are blood and urine tests performed. Very often patients with this incorrect sequence of diagnostic tests ends up with unnecessary examinations that waste their money, health, and nerves.

I remember the case of a woman from Moscow who came to my office with a 5 cm thick binder of test results. These tests had been conducted over the previous two years spent searching for parathyroid adenoma. The problem that brought the patient to my office, some of her respected doctors (professors and even academicians) believed the parathyroid tumor was on the right side and the others (equally respected) were convinced that it was on the left. It was hard for the patient to decide on the operation because she understood the location of the adenoma was still unclear.

Over two years she underwent numerous ultrasounds, some radioisotope scans, and several tomograms. Many of those tests were not only expensive, but unsafe. Still, the result wasn't clear. The first thing I asked her to do is to show me her blood calcium results. In response, the patient started showing me the results of her ultrasounds, tomograms, and scans. I asked her again to give me the results of a blood test for calcium. She kept enthusiastically showing me the results of clinical investigations and telling me about her problem, Academician A could not agree with Academician B on the location of the adenoma. When, after asking three times I finally got to see the results, I discovered that her blood calcium was not increased, but reduced! The parathyroid hormone was elevated which caused this storm of diagnostic tests. I pointed out the reduced level of blood calcium to the patient and explained that this change (reduced calcium and elevated parathormone) is a typical manifestation of vitamin D deficit and doesn't mean there is an adenoma of the parathyroid gland. Quite the opposite, it shows clearly there is no adenoma at all. That is why the distinguished experts couldn't agree on the location of the adenoma, it didn't exist!

Two years of a patient's life and a significant amount of money (not to mention wasted health and nerves) were spent searching for a non-existent tumor. All of that only because the doctors got carried away with the search and broke the sequence of diagnostic stages (first testing to confirm the existence of a tumor and only after that diagnostic tests to locate it). It took me a lot of time to explain to the patient what happened to her (it also took me a lot to make her believe me). After that I prescribed a therapeutic dose of vitamin D and sent her back home to Moscow. Two months later I receive a phone call, "Doctor, it has returned back to normal!" At first, I didn't

even understand what she was talking about, "What went back to normal?" She responded, "Parathormone, of course! It's normal for the first time! Is this really true, that all of that was because of a vitamin D deficit?" Only when she saw for herself how after such a simple prescription her test results changed so much, did the patient finally believed that the treatment could be so simple. That case is not unique.

> **I would like to remind both patients and fellow doctors: primary hyperparathyroidism is a laboratory diagnosis and it is made based on test results.**

Analyses results are quite enough to "figure out" the disease. Only at the next stage, after confirming it, one can proceed to the search for a parathyroid gland tumor as the cause of laboratory changes.

Normocalcemic primary hyperparathyroidism

In this chapter I also provide an overview of diagnostically challenging cases when the blood calcium level remains normal, within the reference limits, even though there is a parathyroid gland tumor. In some patients, the calcium level can be within a normal range but after a closer look one will notice that the calcium concentration is very close to the upper normal limit. If this patient also has elevated or high-normal levels of blood parathormone, in most cases we can say that there is a parathyroid tumor. This form of primary hyperparathyroidism is called **normocalcemic**, meaning that it develops in the setting of a normal blood calcium concentration. In these cases, establishing a diagnosis becomes an extremely difficult task. "Officially" the patient might not have any laboratory anomalies, meaning that both calcium and parathormone levels could be within acceptable limits.

I won't be able to describe the decision-making strategy in this book. What I can say is that the whole concept of "norm" is conditional when assessing levels of calcium and parathormone. When some values are called normal, it only means those were recorded in scientific studies of a healthy population with no parathyroid pathologies. However, if you look closer at similar studies, you'll find that those weren't very big sample sizes and the inclusion criteria is often questionable. For example, reference calcium levels were calculated for young people 20 to 30 years, predominantly men, and then they were offered as a guideline for the world's population. What can be considered normal when you are 20, is no longer a norm when you're 60 since the metabolic rate decreases and the intensity of vital pro-

cesses in the bone tissue also goes down. Over time, this causes a gradual decrease in blood calcium. That is exactly why we often find parathyroid tumors in patients over 60 years old with a formally normal blood calcium level. It is normal as long as we stick to officially accepted norms, however, it becomes unreliable if we take into account the age of a person.

There are two possible therapeutic tactical options in these cases. If the doctor is sure that the patient has a parathyroid gland tumor, then he can schedule a surgery without any additional examinations. If the doctor is not sure whether a parathyroid tumor is present, he might recommend a so-called stress test with vitamin D. During the test, a patient with a normal blood calcium level and an elevated parathyroid hormone is prescribed vitamin D for several weeks. After this, the blood calcium is measured again. If the patient has primary hyperparathyroidism, then the intake of vitamin D causes the blood calcium starts to rise and gradually exceeds the normal limit. Thus, the diagnosis is obvious. If the patient doesn't have a parathyroid gland tumor, then taking vitamin D causes a decrease in the parathyroid hormone level while the blood calcium remains normal.

Chapter 6

Methods for Visualization of Parathyroid Adenomas or How Do I Find It?

Once the doctor has test results that prove the patient has a parathyroid adenoma he faces a new problem, how to locate the adenoma. The imaging stage has one purpose, to get the most accurate information about the location of the adenoma so the surgeon can properly plan his actions and resect the tumor during the operation. Considering how important surgeon's task is, it is necessary to be sure the data is accurate. At least two different methods should be used to locate the adenoma during the examination phase.

Ultrasound examination

Since this method is absolutely painless, harmless, and efficient at locating the adenoma, the examination begins most often with an ultrasound. Normal parathyroid glands are not usually visible in an ultrasound. During the imaging the adenoma looks like a hypoechoic (dark) rounded mass located below or deeper than the thyroid gland (Fig. 6).

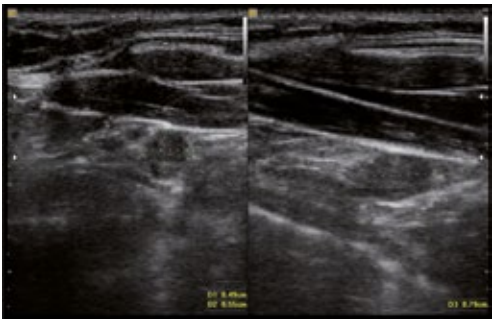

Fig. 6. Ultrasound image of a parathyroid adenoma

Tumors of the upper parathyroid glands are usually located deep below the skin surface, along the posterior surface of the thyroid. Tumors on the lower parathyroid, are most often located on the surface right under the neck muscles (Fig. 7).

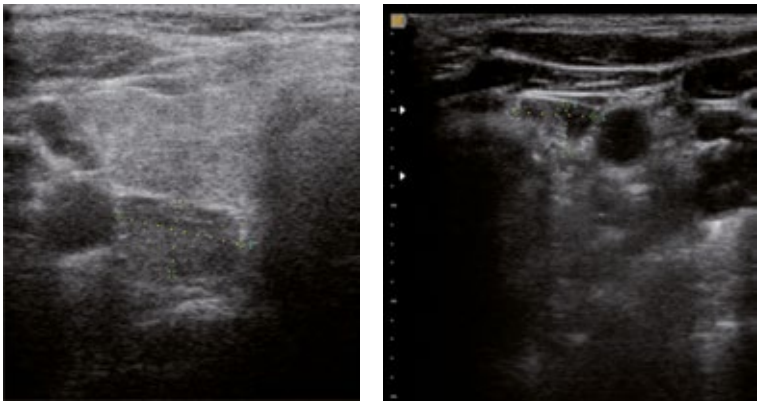

Fig. 7. Adenomas of the upper (a) and lower (b) parathyroid glands on the ultrasound

The ultrasound might not be enough to determine whether the mass is a parathyroid adenoma or just an enlarged lymph node. Many lymph nodes look very similar to parathyroid adenomas (Fig. 8). Data on the location of the adenoma from an ultrasound must be confirmed with at least one more imaging technique.

