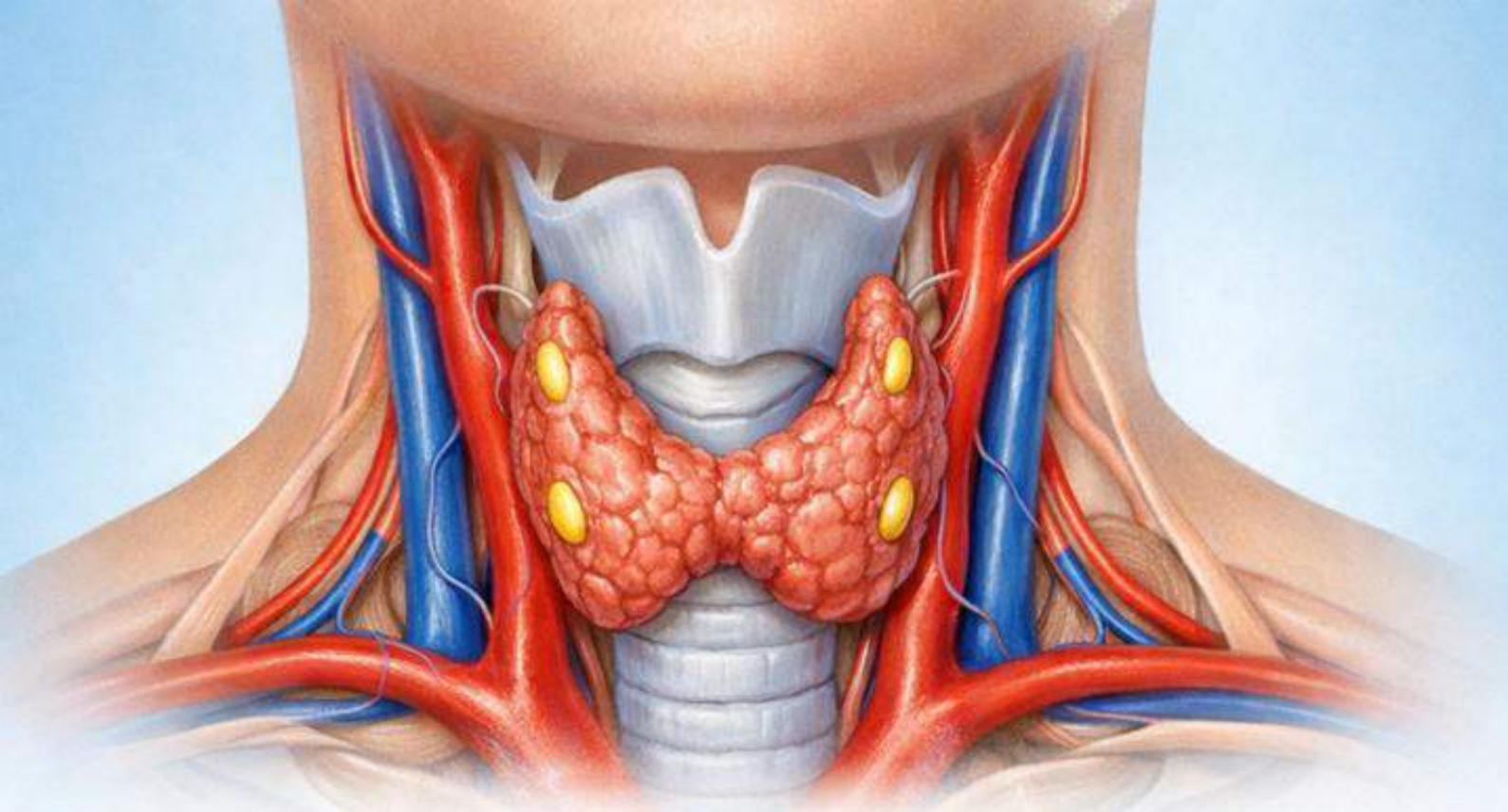
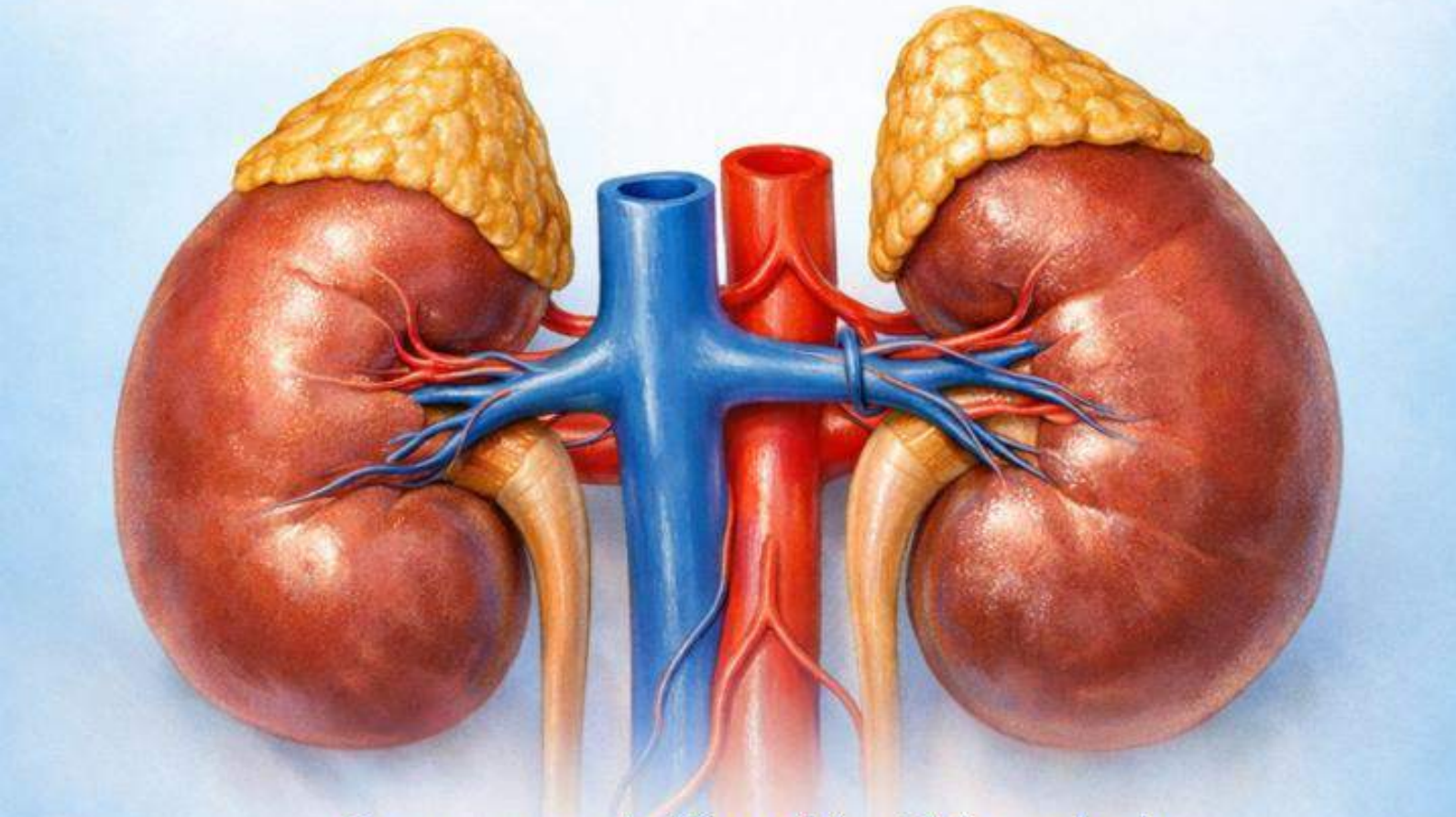


Diseases of the Thyroid, Parathyroid Glands and Adrenal Glands



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BISHKEK - 2026

ADAM UNIVERSITY
HIGHER SCHOOL OF MEDICINE
Department of Surgical Disciplines

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Diseases of the Adrenal Glands, Thyroid Gland, and Parathyroid Glands

Study Guide / ADAM University

— **Bishkek, 2025** —

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Educational and Methodological Counsil of **ADAM University**

This study guide is devoted to the clinical features, diagnosis, and surgical treatment of diseases of the adrenal glands and the thyroid gland.
The manual is intended for medical students, clinical residents, and postgraduate trainees of medical faculties, as well as for practicing surgeons dealing with these conditions.

Reviewer:

Candidate of Medical Science Subanov A. A, National Hospital.

ABSTRACT

This study guide presents, at a contemporary level, issues related to the clinical features, diagnosis, and surgical treatment of Cushing's disease (Cushing disease), as well as diseases of the thyroid and parathyroid glands.

The manual provides a detailed description of diagnostic methods, hormonal investigations, fine-needle aspiration biopsy techniques for thyroid diseases, and surgical treatment methods for Cushing's disease and thyroid gland disorders.

This publication is intended for medical students, clinical residents, postgraduate trainees, and practicing surgeons involved in the management of these conditions.

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MD (General Medicine)

My cooperative student

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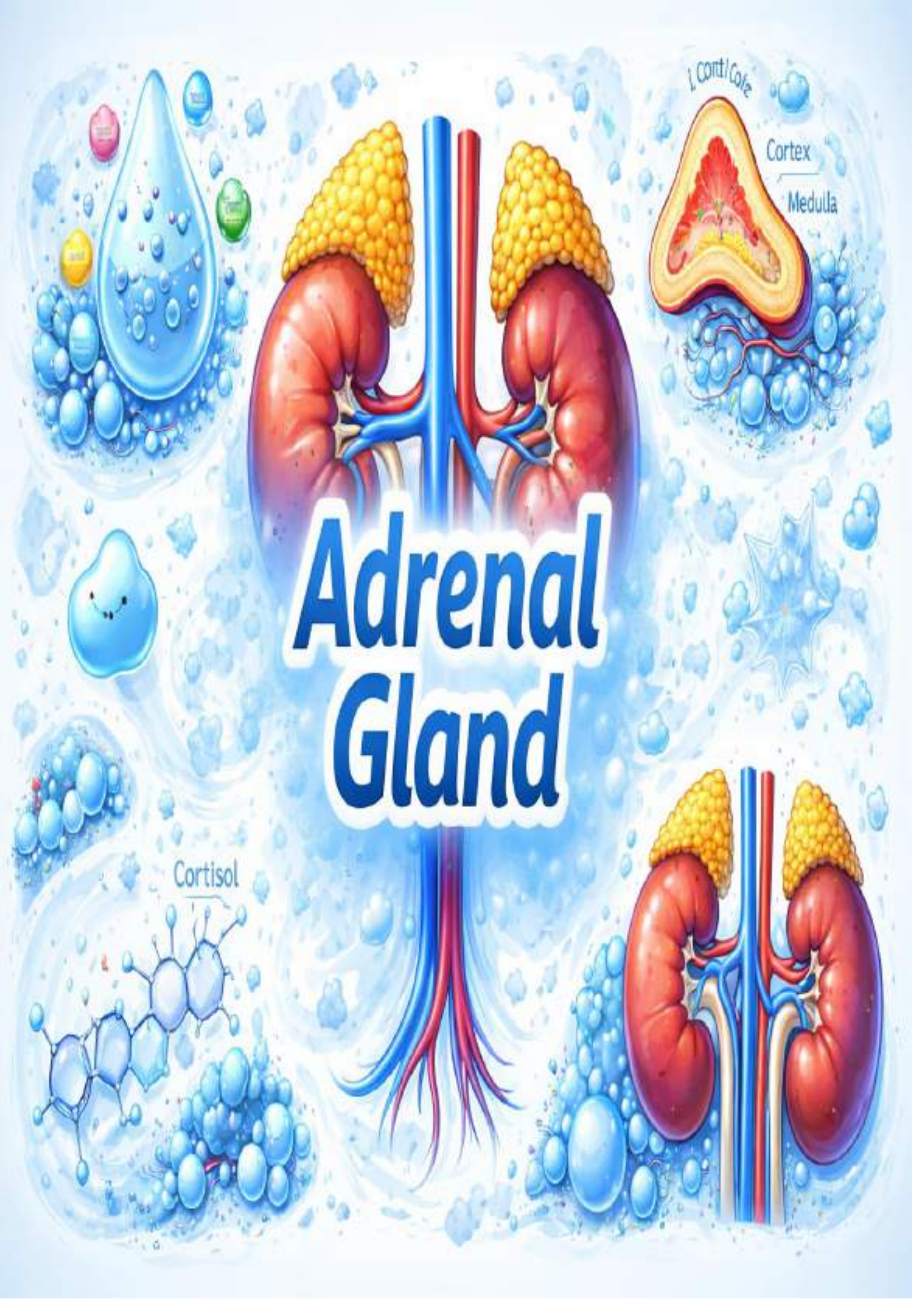
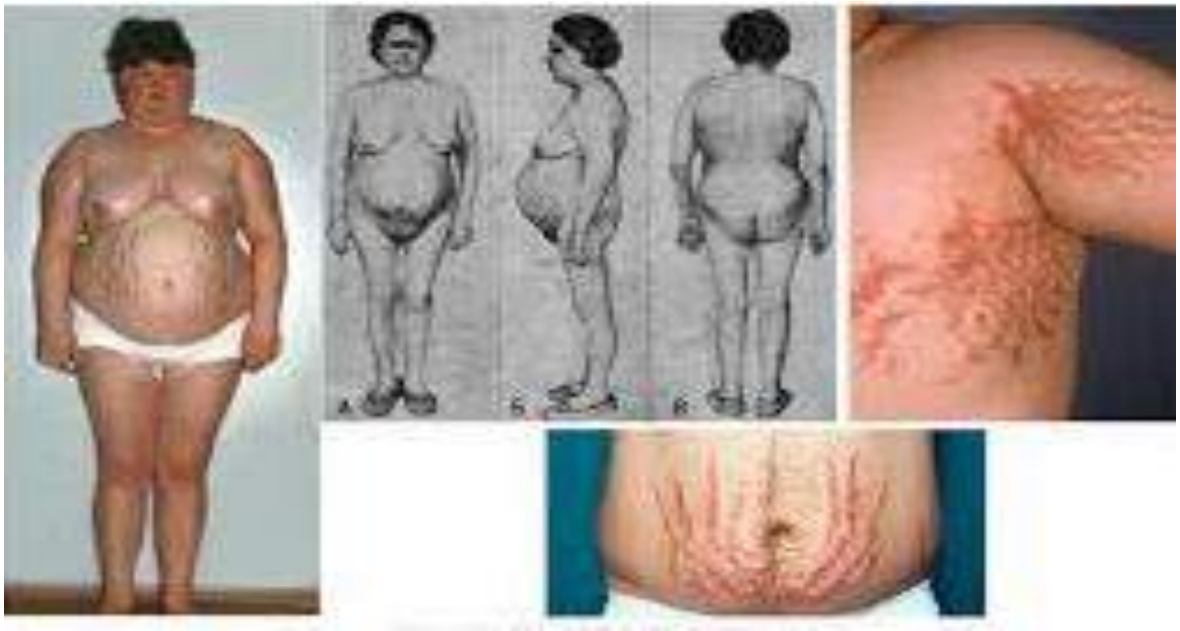