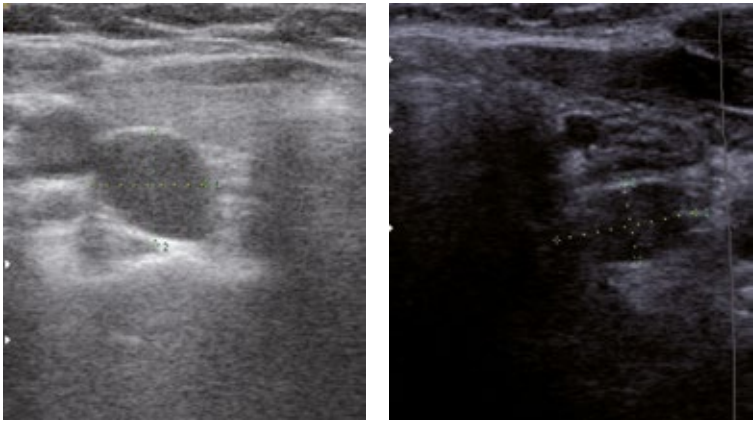

Fig. 8. Parathyroid adenoma (a) and enlarged lymph node (b) – ultrasound image

One should also remember, that this technique can only help to detect adenomas located in the neck area that can be accessed with an ultrasound. Since the ultrasound can't penetrate through bone elements like ribs or sternum, this method won't help detect adenomas located in the thorax. It is also impossible to locate adenomas behind the trachea since the ultrasound doesn't pass through it. There is an acoustic shadow behind the trachea, an area where no image can be captured (Fig. 9).

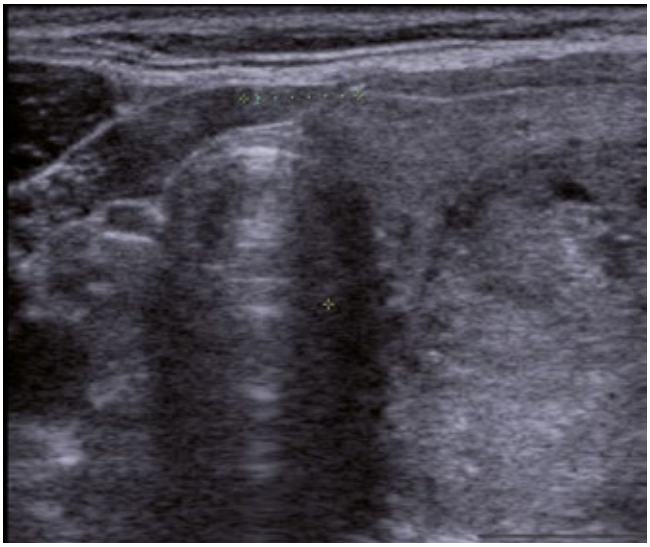

Fig. 9.
Acoustic shadow behind the trachea

Scintigraphy

In 1989, it was discovered that parathyroid adenomas can accumulate a radioactive substance or technetril (MIBI, as it is called abroad). Technetril emits gamma radiation that makes it possible to locate accumulation sites with a gamma camera (a gamma radiation receiver creates an image that is usually blurry and indistinct). With scintigraphy, it is impossible to accurately identify the size of an adenoma. However, if radiation is detected one can be almost sure that the emitting mass is a parathyroid adenoma. Scintigraphy is a radioisotope procedure, which means a certain irradiation of the patient but the harm from this exposure is minimal.

Fig. 10.
Modern gamma camera

There are two ways to perform scintigraphy, with one isotope or with two isotopes. With the single-isotope method, a patient receives an intravenous injection of technetril that can accumulate in the tissues of both the thyroid gland and the parathyroid glands. Technetril leaves the thyroid gland tissue quickly but stays in the parathyroids, allowing the doctor to see an image of the tumor (Fig. 11).

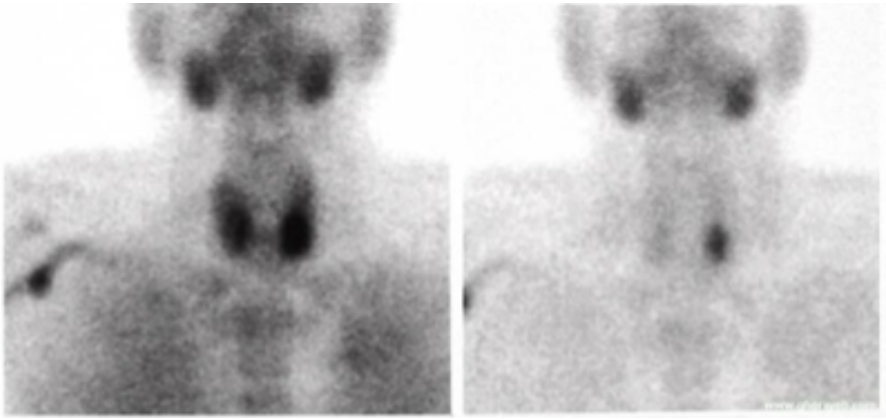

Fig. 11. Single-isotope scintigraphy:
a. accumulation of technetril in the tissues of thyroid and parathyroid glands.
b. technetril leaves the thyroid tissue but stays in the tissues of parathyroid adenoma

The single-isotope technique is quite simple, but the clarity of the resulting image is not very high. Images with a higher quality can be obtained with the two-step two-isotope scintigraphy technique. First, substances that accumulate only in thyroid gland tissue, technetium, or radioiodine, are injected. After that, patients get an injection of technetril that accumulates in the thyroid and the parathyroid glands. Then one image is subtracted from the other, resulting in the image of the parathyroid adenoma (Fig. 12).

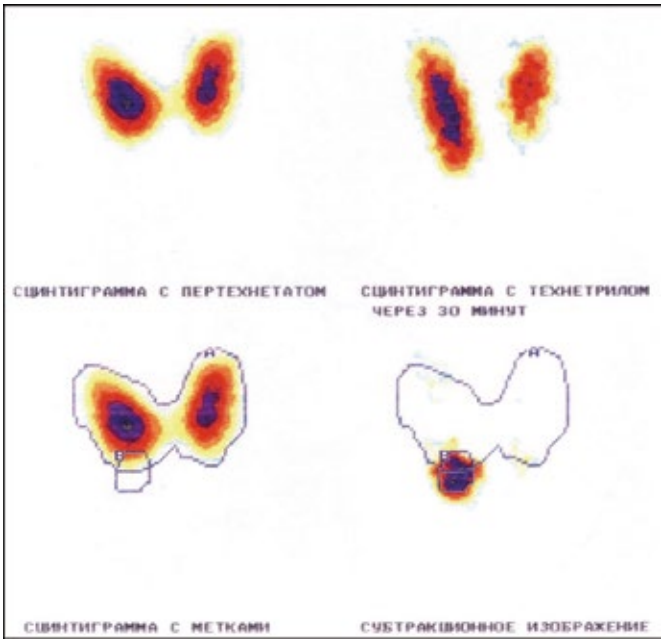

Fig. 12. Two-isotope (subtraction) scintigraphy:
a – image of the thyroid gland (technetium is introduced)
b – image of the thyroid gland and adenoma (technetril is introduced)
c – one image was subtracted from another, only the adenoma is visible

Scintigraphy offers an important advantage detecting parathyroid tumors in the thorax. Gamma radiation can easily penetrate the bones, so the image of the adenoma in the chest can be clear enough (Fig. 13).

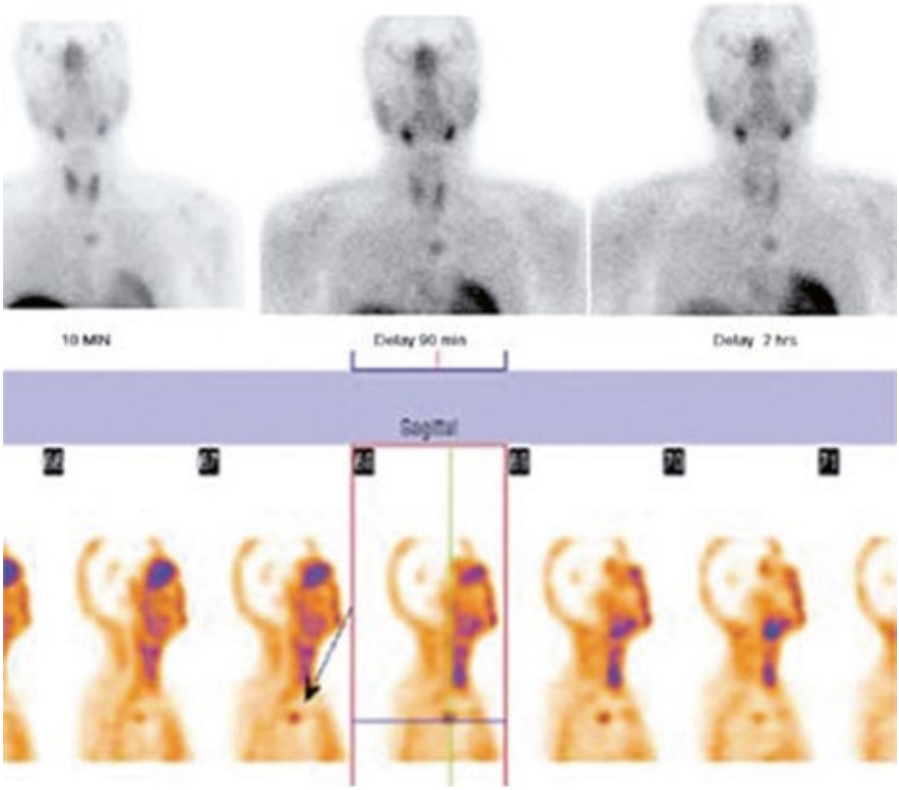

Fig. 13. Image of a parathyroid adenoma in the chest

Unfortunately, because of thyroid nodes that can also accumulate technetril, sometimes it is impossible to get a proper image of the parathyroid adenoma (Fig. 14). In these cases, other imaging methods, such as a CT scan, should be used.

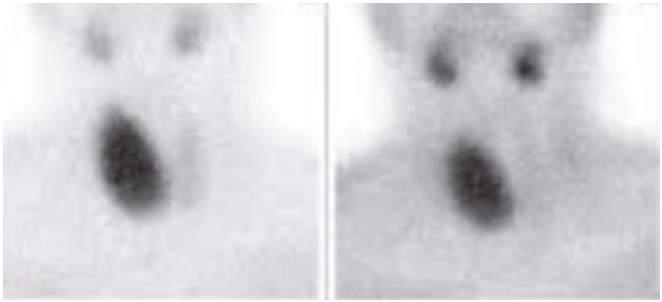

Fig. 14. Accumulation of technetril in the thyroid gland node.

Computed tomography

A CT scan records X-rays passing through the human body. To get a high-quality image, it is necessary to make an intravenous injection of a contrast agent. It improves the contrast of images and helps locate the adenoma. X-ray exposure and the contrast injection are harmful to the patient so computed tomography is never used as a first examination method. There is no very serious threat to the body, but since the contrast agent can cause additional damage to the kidneys, this procedure can be contraindicated for people with renal compromise.

A CT scan offers a very high definition image. This method can efficiently detect parathyroid adenomas in any area of the neck and in the chest (Fig. 15).

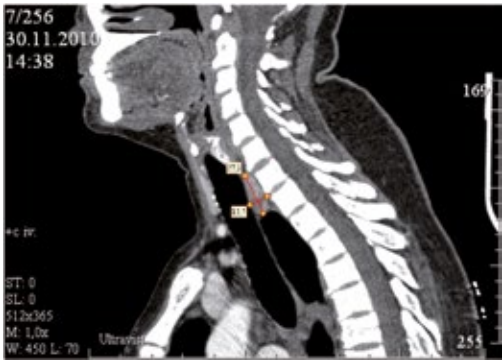

Fig. 15.
Computed tomography –
image of a parathyroid adenoma.

Single-photon emission computed tomography

SPECT/CT (single-photon emission computed tomography) is an exam that applies the scintigraphy image to the computed tomography image. Devices used for SPECT/CT scans can scan the human body in various directions, which ensures a very accurate visualization of the adenoma. However, compared to conventional scintigraphy, this method comes with a higher radiation load for the body.

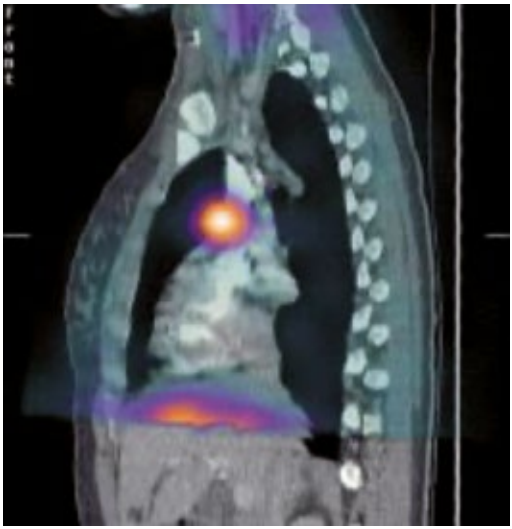

Fig. 16.
Image of a parathyroid adenoma with SPECT/CT

Magnetic resonance imaging

With this method, one can get an image of a parathyroid gland adenoma but the quality of this image will not be very high (Fig. 17). In addition, an adenoma cannot always be detected with an MRI. Therefore, this method is rarely used in clinical practice, only if there is a contraindication in a CT scan.

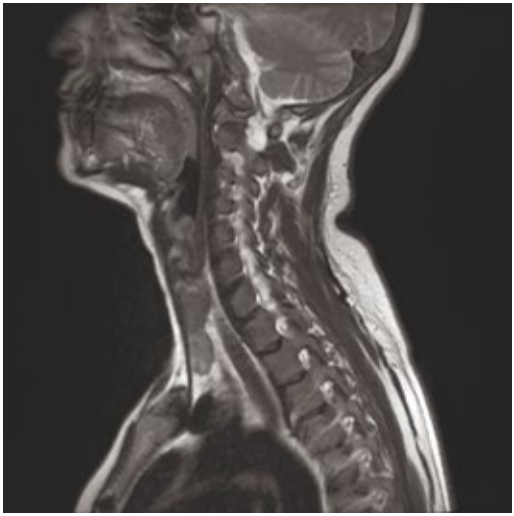

Fig. 17.
Image of a parathyroid adenoma with MRI

Positron emission tomography (PET)

Tomography with 11C-methionine can be used to visualize parathyroid adenomas (Fig. 18). This method is very expensive (with costs several times higher than computed tomography or scintigraphy) and complex equipment is required. As a result, doctors now only use PET as a method to locate parathyroid gland adenomas.

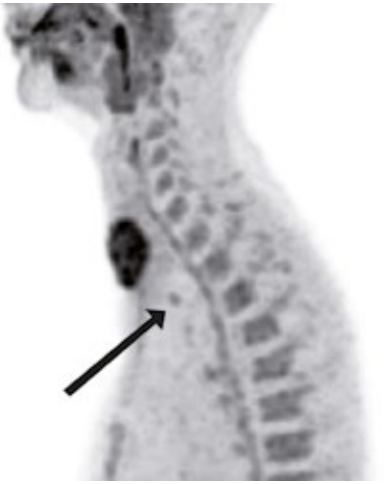

Fig. 18.
Image of a parathyroid adenoma with PET

Fine-needle biopsy of a parathyroid adenoma

In some cases, a parathyroid tumor can be located inside the thyroid gland (Fig. 19). This happens if the embryonic development of parathyroid glands (more often the lower ones) happens in a specific way so they are surrounded by thyroid tissue. In an ultrasound these parathyroid tumors look like thyroid nodes and even a biopsy with a microscopic study of tumor cells is not always enough to make an accurate diagnosis since the cells of the parathyroid look very much like thyroid cells.