Adrenal Gland
Cortex
Medulla
Cortisol

CUSHING SYNDROME

Cushing Syndrome is a disorder of adrenal origin, caused by the presence of a tumor of the adrenal cortex (either a benign corticosteroid adenoma or a malignant corticoblastoma), or arising as a result of micro- or macronodular adrenal hyperplasia. These conditions lead to the secretion of excessive amounts of adrenal cortical hormones, resulting in the clinical picture of hypercortisolism.



CLASSIFICATION

A. ACTH-Dependent Form

1. Cushing's disease, caused by a pituitary tumor or hyperplasia of corticotrophs in the adenohypophysis.
2. Ectopic ACTH syndrome caused by tumors of endocrine or non-endocrine origin that secrete corticotropin-releasing hormone (CRH) and/or ACTH.

B. ACTH-Independent Form

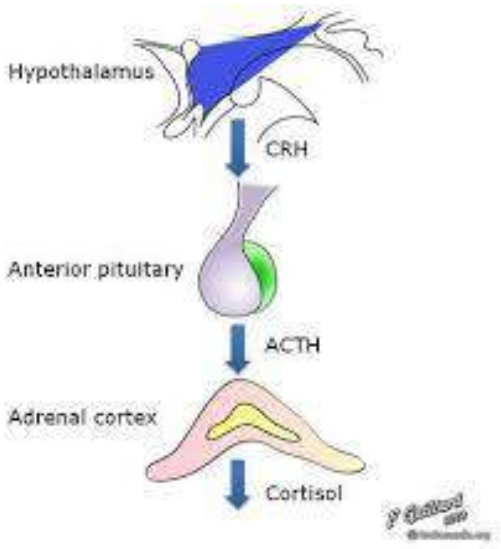
1. Cushing's syndrome caused by an adrenal cortical tumor (benign – corticosteroid adenoma, or malignant – corticoblastoma).
2. Cushing's syndrome – juvenile adrenal cortical dysplasia.
3. Cushing's syndrome – macronodular form of primary adrenal disease.
4. Incomplete hypercortisolism syndrome, observed in "inactive" adrenal tumors.

ETIOLOGY AND PATHOGENESIS OF CUSHING SYNDROME

Cushing syndrome is more commonly observed in **women**, and the disease usually develops after childbirth or abortion. Less frequently, it may occur in children or the elderly.

In Cushing syndrome, there is uncontrolled secretion of adrenal cortical hormones – **cortisone, cortisol**, and **corticosterone** – which disrupt metabolic processes and lead to severe organic changes in the central nervous system and parenchymal organs. Chronic and prolonged hypercortisolemia results in the development of the **hypercortisolism** symptom complex.

Muscle tissue atrophy and the appearance of **reddish striae** on the skin of the abdomen and thighs are caused by disturbances in protein metabolism. The atrophic processes affect



These changes affect striated skeletal muscles and are especially noticeable in the muscles of the upper and lower limbs.

Characteristic features of hypercortisolism include **redness, marbling, thinning, and dryness of the skin**. These manifestations are associated both with polycythemia and with skin atrophy caused by increased catabolism and decreased collagen synthesis. Skin thinning combined with rapid fat deposition leads to the formation of stretch marks (striae). These are observed in the vast majority of patients and usually appear before or simultaneously with other symptoms. However, their absence does not exclude the diagnosis of hypercortisolism.

Disturbances in protein metabolism lead to increased nitrogen excretion in the urine and reduced serum albumin levels.

Potassium levels in plasma, erythrocytes, and muscle tissue (including the myocardium) are significantly reduced.

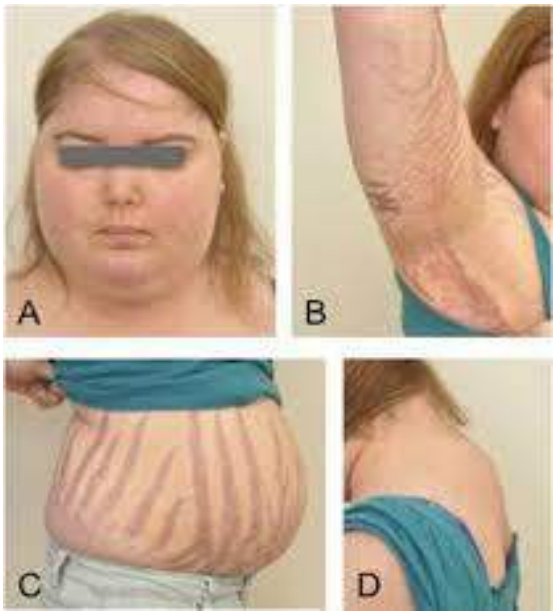
The pathogenesis of arterial hypertension in hypercortisolism is highly complex. Dysregulation of central mechanisms controlling vascular tone plays a key role. Equally important is the hypersecretion of steroids with pronounced mineralocorticoid activity (corticosterone and aldosterone). Dysfunction of the renin–angiotensin system contributes to the development of persistent hypertension. Prolonged overproduction of cortisol increases renin levels. Potassium loss from muscle cells alters vascular reactivity and elevates vascular tone. Glucocorticoids also contribute to hypertension by potentiating the effects of catecholamines and other biogenic amines.

The catabolic effects of glucocorticoids on bone tissue lead to decreased bone mass and reduced content of organic components, such as collagen and

mucopolysaccharides; alkaline phosphatase activity is reduced. The ability of bone to store calcium is also diminished. A significant factor in the development of osteoporosis (OP) is reduced calcium absorption in the gastrointestinal tract, associated with inhibition of calciferol hydroxylation. Excessive renal calcium excretion contributes to nephrocalcinosis, secondary pyelonephritis, and the development of renal insufficiency.

In the pathogenesis of steroid-induced diabetes, important factors include relative insulin deficiency, insulin resistance, and elevated levels of counter-regulatory hormones.

CLINICAL FEATURES



The clinical picture of Cushing syndrome is highly diverse, which is explained by the involvement of multiple organs and systems in the pathological process. Prolonged overproduction of corticosteroids leads to the development of a variety of disease manifestations. The term “hypercortisolism” encompasses dysplastic obesity, trophic changes of the skin, steroid cardiopathy, hypertensive syndrome, impaired sexual function, systemic osteoporosis,

secondary diabetes, secondary immunodeficiency, and psychiatric disturbances.

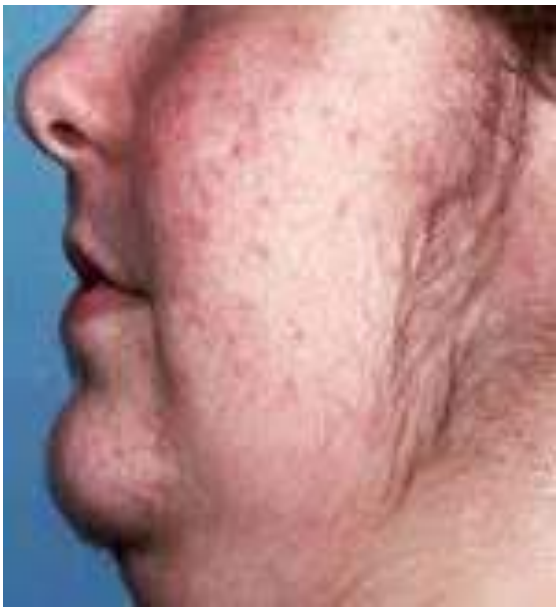
The disease can develop at any age, but it is most commonly observed between 20 and 40 years, with women affected more frequently than men

Dysplastic Obesity

One of the earliest symptoms of the disease is **weight gain.** Obesity occurs in the majority of patients and, in some cases, shows a characteristic uneven distribution, with fat accumulating predominantly in the face, neck, and abdomen, while the limbs remain thin. The supraclavicular fossae are filled with fat, and the face acquires a rounded appearance with a reddish-cyanotic hue.

Thinning of the limbs is explained by muscle atrophy, which can be significant. Fat deposits may form a “buffalo hump” over the upper thoracic vertebrae. In patients without generalized obesity, there is redistribution of subcutaneous fat, primarily to the chest and abdominal regions. In children and adolescents, obesity with redistributed subcutaneous fat is often the first noticeable symptom of the disease.

The skin is dry and markedly thin. Cutaneous changes include a reddish-cyanotic coloration, often accompanied by a marbled or reticular vascular pattern. Wide stretch marks (striae) of a red-purple color appear on the inner thighs, chest, shoulders, and abdomen. The striae are typically atrophic in nature ("minus tissue"). In some cases, hyperpigmentation of the skin is observed, particularly in areas of friction, such as the neck, elbows, and axillae.



Hirsutism and Skin Manifestations

Hirsutism is often observed on the face (upper lip, beard, side burns), chest, and upper and lower limbs. Pustular eruptions may appear on the back, chest, and face. Hair loss on the scalp is common, and in women, balding often follows a male pattern. The skin of the back and chest may develop pustular lesions (acne), and there is a predisposition to furunculosis and pyoderma.

The virilizing features of the disease are believed to be associated with increased secretion of adrenal androgens.

Clinical Features in Children and Adolescents

In children and adolescents, one of the earliest symptoms of hypercortisolism is **slowed growth** or complete cessation of growth. Typically, these children are followed by a pediatrician for a long period due to delayed physical and sexual development, and a correct diagnosis is often established only after several years, as additional disease manifestations appear. Alongside slowed growth, adolescents often show delayed skeletal maturation, with a discrepancy between chronological age and bone age ranging from 1 to 5 years.

Musculoskeletal Changes

Atrophic processes affect striated skeletal muscles, particularly in the **proximal muscles** of the upper and lower limbs. The combination of hypokalemia and muscle atrophy results in marked muscle weakness. Excess glucocorticoids increase protein breakdown and slow protein synthesis. Peripheral protein catabolism and impaired amino acid uptake at the microsomal level occur due to increased amino acid degradation in the liver under the influence of excess cortisol.

Cardiovascular System and Cardiac Involvement

Among the various manifestations of hypercortisolism, cardiovascular involvement is one of the most significant, as it largely determines the severity and prognosis of the disease.