In these cases, to establish an accurate diagnosis it is necessary to make a tumor biopsy and then assess the level of parathyroid hormone in the needle that was used for the injection. This is simple, the needle is washed with 1 ml of saline and then the washing liquid is sent to study the level of parathyroid hormone. If the analyzed mass was a parathyroid gland tumor, then the level of parathormone will be very, very high (Fig. 20).

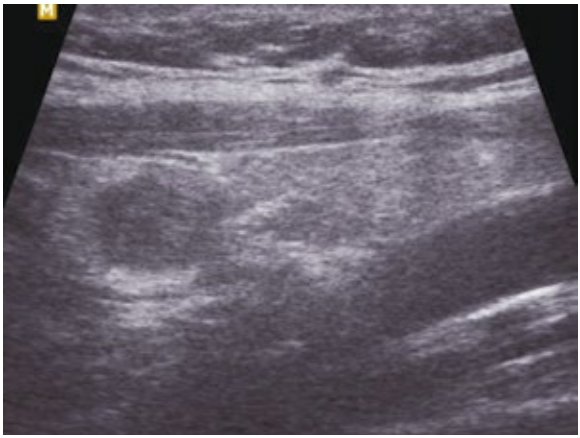

Fig. 19.
Parathyroid adenoma located inside thyroid tissue (intrathyroidal adenoma) – ultrasound image

This test has a very high accuracy rate even though it is only used when other methods can't confirm the presence of a parathyroid tumor. However, because of this method's specifics, it has very limited use. First, a biopsy is an invasive procedure involving a small trauma (an insignificant puncture with a regular needle in the node that feels like a puncture in the buttock). Second, when a biopsy is performed, the needle violates the integrity of the adenoma capsule. This can potentially lead to a proliferation of adenoma cells to the neighboring tissues and to the development of other tumors in these cells (this phenomenon is called parathyromatosis but is very rare).

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Код в реестре внешнего контроля качества ФСВОК 10914

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29/10/2009. Паратгормон
Индивидуальный номер:4535729. Штрихкод:F19953751

N	Наименование теста	Результат	Норма
1.	Паратгормон , пмоль/л (анализатор Liaison)	4300	1.83 - 7.73

Комментарий:

Пунктат.

Автор комментария: Гринжола Е Н

Выполнили:14/10/2009 Гринжола Е.Н.
Авторизация:Гринжола Е.Н.

Fig. 20. Parathormone test result, swab from the needle

What research methods should I use?

As a rule two methods are used to determine the location of an adenoma. Most often, those are ultrasound and scintigraphy. If both of these methods provide information about the location of the adenoma, no further examination is required. If the result of these methods differs or one (or both) of them do not result in an image of the adenoma, a third method should be used. Usually, this is a CT scan. Only if all three methods combined can't help to locate the adenoma, should the additional examination methods positron emission tomography or adenoma biopsy be used.

Chapter 7

Surgical Treatment of Primary Hyperparathyroidism or Why All Operations Are Not Equally Safe and Efficient

If there is one thing we know for sure about the treatment of primary hyperparathyroidism, it is that the most efficient method is surgery. None of the conservative methods or drug therapies can compare to the efficiency of a properly performed operation.

> **The surgery goal is to resect completely the tumor tissue that produces excessive hormones.**

That is the most difficult part of the operation because the tumor tissue has to be removed completely. If there's one adenoma, one adenoma must be removed, if there are two, then two adenomas must be removed. If tumors developed in all the parathyroids, it might be necessary to completely resect these glands (but a small part of one of the glands will be preserved).

Two or more adenomas in one patient develop in 5-15% of all cases. Unfortunately, if this happens it is rarely possible to see all the adenomas during an examination. Usually only the largest tumor is clearly visible. That is why during the operation the surgeon has to complete several tasks at once:

- find the parathyroid adenoma and remove it;
- confirm that there are no other adenomas (or find other adenomas and remove them);
- be careful not to damage the function of normal parathyroids;
- be careful not to damage the function of the laryngeal nerves that are responsible for the strength and quality of the voice;
- perform a minimally traumatic operation and achieve a positive cosmetic result.

All operations for primary hyperparathyroidism should be performed by surgeons with substantial experience in neck surgery (both for thyroid and parathyroid diseases). The effectiveness of surgical treatment direct-

ly depends on how many operations the surgeon has performed in the past. Unfortunately, there are very few clinics in the world that specialize in the treatment of primary hyperparathyroidism. In our clinic, Northwestern Center of Endocrinology and Endocrine Surgery, more than 800 operations for hyperparathyroidism are performed every year. In terms of number of surgeries, our center ranks first in Russia and Europe.

Currently, endocrine surgeons use three main methods to perform operations for primary hyperparathyroidism: selective parathyroidectomy, bilateral neck revision, and unilateral neck revision. Every method has its advantages and disadvantages. We will now do a deep dive into all of them.

Selective parathyroidectomy

In cases where the adenoma is clearly located during the examination, the surgeon only exposes the gland with the tumor and there is no need to examine other parathyroid glands. This type of operation doesn't take much time, doesn't leave a long skin suture, and doesn't require the surgeon have profound knowledge of parathyroid anatomy. If the surgery is performed using the endoscopic technique, the skin suture can be only 2-3 centimeters long. Due to the low surgical injury rate and speed of these surgeries, they are popular among surgeons in many countries of the world.

However, this method has serious drawbacks. The main disadvantage is the probability of not finding a second adenoma (or several adenomas) in those patients who have multiple parathyroid glands affected by the neoplastic process (as we have already said, the share of these patients is quite large 5-15%). After the resection of the adenoma, the surgeon has to confirm that the patient doesn't have any other tumors in the parathyroid glands. In some clinics, a parathyroid hormone test is used. However, parathormone remains in the blood for a very short period of time (about 5 minutes), after which it degrades completely. As a result, after the adenoma is resected there is a sharp decrease in the level of blood parathyroid hormone (if there are no tumors in the other parathyroid glands). If a blood test for the parathyroid hormone made 10 minutes after the resection of the tumor shows that the level of parathormone is two or more times lower than before the surgery or before the resection of the adenoma, then the probability of a second adenoma is low. That is the main reason why a rapid test for parathormone is used during the surgery. However, the use of this test can be challenging.

The main problem is that the surgery takes more time and the patient is anesthetized until the results for parathormone in the blood are available. The classical way to administer a rapid test is to take a blood sample 10 minutes after the resection of the adenoma. The minimal world record of time required to perform the test is 10 minutes. In typical clinical practice (not only in Russia, but in all other countries), most clinics receive the blood parathormone test results 20-25 minutes after the blood is collected. Thus, a patient is anesthetized for 30-35 minutes. This time is spent waiting for the results of the blood test to confirm there are no other parathyroid adenomas in the body. If the test shows the parathormone level has decreased by two or more times, the surgery is finished. However, if parathyroid hormone levels remain the same, the surgeon must examine the remaining parathyroid glands to locate additional tumors.

A waiting time of 30-35 minutes is considered quite long. There are numerous studies demonstrating that the overwhelming majority of the world's surgeons (more that 90%) do not wait for the results of the parathormone test and finish the operation immediately after they resect the adenoma. Thus, the results of the parathormone test arrive when the patient is already in the recovery room. If the test shows there is a second adenoma, the patient is again transferred to the operating room for another surgery with more anesthesia. In some clinics, the results of blood parathormone tests are available only several hours after the surgery or even the next morning. In these cases, a reoperation (if needed) can be scheduled one or two days after the initial surgery.

There are no clinics in Russia that can get parathormone test results 20 minutes after the adenoma resection. Unfortunately, in real life the method of selective parathyroidectomy (the surgery that examines only the parathyroid gland affected by tumor) results in 1/6-1/20 of all patients having to undergo a second surgery. This is the first major drawback of this method.

The second drawback was identified when we conducted a large trial analyzing the way the rapid parathormone test is used to rule out additional adenomas. In half the patients who had two adenomas, the level of parathormone did go down by half after the bigger adenoma was resected. Thus, in half of the patients a rapid test for parathyroid hormone was providing false data indicating there is no additional tumor in parathyroid glands. The results of our study have shown that a rapid test for parathormone does not only extend the time of surgery and anesthesia, but is also very inaccurate.

As our clinic gained more experience, we gradually started to give up selective parathyroidectomy as the main treatment method for primary hyperparathyroidism. We started performing a bilateral revision of the neck. This surgical procedure involves examining all the parathyroid glands. It is worth noting that the world's largest clinic for the treatment of primary hyperparathyroidism has arrived at the same conclusion. That is the Dr. Jim Norman Parathyroid Center in the USA, where they perform more than 3000 parathyroid surgeries every year. For many years, Professor Norman has been an active advocate of selective parathyroidectomy and rapid parathyroid hormone analysis. He changed his tactics after several years analyzing the treatment results of thousands of patients. Today, every surgery for primary hyperparathyroidism involves a mandatory examination of all parathyroid glands.

Bilateral neck dissection

With a bilateral neck dissection, the surgeon performs a mandatory examination of all parathyroid glands, regardless of where the adenoma was located at the examination stage. Many textbooks and articles say this kind of operation is too traumatic and presents the risk of damaging healthy parathyroid glands. Our experience doesn't confirm this. Everything depends on the experience of the surgeon, the operation methodology, and on how carefully and gently the surgeon is handling live tissue. We have been using this method for a long time and have not noted any cases of the parathyroid function decreasing after the operation.

In our experience, a bilateral neck dissection for an anatomically typical patient can be performed much faster than selective parathyroidectomy with a rapid parathormone test. Reducing the time in surgery with anesthesia is a significant advantage for this kind of operation. However, even more important is the fact that with a bilateral neck dissection, the surgeon can assess the condition of all parathyroid glands. Glands affected by the neoplastic process, are removed and healthy normally functioning glands are preserved. There is no need to perform a rapid test because it can no longer improve the treatment outcome. Numerous studies have proven there is no need to perform a rapid parathormone test with this surgery.

A bilateral neck dissection is the "gold standard" for the treatment of primary hyperparathyroidism. Many textbooks confirm this. Regardless of this fact, a small number of clinics use this method as a first option when it comes to parathyroid gland surgery of. Why is such an effective operation so "unpopular"?

The main reason is that a bilateral neck dissection requires the surgeon have a very high level of qualification, a lot of experience in hyperparathyroidism surgery, and knowledge of all the anatomical specifics for the parathyroids location in the body.

Unfortunately, we often see that during an operation an endocrine surgeon searches for parathyroid glands by "digging" in the adipose tissue, completely ignoring anatomical landmarks. These "searches" can last a long time, which makes the operation more invasive and less tolerable for the patient.

In this book, I won't describe the way to look for parathyroid glands during surgery. This book is written for patients, not for surgeons. However, I can say with confidence that the search for parathyroid glands is a very logical process that requires a minimal number of surgical movements. The search is based on an analysis of numerous landmarks that are often very small. That is why we use optical magnification during surgery. We operate using binocular loupes that magnify the image several times.

To finish the description of a bilateral neck dissection, I want to add that our clinic spent a long time mastering the surgery for primary hyperparathyroidism. The transition to this method was the logical finale of this process. Having performed several thousands of surgeries on parathyroid glands, we realized examination of all parathyroid glands allows us to ensure the maximum recovery rate. However, I cannot recommend this method for surgeons who don't have enough experience in this field of surgery and have not been trained at a hyperparathyroidism treatment center.

Unilateral neck dissection

In our clinic, we use neuromonitoring during parathyroid gland operations. This provides electrophysiological control of the condition of the laryngeal nerves that are responsible for vocal function. Neuromonitoring requires specialized equipment that is currently available only in few Russian clinics. The use of neuromonitoring helps detect laryngeal nerves faster, identify an atypical structure of their anatomy (e.g. several nerve trunks, an atypical turn of branches), and assess the integrity of the laryngeal function during the surgery.

During the surgery, if neuromonitoring shows that the function of the laryngeal nerve is impaired, there is a high probability that one of the vocal folds will lose its function in the post-op period. To impair the laryngeal nerve function, a surgeon doesn't need to cut a nerve or damage it with an instrument. Sometimes the surgeon performs all the stages of the sur-

gery correctly and accurately, but the function of the nerve still disappears. For example, as the result of a spasm in nerve vessels or its tension during surgical manipulations.

If this happens and the nerve on one side stops transmitting electrical signals, the surgeon should avoid any manipulations on the opposite side of the neck. Otherwise, the function of the second laryngeal nerve can be impaired and cause a patient to become disabled. In this situation, a unilateral neck dissection is an option. The surgeon resects the adenoma, examines the second parathyroid gland on the side of the adenoma and ends the operation. Of course, there is the risk of another adenoma on the opposite side of the neck. Still, if there is the threat of a double-sided laryngeal dysfunction, it is better to refrain from examining the parathyroids on the other side of the neck. During the postoperative period, the patient undergoes another parathyroid hormone test in the blood. If it is reduced to normal values, the doctor can confirm there has been a full recovery from hyperparathyroidism. If the blood parathormone has not normalized, it is better to refrain from repeated surgery for the next 2-3 months. In more than 95% of patients, this is enough time for the laryngeal function to recover enough so the surgery on the other side of the neck can be performed safely.

In modern parathyroid surgery, a unilateral neck dissection is a non-elective surgery to avoid the risk of bilateral laryngeal dysfunction. This surgery is almost never conducted as an independent treatment method.

What is a “blind neck dissection”

In recent years, diagnostic capacities have increased more than ever. The accuracy of lab tests these days is extremely high, which makes it possible to detect even a slight increase in blood calcium levels and diagnose primary hyperparathyroidism at an early stage of the disease. Patients with slightly elevated calcium usually have such small parathyroid tumors that they can’t be detected by ultrasound, scintigraphy, or tomography. A growing number of patients have clear laboratory signs of primary hyperparathyroidism, but there is no diagnostic tool to locate the adenomas. In these cases, there are two possible therapeutic approaches.

The first option is not to perform the surgery until the parathyroid adenoma is located. In my opinion, this is not the right approach. It is based on the surgeon’s fear of not locating the adenoma. Sometimes operations are postponed for decades. All this time the disease is present in the pa-

tient's body, damaging numerous body functions. For example, significantly increasing the risk of dying from a stroke.

The second option, which I support, is to perform the surgery and locate the parathyroid adenoma even if there is no data on where it might be located. If the lab data shows that the patient has an adenoma, it should be enough for us to understand that this patient needs surgery. If no diagnostic method helped locate the adenoma, we can be almost sure of one thing, it is not located in the chest. That means we don't need to resect it through special access. Intrathoracic adenomas are clearly visible with scintigraphy and tomography. All adenomas located in the neck area can be found easily during the surgery. There are not many options for their location in the neck area so an experienced surgeon will be able to find the tumor quite quickly.

Performing surgery without knowing the location of the adenoma is often referred to as "blind neck dissection". There is no need to be afraid of this surgical procedure. The more advanced medicine becomes, the earlier we will detect hyperparathyroidism, and the more often we will conduct "blind dissections". However, there is one condition to insure the success of this surgery, it should only be conducted in specialized clinics by surgeons with significant experience in parathyroid surgery. Doctors who have conducted less than 500 parathyroid surgeries should never perform this surgery.