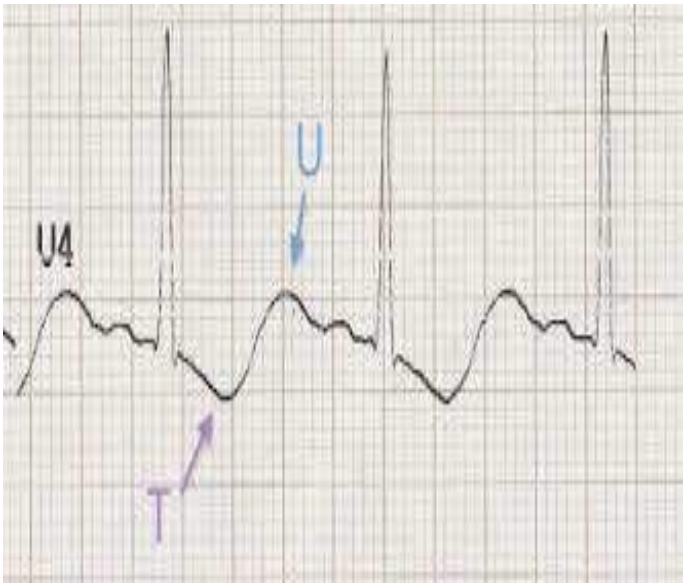
Clinical observations indicate that angina pectoris, myocardial infarction, and rhythm or conduction disturbances are rare. More commonly, patients present with sinus tachycardia, leftward enlargement of the heart borders, systolic murmur at the apex, and accentuation of the second heart sound over the aorta. Chest pain is usually described as cardialgia.

Arterial hypertension is common, with elevated systolic and diastolic blood pressure. Hypertension and metabolic disturbances in the myocardium often lead to chronic circulatory insufficiency. In most patients, blood pressure elevation is persistent and difficult to correct. Hypertension may also be complicated by retinopathy, cardiac, and renal involvement.

Cardiac involvement in Cushing syndrome is multifactorial, primarily due to the effects of glucocorticoid excess on the myocardium and disturbances in electrolyte and protein metabolism. Excess glucocorticoids can alter myocardial cell membrane permeability, enhance tissue respiration, and simultaneously cause electrolyte imbalances, notably **hypokalemia** and **hypernatremia**. Potassium deficiency is the primary cause of electrolyte-steroid cardiopathy.

Electrocardiographic findings in most patients include T-wave flattening, prolonged QT interval, ST-segment depression, and the presence of a U wave. Excess glucocorticoids also lead to marked protein metabolism disturbances (dysproteinemia), which contribute to myocardial structural changes.

Excessive glucocorticoid production also **increases plasma renin**, promoting angiotensin I formation and contributing to elevated blood pressure. Aldosterone is considered to play a secondary role in the pathogenesis of hypertension in Cushing's disease.



Steroid Cardiopathy

In most patients with steroid cardiopathy, electrocardiography (ECG) shows **T-wave flattening, prolonged QT interval, ST-segment depression, and the presence of a U wave.** It is also known that excess glucocorticoids cause significant disturbances in protein metabolism (dysproteinemia), which further contribute to structural and functional changes in the myocardium.

Excess glucocorticoid production leads to an increase in plasma renin, which participates in the formation of angiotensin I and contributes to elevated blood pressure. Aldosterone is considered to play a secondary role in the pathogenesis of arterial hypertension in Cushing's disease.

Carbohydrate Metabolism

In hypercortisolism, carbohydrate metabolism disorders of varying severity are observed in a large proportion of patients. More than 80% of patients exhibit impaired glucose tolerance, while the remainder develop **diabetes mellitus.** A characteristic feature of steroid-induced diabetes caused by excess glucocorticoids is insulin resistance with rare occurrences of ketoacidosis.

It has been established that levels of **immunoreactive insulin (IRI), C-peptide, glucagon, somatostatin, as well as their molar ratios and glycated hemoglobin (HbA1c) levels**, are elevated in patients with Cushing syndrome even before abnormalities appear in the glucose tolerance test. Therefore, assessing this panel of markers is most effective for early detection of carbohydrate metabolism disorders and timely treatment.

Thus, hyperglycemia in these patients develops not due to absolute insulin deficiency, but primarily as a result of marked insulin resistance caused by excess cortisol production.

Sexual Disorders

Sexual dysfunction is often one of the earliest and most persistent symptoms of Cushing syndrome. In women, **menstrual irregularities** such as oligomenorrhea or amenorrhea are common, and secondary infertility frequently occurs. Gynecological examination often reveals uterine hypoplasia and polycystic ovaries.

If pregnancy occurs in these patients, it is typically associated with spontaneous abortion or preterm birth. When the disease is diagnosed during pregnancy, this combination is generally undesirable for the health of both the fetus and the mother.

Sexual Disorders in Men and Women

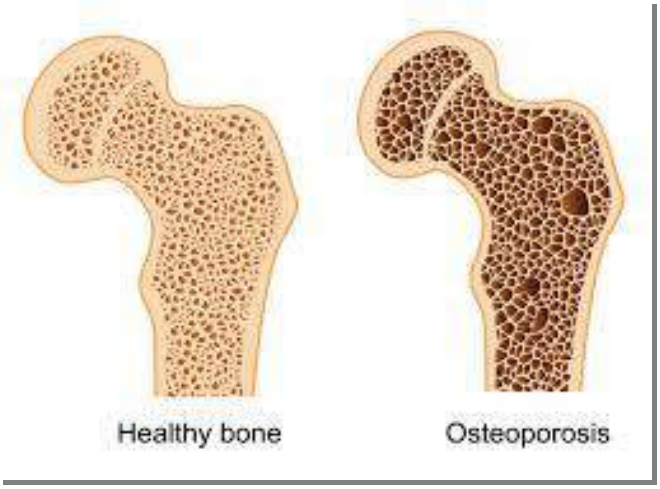
In men, reduced potency is frequently observed, and in some cases, true **gynecomastia** may develop. During puberty, boys often present with underdevelopment of the testes and penis, accompanied by reduced plasma levels of testosterone and gonadotropins.

In girls, sexual development is characterized by **underdeveloped mammary glands** and **absence** of **menstruation**, often accompanied by excessive facial and body hair. Delayed sexual maturation is frequently associated with uterine and ovarian hypoplasia.

These disorders are likely related to increased production of adrenal cortical steroids with androgenic activity and elevated testosterone secretion.

Steroid Osteoporosis

Osteoporosis is the most frequent and often severe manifestation of endogenous hypercortisolism. The severity of osteoporosis and bone pain in Cushing disease generally correlates closely with the degree and duration of hypercortisolism.



Osteoporosis initially develops in the bones of the skull, vertebrae, pelvis, and ribs, and later affects peripheral skeletal sites. The pathogenesis of steroid osteoporosis is complex.

Key factor is the direct suppressive effect of excess glucocorticoids on osteoblast number and activity, which leads to reduced bone formation. In addition, excess glucocorticoids decrease calcium absorption in the intestines and reduce calcium reabsorption in the renal tubules, resulting in a **negative calcium balance** and transient **hypocalcemia**. This, in turn, stimulates parathyroid hormone secretion and enhances bone resorption.

A further contributing factor is the reduced calcitonin levels observed in patients with Cushing syndrome, which also accelerates bone resorption. Collectively, these effects of glucocorticoid excess promote rapid development of osteoporosis, leading to significant loss of bone mass in these patients.

Steroid Immunodeficiency

A characteristic feature of Cushing syndrome is steroid-induced secondary immunodeficiency. Most patients exhibit one or more clinical signs typical of secondary immunodeficiency: pustular or fungal lesions of the skin and nails, trophic ulcers of the lower legs, purulent fistulas, delayed healing of injuries and postoperative wounds, recurrent blepharitis, chronic pyelonephritis resistant to conventional therapy, septic states, and miliary tuberculosis.

Cellular immunity parameters in patients with active Cushing syndrome are significantly altered. There is suppression of all aspects of cellular immunity, including **lymphopenia** with reduced absolute numbers of T- and B-lymphocytes. Additionally, neutrophil phagocytic activity is reduced, which, combined with other factors, indicates the presence of secondary immunodeficiency.

Excess steroids exert a direct cytotoxic effect on blood cells and also have a direct immunosuppressive action.

Assessment of humoral immunity shows that while immunoglobulins A and M may remain normal, there is a clear tendency for reduced IgG levels. This glucocorticoid-induced immunosuppression, manifested by cellular immune suppression and

decreased IgG, contributes to the high incidence of nonspecific inflammatory processes in the vast majority of patients with Cushing syndrome.

Autonomic Nervous System and Psychiatric Disturbances

Changes in the autonomic nervous system in Cushing syndrome are pronounced and diverse, forming a syndrome of **autonomic dystonia**. Clinically, this often manifests as emotional and personality changes, psychiatric disturbances, and a wide spectrum of symptoms ranging from mood and sleep disorders to severe psychoses. Acute psychotic states sometimes require specialized treatment, but successful management of the underlying disease usually restores normal mental function.

Thus, the clinical presentation of Cushing syndrome is characterized by a wide variety of symptoms of varying severity. Diagnosis is often delayed, making hormonal assays and topographic diagnostic methods critically important for timely and accurate detection. These methods are also essential for monitoring treatment effectiveness.

Diagnosis and Differential Diagnosis

Since the clinical presentation of Cushing syndrome, Cushing's disease, and ACTH-ectopic syndrome is often similar, laboratory and instrumental investigations are essential for differential diagnosis, establishing an accurate diagnosis, and determining appropriate treatment.

Evaluation of patients with suspected hypercortisolism, depending on the severity of the disease, can be performed in outpatient clinics or in an endocrinology hospital setting.

Laboratory and Instrumental Methods for Evaluating Suspected Cushing Syndrome

- Assessment of **ACTH and cortisol** secretion rhythm in plasma; measurement of 24-hour urinary free cortisol; dexamethasone suppression test.
- **Computed tomography (CT)** or magnetic resonance imaging (MRI) of the adrenal glands, ultrasound of the adrenal glands, or radioisotope imaging (to detect adrenal pathology).
- **CT or MRI** of the brain, as well as lateral skull radiography (for detection of pituitary adenoma).
- Measurement of **blood levels** of prolactin, LH, FSH, and testosterone (to assess reproductive system function).
- **Biochemical blood tests** (total protein, creatinine, potassium, ACTH, ALT).
- **Blood levels** of ionized calcium, phosphorus, and alkaline phosphatase (to assess bone metabolism and calcium balance).
- **Complete blood count** and **urinalysis**.

- Fasting **blood glucose**, 2-hour postprandial glucose, and urine glucose (to detect carbohydrate metabolism disorders).
- **Chest radiography** (to rule out pulmonary pathology).
- **X-rays** of the thoracic and lumbar spine (to assess skeletal integrity).
- **Densitometry** of the lumbar spine and femur (to diagnose osteoporosis and determine bone mineral density).

Laboratory Diagnosis

- Measurement of plasma adrenocorticotropic hormone (ACTH) and cortisol, including assessment of their circadian rhythm (typically at 8 a.m. and 11 p.m.).

Hormonal Diagnosis of Cushing Syndrome and Differential Diagnosis

A key diagnostic indicator in Cushing syndrome, Cushing's disease, and ACTH-ectopic syndrome is the measurement of ACTH levels in plasma. However, individual ACTH values in the morning can vary widely.

- **In Cushing syndrome, ACTH levels are typically reduced.**
- **In Cushing's disease, morning ACTH levels are elevated in most patients.**
- **In ACTH-ectopic syndrome, ACTH levels are markedly elevated**.

Another important marker for confirming hypercortisolism is the measurement of cortisol levels in plasma. Advances in hormonal assay techniques have allowed detailed study of cortisol secretion in patients with Cushing's disease. In most patients, cortisol secretion in plasma is significantly and consistently elevated, both in the morning and evening, though levels may fluctuate considerably over several days, which must be considered when making the diagnosis.

In Cushing syndrome, Cushing's disease, and ACTH-ectopic syndrome, morning cortisol levels are elevated. Currently, the most reliable diagnostic indicator for Cushing's disease is the measurement of plasma ACTH and cortisol levels in the late evening or early night, i.e., assessing their circadian rhythm. In clinical practice, ACTH and cortisol are usually measured at 8 a.m. and 11 p.m.

- **In healthy individuals and those with functional hypercortisolism, ACTH and cortisol levels are lowest at night.**
- **In patients with Cushing syndrome, the evening secretion rhythm of cortisol and ACTH is disrupted, resulting in elevated levels at night.**

However, elevated nocturnal levels can also occur in ACTH-ectopic syndrome and Cushing's disease, requiring further diagnostic evaluation.