How to operate on adenomas located in the chest

Statistically, one out of 300 adenomas may be located in the chest. Some intra-thoracic adenomas can be resected through the neck. However, some of them are located so deep they cannot be seen with cervical access. In the past, a painful and traumatic intervention was use to resect intrathoracic adenomas. The sternum was dissected, the chest was opened, and then the adenoma was removed. After this surgery patients suffered severe pain syndrome and recovery took a long time. Today, adenomas in the chest are resected using an endoscopic technique. The surgery is performed with a video camera and instruments inserted through several punctures in the chest wall. Endoscopic surgeries are minimally traumatic so the patient can quickly return to normal life. These surgeries are usually performed by endocrine surgeons together with thoracic surgeons who are used to operating on the chest organs.

Endoscopic and video-assisted neck surgery

Surgery for a parathyroid adenoma located in the neck area, can also be performed endoscopically. Video-assisted surgery leaves a suture about 2 cm long in the neck area. If the operation is performed endoscopically, the suture is longer but it is located in the less visible axillary area. Both types of surgeries offer good cosmetic results. However, most often an experienced surgeon can operate on primary hyperparathyroidism through a skin access of 2 cm without using the endoscopic technique. Any primary hyperparathyroidism surgery can provide ideal cosmetic results. It doesn't matter whether or not it was performed endoscopically. Endoscopic surgery through auxiliary access has one important disadvantage, the surgeon can't perform a bilateral neck dissection. It can, only examine parathyroids from one side.

How to Evaluate Surgical Results

After the operation is performed, there are three possible scenarios:

The first and most favorable scenario is a **complete recovery** with the normalization of calcium and parathyroid hormone levels. In this case, the patient is usually prescribed calcium and vitamin D to restore bone strength (we will talk about this a bit more in Chapter 9).

The second scenario is **persistent hyperparathyroidism** when increased levels of calcium and parathormone remain after the surgery. These laboratory results indicate that the parathyroid adenoma wasn't removed (or only one of several adenomas was removed leaving at least one more that is uncontrollably producing parathormone). Persistent hyperparathyroidism indicates the surgery was not complete and the patient needs another intervention. The best option is to have additional examinations and then perform the next surgery that should locate the remaining adenoma. Repeated operations are complex so they should only be done in specialized clinics.

The third scenario for a patient's life after the surgery is the normalization of calcium and parathormone levels for at least 6 months, followed by new increases above the normal levels. This situation is called **hyperparathyroidism relapse**. It is not always the result of poorly performed surgery. In some patients, new adenomas may develop in previously perfectly functioning parathyroid glands. In patients with hyperparathyroidism, the overall risk of relapse sometime after the surgery varies from 1 to 5%. Sometimes hyperparathyroidism patients relapse because of genetic factors that make

parathyroid glands transform into adenomas. These hereditary cases may be accompanied with tumors in other endocrine glands (thyroid, pancreas, pituitary gland). To determine the causes for the development of new tumors, patients with recurrent hyperparathyroidism should visit specialized endocrine centers for an in-depth examination that includes genetic tests.

> **The relapse of hyperparathyroidism is the most difficult case and requires maximum attention and highly qualified doctors involved in the treatment.**

Chapter 8

Drug Treatment for Primary Hyperparathyroidism or Pills Lose to Surgery

It turns out that when it comes to treatment of primary hyperparathyroidism, drugs lose to surgery. To be more precise, even long-lasting, expensive drug therapy will be less effective than successfully performed surgery. That is why an operation is indicated for primary as the best treatment option. At the same time, in some situations drugs can be useful.

Preparation for surgery

There are cases when a patient is admitted to the clinic in such bad condition that immediate surgery can be dangerous. In this situation, the patient is transferred to the intensive care unit where they are treated with medication to reduce blood calcium levels and stabilize the main functions of the body. This preparation usually takes several hours, after which the surgery is performed.

Surgery refusal

Patients rarely refuse to have surgery. It is the doctor's responsibility to fully explain the advantages of surgery for primary hyperparathyroidism over any other treatment. If the patient doesn't feel like having surgery, the doctor must find the right words so the patient makes the optimal choice. Especially since the surgery for primary hyperparathyroidism is not major or disabling, and the cosmetic result is always very good. In the course of the conversation, the doctor must gradually discuss all the patient's doubts and fears and convince them that the surgery is the best option. Regardless, sometimes the patient cannot be convinced and refuses the surgery. If this happens, the doctor must recommend treatment to reduce the level of blood calcium and prevent the destruction of bone tissue.

Very often in textbooks and guidelines for patients with primary hyperparathyroidism, you can find recommendations to limit the intake of food rich in calcium (primarily, dairy products) as well as to increase their daily consumption of fluids. In my opinion, dietary approaches rarely affect blood calcium levels. In these cases, it is impossible to do without drugs.

The main therapeutic agents in the drug therapy for primary hyperparathyroidism are **bisphosphonates**. They stop the destruction of the bone tissue. Bisphosphonates act on osteoclasts, cells that directly destroy bone tissue and block their work. Long-term use of bisphosphonates (they are usually prescribed for several years) can stop the reduction of bone density and even slightly increase the content of calcium in the bone tissue. However, it is still not as effective as a successful operation to resect the parathyroid adenoma. Some bisphosphonates are taken once a week in the form of tablets (sodium alendronate) and some are administrated intravenously (sodium ibandronate, zoledronic acid) once every few months. Less degradation of bone tissue means lower blood calcium levels or, at a minimum, lower risk of an even greater increase.

Denosumab, an artificially created antibody against the receptor on the osteoclasts' surface, has a similar effect preventing the destruction of bone tissue and inhibiting calcium excretion from it. The antibody blockade of the receptor prevents activation of osteoclasts and reduces their lifespan. Denosumab is administered subcutaneously once every 6 months. After the course of denosumab is completed, the patient must be treated with bisphosphonates for at least one year or the bone density might sharply reduce up to development of fractures.

Another drug that can also be used in patients with primary hyperparathyroidism is cinacalcet. This drug has an effect on the receptor's sensitivity to calcium located on the surface of parathyroid gland cells. Cinacalcet reduces the level of parathormone and calcium in the blood, which can be beneficial in severe forms of hyperparathyroidism. However, this drug has no influence on the density of bone tissue and risk of fractures.

Contraindications to surgery

As I have already said many times, surgery for primary hyperparathyroidism is not traumatic. If the surgeon is experienced enough, it also not a long operation, the duration of standard surgery rarely exceeds one hour. That is why there are very few situations when the surgery is contraindicated for medical reasons. Possible contraindications include severe blood

clotting disorders, massive immunodeficiency, and severe mental disorders. If the surgery is contraindicated, the above-mentioned group of drugs can be used: bisphosphonates, denosumab, and cinacalcet.

Sometimes patients with primary hyperparathyroidism are admitted to the clinic in a very serious condition associated with very high blood calcium levels. This condition is called a hypercalcemic crisis. It is sometimes characterized by cognitive impairment up to the state of a coma, as well as fever, muscle pain, convulsions, and vomiting. Without proper treatment, a hypercalcemic crisis can lead to death. Despite a patient's poor general condition, in these cases the most effective treatment is urgent surgery to remove the parathyroid adenoma. After short medical pre-treatment, the patient goes to surgery. I want to emphasize that the patient's critical condition is not a contraindication to surgery since the life of the patient directly depends on the timing.