Measurement of Free Cortisol in 24-Hour Urine

Measurement of free cortisol in 24-hour urine is now recognized as one of the reliable indicators of adrenal glucocorticoid function for diagnosing hypercortisolism of various etiologies. This test measures the total excretion of cortisol metabolites, but a single measurement may not always accurately reflect adrenal function. In some cases, repeat testing is necessary to reach the correct diagnosis.

- **In Cushing syndrome, urinary cortisol excretion is significantly increased.**
- **In Cushing's disease and ACTH-ectopic syndrome, urinary free cortisol is also elevated.**

Thus, when urinary cortisol is markedly increased, the differential diagnosis must distinguish among Cushing's disease, Cushing syndrome, and ACTH-ectopic syndrome.

If urinary free cortisol cannot be measured, 24-hour urinary 17-hydroxycorticosteroids may be used as an alternative indicator of adrenal function.

Dexamethasone Suppression Test (Low- and High-Dose Liddle Tests)

The dexamethasone suppression test is based on inhibition of ACTH secretion by high concentrations of corticosteroids in the blood via the negative feedback mechanism. Functional tests provide significant diagnostic value in differentiating hypercortisolism.

Low-Dose Dexamethasone Test

The low-dose test is used to differentiate pathological hypercortisolism from functional hypercortisolism (e.g., obesity, hypothalamic syndrome, pubertal-juvenile hypopituitarism). It can be performed in two variations:

1. **Classic Low-Dose Liddle Test:**
    - Dexamethasone is administered 0.5 mg every 6 hours for 2 days (total 4 mg).
    - Free cortisol in 24-hour urine is measured before the test and on the second day of administration.
2. **Overnight Low-Dose Test:**
    - Plasma cortisol is measured at 8 a.m.
    - The patient receives 1 mg dexamethasone at midnight
    - Plasma cortisol is measured again at 8 a.m. the next day

Interpretation:

- In healthy individuals and patients with functional hypercortisolism, cortisol levels (plasma or urinary free cortisol) decrease by ≥50% from baseline.

- In patients with Cushing's disease, Cushing syndrome, or ACTH-ectopic syndrome, this suppression is absent.

High-Dose Dexamethasone Test

The high-dose test is used to differentiate Cushing's disease from Cushing syndrome caused by adrenal tumors or ACTH-ectopic syndrome. It can also be performed in two variations:

1. **Classic High-Dose Liddle Test:**
    - Dexamethasone 2 mg every 6 hours for 2 days (total 16 mg).
    - Cortisol in 24-hour urine is measured before and on the second day of administration.
2. **Overnight High-Dose Test:**
    - Plasma cortisol is measured at 8 a.m.,
    - Patient receives 8 mg dexamethasone at midnight,
    - Plasma cortisol is measured again at 8 a.m. the next day

Interpretation:

- In Cushing's disease, cortisol (plasma or urinary) decreases by ≥50% on the second day.
- In patients with adrenal corticoseroma, no suppression occurs.
- In ACTH-ectopic syndrome, the test is usually negative, but some patients may show partial suppression.

Metopirone Test

Metopirone is a drug that selectively inhibits 11-β-hydroxylase activity in the adrenal cortex, which results in decreased secretion of cortisol, corticosterone, and aldosterone. In response to the fall in plasma cortisol, ACTH secretion increases. This enhanced stimulation of the adrenal cortex leads to increased excretion of 17-hydroxycorticosteroids (17-OHCS) in urine, which reflects the reserves of ACTH in the pituitary.

The Metopirone test can be performed in two ways:

1. **Intravenous method:**
    - Administer 1–2 mg of Metopirone in 500 ml isotonic saline over 4 hours.
    - Measure 17-OHCS in 24-hour urine collected before the test (baseline) and during the test day.
2. **Oral method:**
    - Administer 500–750 mg Metopirone orally every 4 hours (6 times per day) for 2 days.

- Measure 17-OHCS in 24-hour urine before the test and during the test days.

Interpretation:

- In healthy individuals, 17-OHCS excretion doubles or increases by 5–10 mg/day after Metopirone administration.
- This test helps differentiate juvenile obesity with striae, Cushing disease, and adrenal corticoseroma.
- In adrenal tumors (corticoseroma), 17-OHCS excretion does not increase.
- In adrenal hyperplasia, the increase in 17-OHCS excretion persists.

ACTH (Synacthen) Test

In addition to glucocorticoid suppression tests, differential diagnosis can be aided by administration of ACTH (Synacthen depot):

- In corticoseroma, ACTH does not increase cortisol secretion.
- In Cushing disease, cortisol levels rise after ACTH administration.

Topographic (Imaging) Diagnostics of Adrenal Lesions

Topographic methods are necessary to differentiate various forms of hypercortisolism (Cushing's disease, Cushing syndrome, ACTH-ectopic syndrome).

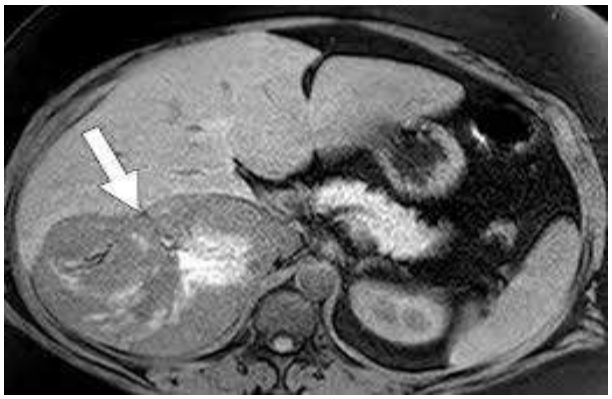
The primary diagnostic methods include:

- Computed Tomography (CT) of the brain and adrenal glands
- Magnetic Resonance Imaging (MRI) of the brain and adrenal glands

Additional techniques:

- For microadenomas in Cushing's disease, contrast-enhanced CT and MRI with paramagnetic contrast agents may be necessary for accurate detection.

Topographic Diagnostics of the Adrenal Glands



1. CT or MRI of the Adrenal Glands Direct and indirect signs of adrenal changes include:

- Enlargement of linear dimensions (thickness of the lateral and medial limbs, length of the adrenal glands)
- Presence of nodules in one of the adrenal glands

- Uneven sizes, scalloped contours of the adrenal glands without clear visualization of nodules
- Increased parenchymal density of the gland above 20 Hounsfield units

Notes:

- Corticosteroma on CT or MRI does not have pathognomonic features and appears similar to other adrenal cortical tumors.
- Overall, the diagnostic informativeness of CT or MRI for Cushing syndrome is 90–95%.

2. Radioisotope Study of the Adrenal Glands with Iodocholesterol (Scintigraphy)

- This method evaluates the functional activity of the adrenal glands.
- In cases of asymmetric isotope uptake in Cushing syndrome, surgery can be planned on the side with the highest accumulation.
- Unilateral accumulation of iodocholesterol indicates the location of an adrenal tumor in Cushing syndrome.
- Limitations: Scintigrams do not always provide a clear image of the adrenal glands.
- Advantages: Can detect extra-adrenal steroid-producing tissue.

3. Ultrasound of the Adrenal Glands

- Ultrasound is highly sensitive, non-invasive, and relatively safe, making it one of the first-line diagnostic methods.
- Sensitivity depends on tumor size and ranges from 71–94%.
- Corticosteroma appears as a mass of variable size (≥3–5 cm), with an indistinct capsule and homogeneous structure; the tumor is usually round or oval.
- The remaining part of the adrenal gland may be deformed.
- The contralateral adrenal gland is often hypo- or atrophic.
- Ultrasound can also detect diffuse and/or nodular adrenal hyperplasia, although its resolution (60–80%) is lower than CT.

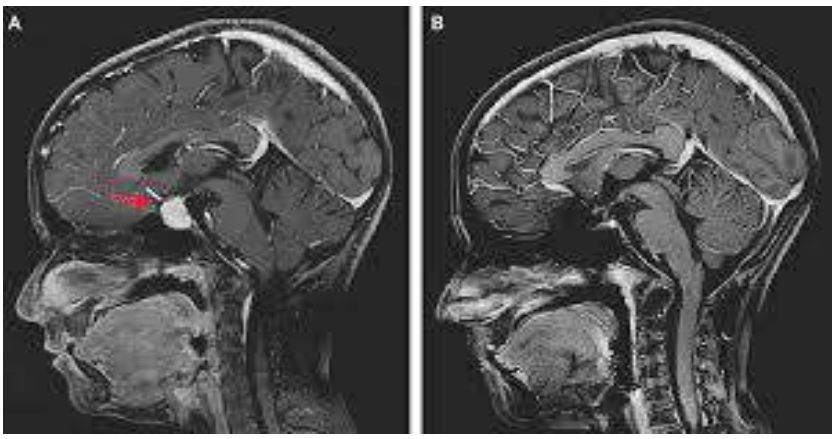
Additional Studies

- **Abdominal X-ray**
    - A plain abdominal radiograph can sometimes provide information about the adrenal glands.
    - It may reveal calcifications in the adrenal region (which can indicate tuberculosis), organized hematomas, etc.
    - On X-ray, a soft tissue shadow of a tumor may be visible if it is large.
    - Inferior displacement of the kidney can also indirectly suggest the presence of an adrenal mass.

- **Urography**
  - Contrast imaging of the renal calyces, pelvis, and ureters may provide indirect information about adrenal gland status.
  - A large adrenal tumor can displace the kidney and even deform the renal pelvis or alter the position of the ureter.
- **Pneumoretroperitoneum**
  - This technique is now rarely used for adrenal topographic diagnostics but allows simultaneous visualization of both adrenal glands.
  - The amount of insufflated gas depends on the patient's body mass: the higher the degree of obesity, the larger the gas volume required (1.5–3 liters).
  - Interpretation of X-rays or tomograms obtained this way requires experience.
  - The stomach base, pancreatic tail, or spleen pole can be mistaken for adrenal tumors, and other errors are possible.
  - Excessive fat tissue can obscure the adrenal glands, making assessment difficult and sometimes preventing tumor detection.
- **Adrenal Arteriography**
  - Performed via retrograde aortography using the Seldinger technique.
  - Its informativeness in Cushing syndrome is limited because adrenal cortical tumors are usually poorly vascularized, making it difficult to assess the glands.
  - Arteriography is useful, however, if combined renal vascular pathology is suspected.
- **Adrenal Venography (Phlebography)**
  - Provides more reliable results than arteriography.
  - Diagnostic value increases with selective blood sampling at different levels to determine cortisol concentrations.
- **Pituitary Evaluation**
  - If necessary, pituitary studies are conducted for the differential diagnosis of Cushing syndrome and disease.

Topical Diagnosis of Pituitary Adenoma

Visualization of corticotropin-producing adenomas is the most diagnostically challenging task, as their size is often very small (in 90–93% of cases, their diameter does not exceed 0.2–10 mm), which significantly complicates their topical (localization) diagnosis.



1. **Lateral Skull Radiography**
   Traditionally visualization of the sella turcica is performed using direct and lateral skull radiographs. This method remains relevant and is the first step (before performing CT or MRI of the brain) when examining a patient suspected of having Cushing's disease in an outpatient setting. Careful analysis of cranial radiographs, in correlation with clinical data, allows suspicion—and less frequently, diagnosis—of pathology in the sellar region.

Direct and indirect signs of pituitary adenoma on radiographs:

- Enlargement of the sella turcica;
- Double contour of the sella turcica floor;
- Local or total osteoporosis of the sella turcica walls;
- Thinning of the sella turcica walls;
- Straightening of the anterior and posterior clinoid processes.

2. **CT or MRI – Brain Tomography**
   These methods provide a detailed assessment of the sellar region, including evaluation of the sella turcica parameters, cavernous sinuses, internal carotid arteries, the sphenoid sinus, and the sellar space. They allow both topical and differential diagnosis of various forms of pituitary pathology. Often, a combination of CT and MRI is necessary for accurate diagnosis, as pituitary microadenomas smaller than 2–3 mm in diameter may not be visualized on contrast-enhanced CT. MRI is especially valuable in diagnosing corticotropin-

producing adenomas due to its higher resolution (85% for MRI versus 60–75% for CT).

Accordingly, additional tissue contrast significantly increases the resolution of MRI in the diagnosis of ACTH-producing adenomas.

Direct and indirect signs of pituitary adenoma on CT or MRI:

- Increased signal intensity from the tissue;
- Displacement of the pituitary stalk toward the side opposite to the adenoma;
- Asymmetry of the pituitary gland, with bulging of its contour;
- Pattern of accumulation (delayed uptake) of paramagnetic contrast agent by the pituitary tissue;
- Heterogeneity of pituitary tissue density;
- Decreased mineral content of the bony structures of the sella turcica;
- Symptoms of increased intracranial pressure.