Numerous unsuccessful operations

Sometimes an endocrine surgeon consults a patient that underwent multiple surgeries on parathyroid glands without the desired result, the adenoma was not found. This situation is one of the most difficult for an endocrine surgeon. On the one hand, most often an experienced surgeon can locate and remove the adenoma even after several unsuccessful surgeries. On the other hand, after surgical interventions the anatomy of the neck changes dramatically, a pronounced scarring process starts in the affected areas. Sometimes, if an inexperienced surgeon can't find the adenoma, he just resects perfectly normal parathyroid glands making the situation even more complicated.

When dealing one on one with this problem, the doctor has to answer several questions. Does the patient really suffer from primary hyperparathyroidism? Why have previous surgeries been unsuccessful? Where can the parathyroid adenoma be located? It is mandatory to repeat all the tests for finding adenomas: ultrasound, scintigraphy, and computed tomography. Everything is questioned. After all the necessary information is collected, another surgery is usually performed. This one should be the final one, resulting in a full recovery.

More often, in more than 90% of the cases, this surgery is successful, a parathyroid adenoma is detected and resected. Cases when these tests and procedures do not locate a parathyroid adenoma are very rare

and isolated. However, anything is possible in medicine. If this dead end is reached, drug therapy comes to rescue becomes the only effective method of treatment, and it usually lasts for the patient's life.

When all the parathyroid glands are affected

The last scenario when a conservative therapy can be used is the poly-glandular lesion, a neoplastic transformation of all four parathyroid glands. The patient doesn't have a single healthy parathyroid gland, they all turn into tumors and actively produce the parathyroid hormone. In this situation, the surgeon has to make a tough decision. You can't leave the patient without treatment, but you can't resect all the parathyroids since this will have severe consequences such as seizures, constant need for intake of calcium and vitamin D, development of numerous complications (urolithiasis, cerebral calcification, increased risk of strokes, and depression).

When all the parathyroid glands are affected, the surgeon removes the three glands most altered by the neoplastic process and leaves only half of the fourth gland (usually, the smallest one). Of course, the remaining part of the parathyroid gland can still has the potential to release parathormone uncontrollably. This is when you have to choose the lesser of two evils. It is either no parathyroid hormone in the blood with the resection of all the glands, or its erratic release (albeit in small quantities) with a half of one parathyroid left. To lower the risk of complications (primarily fractures, urolithiasis, and strokes), the patient is prescribed medications. We talked about the drug therapy options earlier.

Chapter 9

Recovery After Surgery or You Always Need Calcium

After the surgery is successfully completed, a new life begins for the patient. Calcium, which for a long time was taken away by osteoclasts and accumulated in the blood, begins its way back from the blood to the bone tissue. Within a few minutes after the resection of the parathyroid adenoma, the level of parathormone in the blood normalizes and the function that destroys osteoclast cells is inhibited. Other cells «wake up» in the bone tissue. These are osteoblasts that, similar to bricklayers, start taking calcium from the blood and depositing it back in the bone tissue. Osteoblasts build new bone trabeculae to replace the ones destroyed by the disease. They restore the bone density and make the bones stronger. All these changes are signs of an ongoing recovery from hyperparathyroidism. However, the body needs «help» in order to speed up those positive changes.

To build new bone tissue the body needs calcium. Cells that repair the bone do take calcium from the blood, but they can't «estimate» how much calcium can be safely taken. Very often, in an effort to restore quickly the bone damaged by the disease, osteoblasts take too much calcium from the blood. When the blood calcium level drops, the patient can feel numbness in their hands and feet, have a feeling of «goose bumps» on the skin, experience convulsions, and weakness. In response to a decrease in the blood calcium, the remaining and normally functioning parathyroid glands begin to secrete parathormone to keep calcium in the blood. It is a catch twenty-two when the blood calcium level is reduced or is somewhere near the lower limit of normal and the blood parathyroid is increased. This condition is called «hungry bones syndrome», but it doesn't mean the patient is still sick. On the contrary, it shows that the bone restoration process is happening in the body, only there is not enough calcium for it. At this stage of recovery, calcium (for bone reparation) and vitamin D (to ensure the absorption of calcium in the intestine) are crucial for the patient. For many years,

the disease was taking the calcium «away» from the bone tissue, and now it is the time to give it «back» to the bones. Therefore, there should be a lot of calcium.

In our clinic, after every successful surgery for the resection of parathyroid adenoma, we prescribe calcium and vitamin D supplements stressing that the patient should be taking them for at least a year. During the first months after the surgery in a larger dose, reducing it in the following months. It is crucially important to normalize the level of 25-hydroxyvitamin D in the blood. First, the patient takes a test for this vitamin and the dosage is adjusted according to the test results (the level of this vitamin will always be low but the rate of decline is different in every patient).

In the first month after the surgery, an active form of vitamin D, alfacalcidol, is usually prescribed since this drug is faster acting than any other. In the following months it makes sense to switch to natural vitamin D, cholecalciferol, since its concentration in the blood can be measured and the risk of an overdose can be managed.

One year after the surgery, it is advisable to perform an **osteodensitometry**, a bone density study that helps to assess how the recovery is going after the disease. Annual monitoring of calcium, parathormone, and 25-hydroxy-vitamin D in the blood is obligatory. If a reduction in the vitamin D level is detected, it is very important to bring it back to normal to prevent the redevelopment of parathyroid adenomas. This follow-up process does not require much from the patient, but it means he or she should remain under medical supervision for life.

Chapter 10

Parathyroid Carcinoma or A Few Words About the Biggest Danger

In the vast majority of cases, parathyroid tumors are benign. Malignant parathyroid gland tumors, carcinomas, are very rare, but they are extremely dangerous for a patient.

Carcinomas of the parathyroid glands are in most cases quite big, more than 3-4 cm. The larger the size of the parathyroid tumor, the greater the chance it will be malignant. In addition to the size, another characteristic that can indicate the tumor is malignant is unusually high levels of blood calcium and parathormone, and blurred, fuzzy tumor contours on the ultrasound. Sudden hoarseness, loss of voice strength, respiratory difficulty, trouble swallowing, cognitive impairments, and repeated fractures are all symptoms that are a reason for an immediate visit to a doctor.

Parathyroid carcinomas are always treated surgically. During surgery, not only the parathyroid tumor should be removed, but the nearby muscles, fatty tissue, and lymph nodes. Most often, it is also necessary to remove the nearby part of the thyroid gland. Malignant parathyroid tumors have a tendency to recur in the same place, so the operation should be as radical as possible to reduce the risk of recurrence. Neuro-monitoring should be used during the surgery to control the condition of the laryngeal nerves. If the surgeon has enough is experience, even the most radical surgery doesn't damage vital functions. Often after the operation, the patient doesn't realize the scale of the intervention.

After the tumor is resected, the patient takes calcium and vitamin D. Considering how severely the calcium metabolism was disturbed before the surgery, the dosages might be quite high (at least in the first 2-3 months).

The first thing you will notice if there is a recurrence of the tumor, is an increase in blood parathormone.

> **That is why after the surgery for a malignant parathyroid gland tumor, it is necessary to monitor frequently the levels of blood parathormone. This should be done at least once every three months for the first year after the surgery and not less that once every six months in the following years.**

If the level of parathormone remains within the normal range, it is safe to say there is no recurrence of the disease.

If the carcinoma progresses, the tumor may proliferate into the distant organs including the lungs, bones, and brain. If this happens, chemotherapy is needed. Modern target biologicals (for example, sorafenib) have shown good results. To reduce the level of calcium in the blood, cinacalcet is used. A patient is then required to take bisphosphonates (most often zoledronic acid), that prevent the destruction of bone tissue and reduce the growth rate of bone metastases.

Parathyroid carcinomas are hard to treat. The treatment should continue regardless of how aggressive the disease is. An active treatment ensures a long life for a patient even when a complete cure from the disease is impossible, for example, when there are distant metastases. If there is a recurrent tumor in the neck, repeated surgeries are performed. Brain metastases, if any, are destroyed with a cyberknife, a special type of radiation therapy. When there are lesions in the bones, it is possible to do bone surgery or local radiation therapy. Under no circumstances can the fight stop. Every year we see new chemotherapeutic drugs that are efficient in treating parathyroid carcinomas. Patients now have more treatment options.

Chapter 11

Primary Hyperparathyroidism and Thyroid Diseases or Neighbors in Life and Illness

Even though the thyroid and parathyroids are located next to each other in the neck area, these organs have completely different structures and functions. Their names are similar, but nothing else is. However, there is one thing they have in common, diseases of these glands are frequent so often a patient can suffer from both thyroid and parathyroid diseases.

With the development of diagnostic capabilities in thyroid gland tissue, nodes are often identified, which sometimes can become a reason for surgery. Surgery is only required for malignant nodes or nodes that cause serious symptoms (compression of the neck organs, cosmetic defect, increased hormone levels). In Russia, e very year a large number of patients undergo surgery for thyroid disease, tens of thousands of people. Some patients referred to surgery might be diagnosed with primary hyperparathyroidism. In these cases, the surgery can be performed on both the thyroid and parathyroids. This approach is very beneficial, you can treat two diseases with one surgery that is not much longer than one. There is one requirement. When the surgery begins, the patient must be definitively diagnosed with primary hyperparathyroidism and this often becomes a problem. Very often patients don't have the blood calcium test that is required to establish a diagnosis.

All clinics performing thyroid surgery should remember that the standard for post-op examination must include blood tests for calcium and parathormone. These indicators should be evaluated not only after the surgery (most surgeons know this because it is important in the postoperative period to check the integrity of parathyroid gland functions), but also before the intervention to detect the parathyroid tumor. We often have to deal with patients that have been referred for a consultation from other clinics. They received their diagnosis, primary hyperparathyroidism, the day after the surgery. There is only one reason for this, they had their blood calcium

measured for the first time. It is easy to imagine a patient, just out of the operating room, being told that they must have another surgery because "not everything was removed". It is a shame to realize that such a mistake could have been avoided easily if a blood test for calcium had been conducted in time.

Sometimes during scintigraphy for patients with primary hyperparathyroidism, thyroid nodes can accumulate technetril and make it difficult to find the parathyroid adenoma. In these situations, the diagnostics become much more difficult since nodes can imitate an adenoma during the ultrasound. It should always be remembered that the adenoma can be located inside the thyroid. In this case, it will look just like the ordinary thyroid node on the ultrasound. Even a node biopsy doesn't always help to establish a correct diagnosis. That is why patients with increased blood calcium and nodes in thyroid tissue should only be referred to specialized endocrine surgery clinics that have considerable experience both in treating the thyroid and primary hyperparathyroidism.

Primary hyperparathyroidism is also a component of the type IIa multiple endocrine neoplasm syndrome, in which parathyroid adenomas usually develop after the detection of medullary thyroid cancer. That is why all patients with elevated blood calcium levels must also check the level of calcitonin in the blood. An elevated level is a symptom of medullary thyroid cancer. This disease can also be diagnosed in children, so the clinic that specializes in this treatment should also have a license and experience in pediatric surgery.

Diagnostic Minimum for Primary Hyperparathyroidism

In this section of the book, I will list all the tests and studies that should be performed in a patient with primary hyperparathyroidism. This list includes only the minimum that should always be performed. This list cannot be used as a preoperative examination guide since prior to surgery a patient undergoes many more tests such as a complete blood count, biochemistry, tests for hepatitis, coagulation analyses, etc.

Laboratory blood tests
- calcium (*ionized or general*)
- parathormone
- creatinine
- albumin (*if the total calcium has been measured*)
- calcitonin (*if there are nodes in the thyroid*)

Laboratory urine tests
- analysis for calcium in daily urine
- analysis for creatinine in daily urine

Clinical investigations
- Ultrasound of the thyroid gland, neck lymph nodes
- parathyroid scintigraphy with technetril (99Tc-MIBI)
- computed tomography of the neck with bolus contrast enhancement (*if after the ultrasound and scintigraphy there is no data on the location of the adenoma*)

Clinical investigations to exclude hyperparathyroidism complications
- x-ray osteodensitometry
- fibrogastroduodenoscopy
- Ultrasound of kidneys, bladder

Afterword

In this small manual, I tried to share information about primary hyperparathyroidism and, at a minimum, to show you that this disease exists and is quite widespread. I hope I succeeded.

I am convinced that every one of us must undergo a blood calcium test as a part of an annual medical checkup. Blood calcium should also be measured every time any patient is admitted to the hospital. Simple attention to blood calcium levels can significantly improve detection rates of primary hyperparathyroidism. Every year in our country alone, several thousand people will be diagnosed. All these people will be able to get help and not only live better but live longer.

Surgeries for the endocrine neck organs (thyroid gland, parathyroid glands) should only be performed in specialized clinics with sufficient experience in this surgical field. Equally important is the availability of the necessary equipment including high-quality coagulators, microscopic equipment, devices for intraoperative neuromonitoring, and endoscopic equipment. Surgery of the parathyroid glands can be minimally invasive and very efficient. Endocrine surgeons prove this every day with their work.

> **If after reading this book you realize that you need an appointment with an expert in the field of primary hyperparathyroidism, I recommend you contact Northwestern Center of Endocrinology & Endocrine Surgery. Every year we perform more than 6000 surgeries on the endocrine system organs of adults and children, as well as conducting several thousand endocrine consultations.**

The clinic is located in St. Petersburg but for people from other regions, remote consultations are available through the website **endoinfo.ru**. You can schedule an appointment with a specialist at the Center by phone **(812) 565-1112** on weekdays from 7 am to 9 pm, on weekends from 7 am to 7 pm. To sign up for surgery, contact us by phone **(812) 980-7721** on weekdays from 9 am to 5 pm. For any questions concerning treatment at the Center, contact us by e-mail: **mail@endoinfo.ru**.

We hope to be of service to the readers of this book.

Sincerely,
I.V. Sleptsov

I.V. Sleptsov

MD, Endocrine surgeon, oncologist, pediatric surgeon, professor at the department of theoretical surgery at St. Petersburg State University, chief specialist in endocrinology and endocrine surgery at St. Petersburg State University N. I. Pirogov Clinic Of High Medical Technologies, head of the Northwestern Medical Centre (St. Petersburg), president of Russian Association of Endocrine Surgeons, member of the board of Asia-Pacific Association of Thyroid Surgery, member of the European Thyroidological Association, member of the European Association of Endocrine Surgeons.

Northwestern Center of Endocrinology and Endocrine Surgery

Northwestern Center of Endocrinology and Endocrine Surgery is an integrated clinic that offers treatment to patients with different endocrine system diseases.

The center offers treatment for patients with diseases of the thyroid gland, parathyroid glands, adrenal glands, as well as with diabetes mellitus, osteoporosis, obesity, and infertility.

Northwestern Center for Endocrinology and Endocrine Surgery has brought together endocrinologists with various profiles: endocrine therapists, endocrine surgeons, endocrine gynecologists, and pediatric endocrinologists as well as experts in related areas: urologists-andrologists, breast physicians, therapists, and ultrasound diagnostics doctors.

Among the staff members of the center there are doctors and candidates of medical sciences, doctors in the highest qualification category.

They are all Russia's leaders in conducting thyroid node biopsies (more than 30,000 patients per year), in thyroid gland surgery (more than 6,000 surgeries per year), parathyroid glands (more than 600 surgeries per year), and adrenal glands (200 surgeries per year). The Center performs surgeries for adults and children.

The Center performs more than 1000 types of laboratory tests, ultrasound of internal organs, including expert thyroid gland ultrasounds for adults and children. The Center's website offers options for remote consultations.

The Center has branches in St. Petersburg, Vyborg, Gatchina, Kingisepp, Luga, Svetlogorsk, and Staraya Russa.

Center Website: WWW.ENDOINFO.RU.