These imaging methods provide information for diagnosing pituitary tumors in Cushing's disease, assessing their extension beyond the sella turcica, and determining the involvement of surrounding structures.

TREATMENT

For Cushing's syndrome caused by adrenal cortex tumors, primary micronodular dysplasia, or macronodular hyperplasia, **surgical treatment** is the method of choice.

Medical therapy using steroidogenesis inhibitors is applied as preoperative preparation, as well as specific chemotherapy after removal of malignant corticotropin-secreting tumors, and in cases of inoperable tumors or metastases. For these purposes, preference is given to the o,p'-DDD group of drugs (dichlorodiphenyl-dichloroethane derivatives) – perten, mitotane, chloditan. Other options include aminoglutethimide derivatives (mamamit, orimiten) and ketoconazole derivatives (Nizoral).

A diagnosis of **corticosteroid-producing tumor** (**corticosteroma**) is an indication for surgical intervention. The earlier the surgery is performed, the better the chances for a favorable outcome. The only contraindication to surgery is the presence of distant metastases in malignant corticotropin-secreting tumors. Even a severely compromised patient with pronounced metabolic and trophic disturbances should not be considered inoperable; refusing surgery in such cases condemns the patient to inevitable death.

Atrophy of the contralateral adrenal gland creates conditions for the development of acute adrenal insufficiency after removal of a corticotropin-secreting tumor (corticosteroma). Therefore, prevention of postoperative hypocorticism must be given special attention. The primary focus during preoperative preparation of these patients

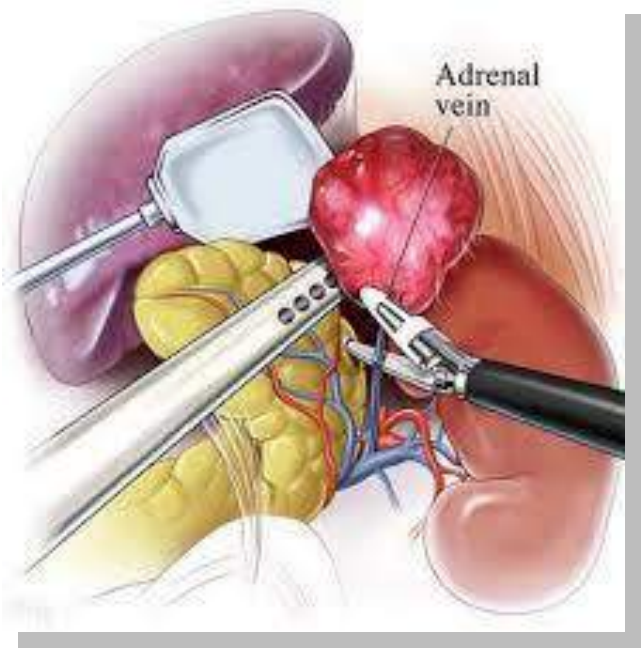
should naturally be on the administration of steroid hormones. The absence of necessary medications in the hospital effectively precludes surgical treatment in patients with total hypercorticism.

Even today, when steroid preparations are widely available, many issues regarding corticosteroid therapy during surgical management of patients with corticotropin-secreting tumors remain unresolved.

Existing protocols for preoperative preparation and postoperative corticosteroid administration in these patients vary in dosages, duration of treatment, and routes of administration. Insufficient hormone administration can lead to acute or chronic hypocorticism, whereas excessive doses suppress ACTH secretion by the pituitary, preventing adequate stimulation of the remaining adrenal gland. In addition, saturating the body with corticosteroids hinders the regression of the clinical signs of hypercorticism and negatively affects surgical wound healing.

When discussing **adrenalectomy**, we refer to **total** unilateral or **bilateral** adrenalectomy.

Bilateral adrenalectomy is a procedure aimed at eliminating the cause of the disease and saving the patient's life.



Adrenalectomy is performed under endotracheal anesthesia. An open adrenalectomy can be performed using several surgical approaches: transabdominal, extraperitoneal, transthoracic, and thoracophrenolumbotomic.

In recent years, endoscopic adrenalectomy with video monitoring has been increasingly used for the removal of adrenal glands and their tumors, including laparoscopic and retroperitoneoscopic adrenalectomy.

Destruction of the Adrenal Glands

This method involves, the destruction of a hyperplastic adrenal gland by injecting a contrast agent into it. After diagnostic adrenal venography, the central vein of the gland is occluded with a catheter, and then the adrenal gland is destroyed by over-injecting radiopaque contrast into the gland's vascular system. Other methods include electrocoagulation of the adrenal vessels and surrounding parenchyma, as well as injection of sclerosing agents into the vascular system and embolization of adrenal

vessels. However, this method is rarely used as monotherapy and is mainly a preparatory step, especially prior to laparoscopic adrenalectomy.

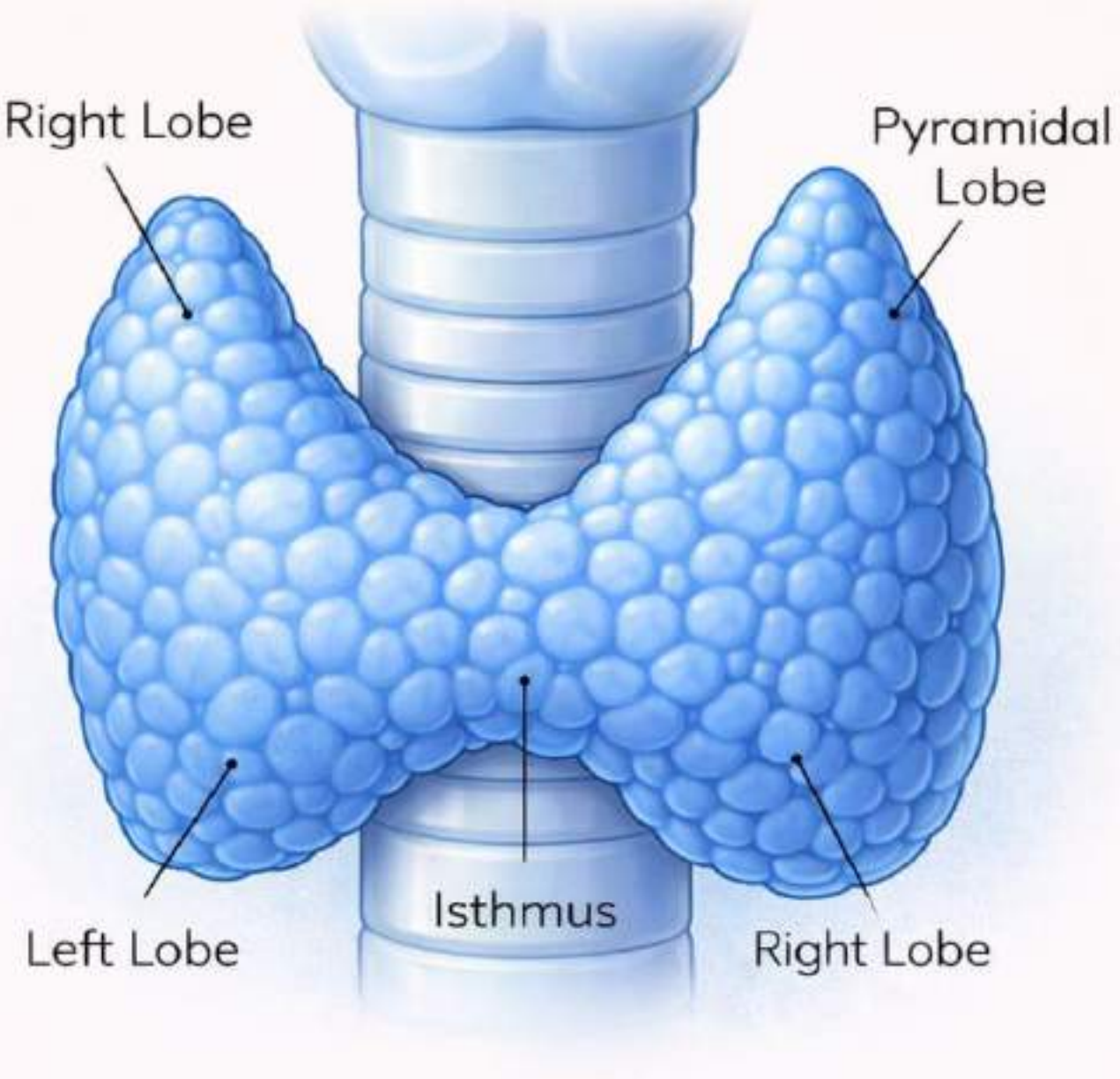
Prognosis

The prognosis of benign corticoid-producing adrenal tumors (corticosteromas) is favorable with proper treatment. Within the first 1.5–2 months after tumor removal, clinical symptoms gradually regress: the patient's appearance normalizes, metabolic processes stabilize, blood pressure returns to normal, striae and facial changes fade, and sexual function recovers. Preoperative diabetes often disappears. In the early postoperative months, patients often experience significant weight loss (sometimes more than 20 kg), and hirsutism usually resolves within 3–8 months. Radiographic signs of bone tissue recovery appear within 10–12 months, although bone pain resolves within 1–2 months after surgery.

In the long term, chronic adrenal insufficiency develops in 5–7% of patients, usually manifesting during infections.

For malignant tumors, surgical outcomes are usually unsatisfactory. The recurrence of clinical hypercortisolism at various times after surgery may indicate distant metastases. However, there are reports in the literature of remission lasting more than 20 years following surgery for malignant corticosteroma.

Thyroid Gland



Thyroid Gland

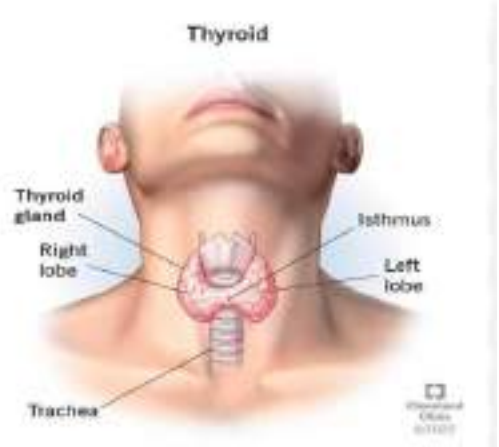
Embryogenesis

Along with the parathyroid glands, the thyroid gland is **one of the earliest organs to develop** ontogenetically. The primordium of the thyroid appears in humans during the 3rd–4th week of intrauterine development, and according to some sources, even as early as the 2nd week.

During embryonic development, the thyroid arises from an outpouching of the cranial end of the endodermal gut epithelium. This primordium later corresponds to the foramen cecum at the root of the tongue. The epithelial primordia transform into the epithelium-lined thyroglossal duct, which later completely atrophies. The lower remnants of this duct form the pyramidal lobe and the isthmus of the thyroid.

Knowledge of embryological development is crucial for understanding the variety of congenital anomalies of the thyroid gland, which often only manifest as disorders in adulthood. The most common anomalies include:

- Thyroid tissue at the midline of the tongue root, forming a lingual thyroid nodule.
- Persistent thyroglossal duct, which can appear as a cyst or, along its full length, as a fistula.
- Thyroid primordium descending abnormally, failing to remain in the neck and reaching the mediastinum, where it may develop into a mediastinal or intrathoracic goiter, sometimes mistaken for a mediastinal tumor.



Anatomy

The thyroid gland (glandula thyreoidea) is the largest endocrine gland. It was first described by Vesalius in 1543. The thyroid is located on the anterior surface of the neck and consists of two lobes and an isthmus. Its shape resembles a butterfly.

The gland is situated in front of the trachea, directly below the thyroid cartilage of the larynx. It has two lateral lobes on either side of the trachea, connected by the isthmus. The weight of the thyroid is 25–30 grams in adults, and 1–2 grams in newborns.

During pubertal development, the thyroid gland rapidly increases in size, while by the age of 50, it undergoes gradual involution.

The dimensions of each lobe are approximately:

- **Length:** 6–8 cm
- **Width:** 2–4 cm
- **Thickness:** 1.5–2.5 cm

Each lobe has **two poles** (upper and lower) and **two layers** (visceral and parietal). The right and left lobes of the thyroid are located at the level of the thyroid cartilage of the larynx, and their lower poles reach the 5th–6th tracheal rings. The lobes partially contact the pharynx and esophagus and cover the medial half of the common carotid arteries in their middle third.

The isthmus is situated in front of the trachea at the level of the 1st–3rd or 2nd–4th tracheal rings. Approximately 50% of individuals have a pyramidal lobe (lobus pyramidalis), which may arise from the isthmus or one of the lobes. In some cases, the isthmus may be absent. Anteriorly, the thyroid is covered by the sternohyoid, sternothyroid, and omohyoid muscles (mm. sternohyoidei, sternothyroidei, omohyoidei).

Externally, the gland is surrounded by the fourth cervical fascia, which consists of two layers—outer (parietal) and inner (visceral):

- The inner (**visceral**) layer is thinner and envelops the organs of the neck, including the pharynx, esophagus, larynx, and thyroid gland.
- The outer (**parietal**) layer lies anterior and lateral to the neck organs, adheres to the posterior wall of the muscle sheath (sternohyoid, sternothyroid, thyrohyoid, omohyoid), and forms a vascular-neural sheath for the common carotid artery, internal jugular vein, and vagus nerve in the carotid triangle.

Additionally, the thyroid has its own **capsule** (tunica fibrosa, capsula propria), from which connective tissue septa extend into the gland, dividing it into lobules. Between the inner layer of the fourth cervical fascia and the thyroid capsule lies loose connective tissue, which contains arteries, veins, nerves, and parathyroid glands. The dense fibers of the fourth cervical fascia form thyroid ligaments:

- The median ligament runs transversely from the thyroid isthmus to the cricoid cartilage.
- Lateral ligaments connect the thyroid lobes to the thyroid and cricoid cartilages and the first tracheal ring.

The thyroid **blood supply** is mainly via the paired superior and inferior thyroid arteries (aa. thyreoidei superiores et inferiores):

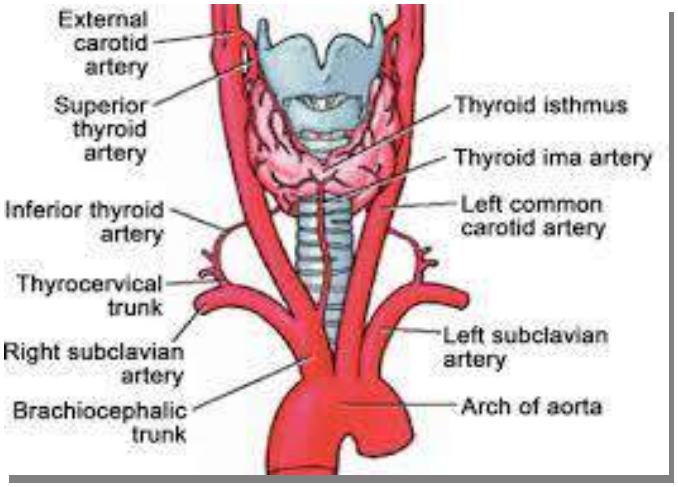
- Superior thyroid arteries arise from the external carotid arteries
- Inferior thyroid arteries arise from the thyrocervical trunk of the subclavian artery

In about 12% of cases, there is an unpaired fifth artery (a. thyreoidea ima), arising from the brachiocephalic artery or the aortic arch. Corresponding veins form venous plexuses, from which the inferior and ima thyroid veins drain, with the latter emptying into the left brachiocephalic vein.

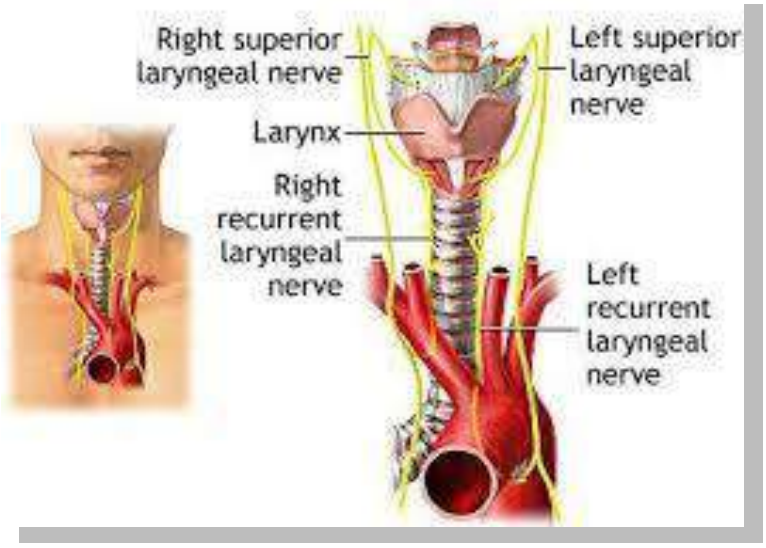
The thyroid arteries form two collateral systems:

- Intra-organ
- Extra-organ, through anastomoses with vessels of the pharynx, esophagus, larynx, trachea, and surrounding muscles.

The anatomical location of the thyroid gland, along with the surrounding organs and tissues, is shown in the figure. Surgical risks are explained by the close relationship of the gland with major blood vessels and the recurrent laryngeal nerve.



The blood supply to the thyroid is extremely rich. In a normally functioning thyroid, 40–60 ml of blood per minute flows through the gland; in cases of hyperthyroidism, this amount can reach up to 1000 ml per minute.



Innervation of the thyroid gland is provided by sympathetic and parasympathetic nerves, which arise from the sympathetic trunk and both laryngeal nerves.

Lymphatic drainage from the thyroid flows to lymph nodes located in front of and alongside the trachea.

Three types of cells are found in the thyroid.

The main bulk of the gland consists of **A-cells** of the follicular epithelium (thyrocytes), which synthesize thyroid hormones.

B-cells (Hürthle–Askanazy cells) accumulate serotonin and other biogenic amines. Many researchers consider B-cells to be modified thyrocytes, appearing in the thyroid only under various pathological conditions.

In the interfollicular connective tissue, there are **C-cells** (parafollicular cells), which produce calcitonin.

Physiology:

The thyroid gland secretes iodine-containing hormones – **triiodothyronine (T3)** and **thyroxine** (**T4**) – as well as non-iodinated calcitonin. The main components of thyroid hormones are iodine and the amino acid tyrosine.

Iodine enters the body from food and water in the form of inorganic and organic compounds. Excess iodine is excreted in urine and bile. The physiological intake of iodine is 110–140 µg/day. Iodine compounds exist in the body as potassium and sodium iodides, which are converted to elemental iodine by oxidative enzymes.

Folicular cells of the thyroid take up iodine from the blood. In these cells, thyroglobulin is synthesized and secreted into the follicular lumen via exocytosis. In the colloid, iodine undergoes organification, meaning it binds to protein and condenses into iodotyrosines. The colloid is then reabsorbed by thyrocytes and undergoes proteolysis, releasing the thyroid hormones into the blood.

Most circulating thyroxine (T4) binds to plasma proteins, mainly thyroxine-binding globulin (TBG) and prealbumin.

Regulation: Thyroid hormone synthesis and secretion are regulated by the hypothalamus, which produces thyrotropin-releasing hormone (TRH). TRH stimulates thyroid-stimulating hormone (TSH) secretion by basophilic cells of the anterior pituitary. The levels of TRH and TSH are controlled by thyroid hormone levels in the blood, forming a negative feedback loop between the CNS, pituitary, and thyroid.

Physiological action of TSH includes stimulation of thyrocyte proliferation. With age, thyroid hormone levels gradually decline, while TSH levels rise.

Physiological effects of thyroid hormones:

- Stimulate oxidative-reductive processes
- Increase tissue oxygen consumption
- Participate in all types of metabolism – water-salt, protein (catabolic effect), fat, carbohydrate, and energy metabolism
- Stimulate protein synthesis
- Enhance intestinal absorption of glucose and galactose and their utilization in tissues
- Activate glycogen breakdown and reduce liver glycogen content

Organ and tissue sensitivity to thyroid hormones. Different organs and tissues of the human body respond differently to thyroid hormones. **Thyrocalcitonin**, along with

parathyroid hormone (PTH), regulates the metabolism of calcium and phosphorus in the body.

Epidemiology: Historically, thyroid disease was primarily associated with geobiochemical factors, and iodine deficiency was considered the leading cause of various forms of goiter. Currently, additional factors related to human activity have emerged, such as environmental pollution with radioactive substances and chemical carcinogens from industrial enterprises, technological disasters, and other sources.

It should be noted that the increase in the number of patients is associated not only with higher disease incidence but also with the widespread implementation of highly effective diagnostic technologies. Studies show that the rise in goiter incidence is mainly due to nodular forms, and among nodular goiters, the proportion of thyroid cancer is increasing.

Thus, accurate and detailed global data on thyroid pathology prevalence are still lacking. Many studies indicate an increase in various forms of goiter, primarily nodular goiter and thyroid cancer. The rising incidence is linked not only to iodine deficiency but also to environmental pollution and other contributing factors [49].

Classification of thyroid diseases

WHO classification (1994):

- **Grade 0**: No goiter
- **Grade I**: Lobes exceed the size of the distal phalanx of the thumb; the goiter is palpable but not visible
- **Grade II**: The thyroid is palpable, and its enlargement is visible to the eye

This classification is convenient for mass screening, but it is less suitable for nodular goiter, cannot be applied to retrosternal goiter, and phalange size is an unreliable parameter.

Currently, it is more practical to classify goiter based on ultrasound measurements, which allow detection of nodules as small as 5 mm, usually undetectable by palpation, and to calculate the overall thyroid volume.

In surgical practice, it is reasonable to classify cervico-mediastinal goiters by degree. This classification takes into account signs of compression of the neck and mediastinal organs (primarily the esophagus and trachea), i.e., the presence of compressive syndrome.

- **Grade I** – the lower poles of the thyroid lobes tend to extend behind the sternum;
- **Grade II** – the lower poles of the thyroid lobes are retrosternal but can be brought forward to the neck during palpation while swallowing;
- **Grade III** – the retrosternal lower portions of the thyroid cannot be brought forward to the neck during palpation while swallowing;
- **Grade IV** – only the upper tips of the thyroid lobes are palpable on the neck;
- **Grade V** – the entire goitrous thyroid gland is located in the mediastinum (intrathoracic goiter).

Classification of thyroid diseases should reflect:

- its functional state,
- morphological changes in the gland, and
- be based on etiopathogenetic features.

Since many thyroid diseases are treated surgically, the classification should also have practical surgical significance.

Based on the analysis and synthesis of various practical classifications, the following generalized classification is recommended:

I. Congenital developmental anomalies

1. Aplasia and hypoplasia
2. Ectopy (lingual thyroid, intrathoracic goiter, etc.)
3. Persistence of the thyroglossal duct (cysts and neck fistulas)

II. Endemic goiter

1. By form: diffuse, nodular, mixed
2. By functional status:
    - euthyroid
    - hypothyroid (hypothyroidism):
      a) primary (thyrogenic), congenital or acquired
      b) secondary
3. By severity: mild, moderate, severe

III. Sporadic goiter

1. By form: diffuse, nodular, mixed
2. By function:
   a) euthyroid
   b) hypothyroid
3. c) Hyperthyroid (thyrotoxicosis) – primary toxic, secondary toxic.

IV.Stages of thyrotoxicosis:

a) Neurovegetative stage
b) Neuroendocrine stage
c) Visceropathic stage
d) Cachectic stage

V.Epithelial tumors

A) Benign: follicular adenoma
B) Malignant:

- Papillary carcinoma
- Follicular carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Medullary carcinoma

VI. Non-epithelial tumors

1. Fibrosarcoma
2. Others (fibroma, leiomyoma, hemangioma, chemodectoma, etc.)

VII. Mixed tumors

1. Carcinosarcoma

2. Malignant hemangioendothelioma
3. Lymphomas
4. Teratomas

VIII. Secondary (metastatic) tumors

IX. Unclassifiable tumors

X. Autoimmune diseases

1. Hashimoto's thyroiditis
2. Riedel's thyroiditis

XI. Inflammatory diseases

1. Acute thyroiditis
2. Subacute thyroiditis
3. De Quervain's thyroiditis
4. Tuberculosis
5. Syphilis

XII. Parasitic diseases

1. Echinococcosis

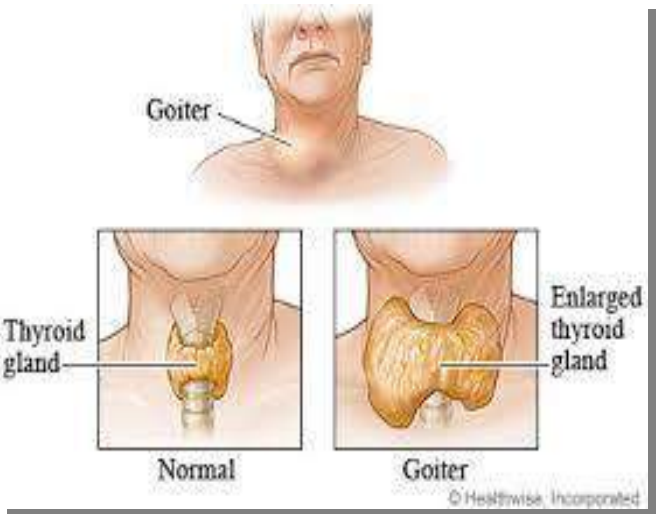
XIII. Fungal infections

1. Actinomycosis
2. Aspergillosis
3. Candidiasis
4. Coccidioidomycosis
5. Madura foot (Madura mycosis)

XIV. Rare diseases:

1. Amyloidosis
2. Sarcoidosis

Diagnosis



I. General Clinical Assessment

A careful analysis of the patient's complaints, behavior, and appearance, as well as the data obtained from physical examination, helps evaluate thyroid status. This allows suspicion of hypo- or hyperfunction of the thyroid gland, which guides the choice of further patient investigations.

II. Visual Assessment of the Thyroid Gland

Visual evaluation of the thyroid region is more informative when examined in a lateral projection. Thyroid enlargement can be symmetrical or asymmetrical. Dilated subcutaneous veins of the neck and anterior chest wall, as well as puffiness of the neck and face, indicate the presence of a compression syndrome caused by the constriction of a large goiter within the rigid bony ring of the thoracic inlet. Changes in the skin color over the gland and its swelling may result from an acute inflammatory process, occur in toxic goiter, or indicate invasion of the subcutaneous tissue by a primary nodule of a malignant thyroid tumor.

III. Palpation of the Thyroid Gland

During palpation of the thyroid, it is possible to determine its shape, size, consistency, the presence or absence of tenderness, and the degree and type of enlargement (diffuse or nodular). If nodules are present, one can assess their number, size, consistency, mobility, and surface characteristics.

Using palpation, nodules with a diameter of 1.0 cm or more can be detected. Thyroid palpation is performed from behind the patient. Using four fingers of each hand, the physician assesses the structure, consistency, size, and position of the thyroid lobes. The patient is then asked to swallow saliva or water. At this moment, the thyroid and any neoplasms arising from it move synchronously with swallowing because the thyroid is closely connected to the larynx and pharynx via the visceral layer of the fourth cervical fascia.

Additionally, during swallowing, the extent of substernal goiter, its mobility, and the position of the trachea relative to the midline of the neck can be assessed. The patient's chin is usually positioned horizontally or slightly lowered during palpation. In patients with a short neck, palpation may be more effective with the patient lying horizontally and a pillow under the shoulder blades. The physician stands at the side of the patient.

IV. Hormonal Studies

Levels of T3, T4, TSH, TRH, and thyro-calcitonin in serum can be determined using enzyme-linked immunosorbent assays (ELISA) or radio-immuno-assays to evaluate thyroid status and secretion abnormalities.

The hypothalamic-pituitary-thyroid system operates on **negative and positive feedback principles**, where tissue levels of thyroid hormones regulate the production

of hypothalamic thyrotropin-releasing hormone (TRH), which controls the synthesis and release of thyroid-stimulating hormone (TSH) from the pituitary.

- **TRH** – a hypothalamic stimulator of TSH and prolactin secretion. As a peptide hormone, TRH interacts with membrane receptors on pituitary cells, regulating the biosynthesis and release of TSH into the pituitary portal system.
- **TSH** – binding of TSH to specific receptors on thyrocytes activates the adenylate cyclase system, stimulating synthesis and release of thyroid hormones into the bloodstream.

In primary hypothyroidism, TSH levels are elevated. Low TSH levels in hypothyroidism indicate pituitary or hypothalamic insufficiency and exclude primary thyroid dysfunction.

In hyperthyroidism, TSH levels are usually decreased, except in rare cases of TSH-dependent thyrotoxicosis.

Radioimmunological assays allow measurement of total T3 (normal: 1.2–2.8 nmol/L) and T4 (normal: 64–146 nmol/L). Typically, hyperthyroidism, regardless of origin, is characterized by elevated levels of both thyroid hormones in the blood.

Hypothyroidism is characterized by decreased levels of T4 and T3 in the blood. However, T3 is a less reliable indicator because its level may remain normal in mild to moderate hypothyroidism, and it is often decreased in patients with non-thyroidal illnesses.

Immunoassay methods expand the understanding of pathogenesis and diagnostic capabilities, as they allow determination of biologically active free thyroid hormones.

- **Free T3** is formed 80% in peripheral tissues through deiodination of T4, while only 20% is directly produced by the thyroid gland. Normal levels of free T3 range from 2.5 to 5.8 pg/mL and, like T4, largely depend on age.
- **Free T4** reflects thyroid function more reliably than total T4. Its normal level is 11–25 pg/mL.

Determination of antibodies to thyroglobulin, microsomal fraction, and anti-receptor autoantibodies (thyroid-stimulating immunoglobulins) helps in diagnosing autoimmune thyroid diseases, such as autoimmune thyroiditis and diffuse toxic goiter.

- **Thyroglobulin** (TG) in serum is used for early detection of recurrences and metastases of well-differentiated thyroid cancer in operated patients, to assess the effectiveness of radioiodine therapy (monitoring the decrease of TG levels to normal), and to evaluate the severity of thyrotoxicosis and monitor treatment effectiveness.
- **Thyrocalcitonin** is a diagnostic marker for medullary thyroid carcinoma, used for screening patients with hereditary and sporadic forms, as well as for early detection of recurrences and metastases of medullary thyroid cancer.

IV. Reothyreography

Electroplethysmography is a non-invasive method based on registering changes in the resistance of the organ under study, which occur due to volumetric fluctuations of its blood filling.

Reothyreography, with a high degree of reliability (86%), allows:

- Differential diagnosis between thyroid cancer and nodular euthyroid goiter.
- Assessment of functional activity of tumors in nodular goiter, indirectly suggesting the nature of morphological changes.
- In toxic adenoma, to specify the localization of the pathological process within the gland.
- To determine the extent of changes in the thyroid in diffuse toxic goiter.

V. Radiologic Diagnostic Methods

Ultrasound (US) – is the first highly effective and screening method for diagnosing thyroid diseases. It is based on the different propagation speeds of sound in tissues of varying density.

Key advantages of ultrasound:

- No radiation exposure
- Non-invasive
- Mobility
- Ability to perform repeated examinations over time (dynamic monitoring)
- Multi-positional evaluation
- Fine-needle aspiration biopsy under ultrasound guidance

The sensitivity and specificity of ultrasound are high, especially when combined with color Doppler mapping and 3D imaging.

Ultrasound allows precise determination of:

- Thyroid size
- Calculation of volume and mass
- Degree of vascularization
- Nature of lesions (structure, density)
- Topographical relationships with neck organs
- Status of regional lymph nodes

Thyroid lobe volume formula:

Volume of lobe (ml)=A×B×C×0.479\text{Volume of lobe (ml)} = A \times B \times C \times 0.479Volume of lobe (ml)=A×B×C×0.479

Where:

- AAA – length

- BBB – width
- CCC – thickness
- 0.479 – conversion factor for an ellipsoid shape

Normal thyroid lobe volume:

- Men: up to 25 ml
- Women: up to 18 ml

VI. Radioisotope Diagnostics

Radioisotope studies of the thyroid are based on the selective uptake of radioactive iodine by thyrocytes and its incorporation into metabolism. This allows visualization of the thyroid and assessment of its functional activity.

- Most commonly used: I-131
- Less commonly: I-123
- Other isotopes: Tc-99m pertechnetate, which is taken up similarly to iodine by the thyroid but is not incorporated into thyroid metabolism.

Over recent decades, the indications for radioisotope diagnostics with iodine or technetium have narrowed significantly.

Currently, it is considered that thyroid scanning provides no additional information for:

- Diffuse toxic goiter
- Multi- or single-nodular euthyroid goiter

It also cannot differentiate between autoimmune thyroiditis and multinodular goiter.

Moreover, there is a real risk of radio-induced thyroid cancer from the carcinogenic effects of I-131, which necessitates cautious use of this method, especially in children and adolescents. However, in certain clinical situations, radionuclide scanning with iodine isotopes is an indispensable diagnostic method that plays a decisive role in selecting the treatment strategy.

- Surgical planning for recurrent goiter: Scanning is invaluable for identifying functioning thyroid tissue and determining whether surgery is required on one or both sides.
- Differential diagnosis: Scintigraphy allows differentiation between a toxic adenoma and diffuse toxic goiter with a nodule, which affects the surgical approach (hemithyroidectomy for the former, subtotal thyroidectomy for the latter).
- It also helps distinguish multinodular toxic goiter from diffuse toxic goiter with nodules.
- Scintigraphy is crucial for diagnosing ectopic thyroid tissue or aberrant goiters, guiding treatment strategy. Removing ectopic thyroid tissue can result in severe hypothyroidism or cretinism, necessitating a more conservative approach in cases of thyroid ectopia.

VII. Radiologic Methods

The most commonly used radiologic method is X-ray imaging of the cervicothoracic region with esophageal contrast. This technique allows:

- Assessment of the extent of goiter spread behind the sternum
- Detection of deviations or compression of the esophagus and trachea
- Approximate evaluation of the extent and severity of structural changes
- Identification of radiopaque calcifications

For a more detailed assessment of the upper airways, tomography of the larynx and trachea can be performed, providing sectional images of these structures.

Even more complete visualization is achieved with computed tomography (CT) of the neck and mediastinum:

- CT slices at the chest level show the extent of goiter spread into the mediastinum
- CT slices at the neck level reveal non-palpable changes in the thyroid parenchyma

Angiographic findings can help differentiate benign from malignant thyroid lesions.

- Selective arteriography through the thyrocervical trunk or inferior thyroid artery facilitates the detection of "hidden" thyroid cancers, allowing identification of foci as small as 3–15 mm in diameter.

VIII. Morphological Diagnostics

Trepan biopsy (TB) has a high resolution, as it allows evaluation of the thyroid at the tissue level. Simultaneously with histological examination, it is possible to study imprint smears obtained by scraping the tissue surface.

False-negative results may occur due to technical errors in performing TB or difficulties in the morphological interpretation of the micro-preparation. Verification of diagnosis using this method reaches 96%.

In recent decades, a less invasive method of morphological diagnostics has become widely used – fine-needle aspiration biopsy (FNAB). This is a cytological examination method, where material is obtained by puncturing the thyroid with a 10 ml syringe equipped with a 21–25G needle, followed by aspiration after the needle is inserted into the lesion.

Some authors recommend obtaining material without additional syringe aspiration, as aspiration can dilute the sample with blood, significantly complicating cytological analysis and increasing the risk of error.

Informative value of FNAB ranges from 52.3% to 93.6%, with diagnostic accuracy ranging from 70% to 97%.

According to international standards, to avoid false-negative results in nodular goiter, six aspirations of the nodule are required, and at least two separate smears must each contain six clusters of epithelial cells.

For dynamic monitoring of the nodular lesion, FNAB should be performed at least twice a year. However, information on how long patients with thyroid nodules should be followed, as well as the processes occurring in the thyroid parenchyma in the short- and long-term post-biopsy period, is lacking in the global literature.

Nodular formations less than 1 cm and larger than 4 cm in diameter are difficult to diagnose using FNAB, as the former are challenging for targeted biopsy, while the latter contain extensive areas of hemorrhage and necrosis, which significantly complicates the collection of informative material.

FNAB under ultrasound guidance – the "gold standard" in the diagnosis of thyroid diseases – significantly increases the diagnostic value of the procedure by providing visual control over the advancement of the needle through the tissue. This method allows sampling from the precise area of the gland, as well as choosing the optimal direction and depth of the puncture.

The final stage of morphological diagnostics is planned histological examination, the accuracy of which is significantly increased by using immunohistochemical methods – sets of antibodies to epithelial markers.

Endemic goiter

Endemic goiter is a disease characterized by a progressive enlargement of the thyroid gland with varying functional activity, affecting large segments of the population in a specific geographic area. The disease occurs in regions where the soil—and consequently the water and food—are deficient in iodine.

The iodine content in soil ranges from 50 to 9,000 μg/kg, depending on the depth of freezing during the last glacial period. The melting of glaciers caused iodine to be washed out from the soil into the layers below the fertile topsoil. The most severe endemic goiters are observed in mountainous regions.

In addition to environmental iodine deficiency, another factor contributing to the severity of endemic goiter is ecological pollution of the area.

The human body contains only 15–20 mg of iodine, and the daily requirement is 0.15–0.20 mg. The richest sources of iodine for humans are marine fish and seafood (800–1,000 μg/g), and seaweed (5,000–900,000 μg/g).

With insufficient iodine intake, thyroid hormone synthesis is impaired, and consequently, thyroid functional activity decreases. Clinical manifestations of endemic goiter do not always appear immediately. This is explained by the body's adaptive mechanisms to iodine deficiency. Several such mechanisms are known:

1. **Compensatory increase in TSH**: Iodine deficiency leads to reduced levels of thyroid hormones, which via negative feedback increases TSH levels. Elevated TSH promotes hyperplasia of thyroid parenchymal cells, enhancing iodine uptake. High TSH also directly increases the process of iodine absorption by

thyrocytes. Thus, the amount of iodine absorbed by the thyroid increases severalfold under deficiency conditions.

2. **Altered hormone synthesis**: With low iodine intake, the thyroid preferentially synthesizes the more active hormone triiodothyronine (T3) instead of thyroxine (T4), which reduces overall iodine consumption.
3. **Increased turnover of thyroid hormones**: High TSH levels accelerate thyroid hormone synthesis and metabolism, which speeds up iodine recycling in the gland.
4. **Conversion of T4 to T3**: In iodine deficiency, the body maintains high thyroid activity by increasing the conversion of T4 to the more active T3.

Clinical manifestations of iodine deficiency vary depending on the severity of endemic goiter and the age of the person. Prominent features include hypothyroidism, elevated TSH, follicular cell hypertrophy and hyperplasia, and thyroid enlargement.

Auxiliary diagnostic methods for assessing iodine deficiency include measuring TSH, thyroid hormones, and thyroglobulin levels. Previously, the degree of iodine deficiency was assessed based on iodine content in soil and water. Currently, for epidemiological studies, it is recommended to measure urinary iodine (ioduria), since 70–80% of iodine is excreted via the kidneys, and urinary concentration accurately reflects dietary intake. The volume of the thyroid gland is determined using ultrasound.

The most severe form of iodine deficiency is **endemic cretinism**. This is a congenital condition associated with reduced thyroid activity in both the pregnant woman and the fetus, leading to impaired central nervous system development in the child. The only preventive measure for this condition is the administration of an adequate amount of iodine before conception or during the first weeks of pregnancy.

In children living in iodine-deficient regions, classical endemic cretinism may not develop, but endemic subcretinism is often observed. These children experience delayed mental development, have difficulty learning in school, often suffer from hearing impairment, and may have speech disorders.

In adults, iodine deficiency in the diet leads to reduced physical and mental performance. Affected individuals tire easily, frequently suffer from respiratory infections, and may develop early atherosclerosis. In women of childbearing age, there is a high incidence of infertility or miscarriage.

Treatment of endemic goiter should begin with **iodine supplementation** in physiological doses. This restores thyroid function, normalizes T3, T4, and TSH levels, and reduces goiter size. Thyroid hormone preparations are prescribed if the goiter persists after six months of iodine therapy.

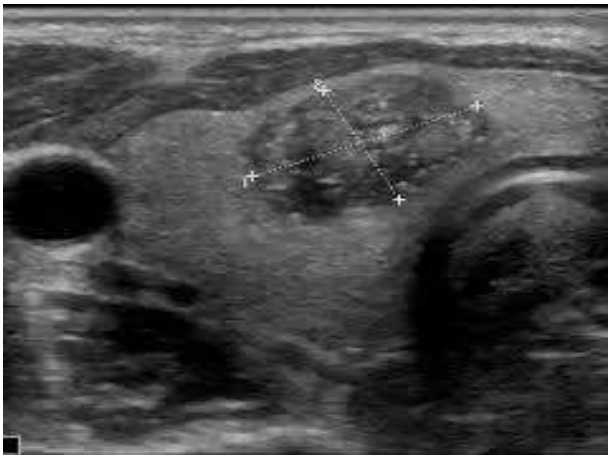
Surgical treatment for endemic goiter is generally not indicated. Exceptions include patients with nodular formations within a diffuse goiter or signs of compression of

neck and mediastinal organs after conservative therapy. The techniques and extent of surgery do not differ from those used for various forms of sporadic goiter.

The most widely recognized method of mass iodine prophylaxis is **iodization of table salt**. This method allows for coverage of the entire population living in iodine-deficient regions at minimal financial cost. The standard iodine content in salt is 40 ± 15 μg/g, which aligns with international recommendations.
For group or individual iodine prophylaxis, children of any age are recommended to receive 150–200 μg of iodine per day in the form of potassium iodide tablets.

Nodular Euthyroid Goiter

The term “nodular euthyroid goiter” encompasses various pathological conditions that share common clinical features: the presence of a localized (nodular) enlargement of the thyroid gland, which can be detected by palpation or other diagnostic methods, and which differs from the surrounding tissue in consistency or other characteristics, while the patient maintains a euthyroid state.



This group includes focal hyperplasias, adenomas, cysts, malignant tumors, autoimmune thyroiditis, subacute thyroiditis, lymphomas, and several other conditions.

The main reason for the increase in the incidence of thyroid cancer (TC) and nodular goiter is the worsening of the environmental situation and the carcinogenic effect of even small doses of external radiation.

As a rule, nodular formations with a diameter of about 10 mm or more are detectable by palpation. Nodules located deep within or on the posterior surface of the thyroid are difficult to detect by palpation. The widespread use of ultrasound (US) in thyroid examinations has allowed a significantly more objective assessment of the prevalence of focal changes.
Worldwide, thyroid nodules are more frequently detected in women than in men, with the female-to-male ratio ranging from 1.2:1 in Belgium to 4.3:1 in the USA.

Currently, there is no consensus on the exact causes of nodular thyroid hyperplasia. Most domestic and foreign researchers associate the prevalence of nodular goiter with chronic iodine deficiency. Some studies emphasize the role of hereditary factors in the formation of nodular hyperplasia. These authors explain the genesis of nodule formation by the presence of cells within the follicular epithelium that have a genetically determined high proliferative potential.

Diagnosis:

The goal of any examination when a thyroid nodule is detected is to determine the subsequent management strategy: observation, conservative treatment, or surgical intervention. The final decision usually depends on determining whether the tumor is benign or malignant, assessing the functional status of the identified nodule, evaluating the size of the goiter, and determining the severity of compression symptoms on the trachea, esophagus, major vessels, and nerves.

The presence of symptoms such as rapid growth of a thyroid nodule, its firm consistency, vocal cord paresis, enlargement of regional lymph nodes, or a history of head or neck radiation indicates a high risk of malignancy. In such cases, histological confirmation of the diagnosis should be pursued rigorously, regardless of additional test results. However, these symptoms often reflect advanced malignant disease, which significantly worsens the prognosis, even when surgery is performed adequately. Currently, ultrasound (US) has become the most accessible and widely used method for examining the thyroid. Compared to radionuclide scanning, US has high sensitivity for detecting thyroid nodules, including those of small size. Common US features suggestive of thyroid cancer include:

- **Irregular and unclear margins** of the nodule
- **Absence of a peripheral halo**
- **Heterogeneous echotexture**
- **Lack of posterior acoustic enhancement**

Computed tomography **(CT)** and magnetic resonance imaging **(MRI)** can provide additional information, but their widespread use is limited by high cost and low accessibility.

Fine-needle aspiration biopsy (FNAB) plays an important role in the differential diagnosis of thyroid nodules. Authors with extensive experience in FNAB note the high diagnostic value of the method. To improve accuracy, FNAB is recommended under US guidance, which can achieve a diagnostic accuracy of 90% or higher.

The main source of diagnostic errors in FNAB is obtaining non-representative material (insufficient for interpretation). According to various studies, the rate of non-representative samples ranges from 0.2% to 30%, largely depending on technique and the experience of the performing physician.

It is important to remember that all patients at high clinical risk of malignancy require surgical intervention, regardless of US or FNAB results. Similarly, patients with low clinical risk should undergo surgery if FNAB results are inconclusive.

Cervicomediastinal goiter. According to various authors, the frequency of cervicomediastinal goiters ranges from 1% to 31%. These goiters are classified as primary or secondary and can be categorized by location. Additionally, they are classified as:

- **Cervicomediastinal** – most of the goiter is located in the neck
- **Mediastinocervical** – most of the goiter is in the chest

- **Intrathoracic** – entirely within the mediastinum

Primary intrathoracic (mediastinal) goiter develops from ectopic thyroid tissue and is extremely rare, accounting for no more than 1% of all cervicomediastinal goiters. Most mediastinal goiters are secondary, arising from thyroid tissue that has descended from the neck into the mediastinum; therefore, the term "cervicomediastinal goiter" is more precise.

Blood supply to these goiters comes from the superior and inferior thyroid arteries.

Factors determining the descent of thyroid tissue into the mediastinum include:

1. A **wide superior thoracic aperture**, especially in patients with a brachymorphic body type.
2. **Increasing thyroid mass** in nodular or diffuse goiters.
3. **Negative intrathoracic pressure**, which "pulls" the thyroid downward.
4. **Force of the anterior neck muscles**, which promotes the downward and backward spread of the enlarging thyroid.

In 1992–1993, A.F. Romanchishin proposed a classification of cervicomediastinal goiter, identifying five degrees:

- **Grade I**: Thyroid nodules are primarily in the neck but show a tendency to extend behind the sternum when the above factors are present.
- **Grade II**: A significant portion of the thyroid has descended below the jugular notch of the sternum, but can be easily drawn back onto the neck during swallowing.
- **Grade III**: During swallowing, the thyroid cannot be fully extracted, and the mediastinal portion is not palpable.
- **Grade IV:** Only the upper poles of the thyroid lobes are palpable in the neck; the majority of the gland lies behind the sternum.
- **Grade V:** The thyroid is entirely intrathoracic, representing mediastinal thyroid ectopia.

Most common symptoms of cervicomediastinal goiter due to compression of neck and mediastinal structures

Symptoms of cervicomediastinal goiter

System:	Symptoms:
Respiratory	Dyspnea, stridor, suffocation
Esophageal	Dysphagia, sensation of a "lump in the throat"
Vascular	Superior vena cava syndrome, angina attacks, cerebral edema, gastrointestinal bleeding
Neurological	Paresis/paralysis of vocal cords, hoarseness
Metabolic	Thyrotoxicosis, weight loss

During physical examination of patients with cervicomediastinal goiter, the thyroid is usually partially or fully palpable in the neck; however, in 10–20% of patients, it

cannot be palpated at all. Therefore, additional diagnostic methods are often required to confirm the diagnosis.

Radiographic examination of the chest in two projections with esophageal contrast allows the detection of mediastinal masses with fairly high accuracy. A radiographic sign suggesting the presence of a cervicomediastinal goiter may be tracheal deviation. Fluoroscopy can determine whether the detected mass moves during swallowing, which confirms the diagnosis.

For precise localization of the mediastinal mass and assessment of its relationship with surrounding organs and tissues, CT (computed tomography) and MRI (magnetic resonance imaging) are used.

Radionuclide thyroid imaging is generally less informative for cervicomediastinal goiters because most of these masses do not uptake radiopharmaceuticals. Traditional ultrasound is also insufficient since it cannot assess thyroid tissue located behind the sternum. The diagnostic utility of ultrasound may be improved with the use of a special transesophageal probe.

Additional studies:

- Indirect laryngoscopy is performed if there is suspicion of vocal cord dysfunction due to compression of the recurrent laryngeal nerves by the goiter.
- Fine-needle aspiration cytology is generally not recommended for mediastinal portions of the goiter because they are difficult to access, and performing a puncture may cause bleeding with subsequent respiratory complications.

Differential Diagnosis of Mediastinal Masses in the Anterior-Superior Region

Differential diagnosis of masses in the anterior-superior mediastinum includes:

- Dermoid cysts
- Thymomas
- Tuberculomas
- Aneurysms
- Lymphomas
- Teratomas
- Schwannomas (neurinomas)
- Secondary carcinomas

These masses are usually not associated with a goiter in the neck, do not rise with swallowing, and do not shift on radiographic examination.

Treatment of Nodular Thyroid Diseases

Surgical treatment is most commonly used for thyroid nodules, especially when it is impossible to exclude malignancy.

Medical treatment with thyroid hormones is performed only when there is complete confidence in the benign nature of a palpable nodule, which should be confirmed via

fine-needle aspiration biopsy (FNAB). The goal of this therapy is to stop the growth of the nodule by reducing thyrotropic stimulation, if present.

Some authors note that long-term therapy with thyroid hormones may lead to osteoporosis and cardiovascular complications. Based on analyses, the recommended approach is to observe patients with thyroid nodules, perform repeat FNAB if nodules increase in size, and consider surgery if necessary.

The dose of L-thyroxine is adjusted according to serum TSH levels, aiming to maintain TSH between 0.1–0.5 mIU/L.

Sclerotherapy of Thyroid Nodules

In 1990, Livraghi proposed percutaneous ethanol injection under ultrasound guidance as a possible treatment for autonomously functioning thyroid nodules.

Other sclerosing agents proposed include:

- Tetradecyl sulfate
- Tetracycline
- Hydroxypolyethoxydodecane
- Hyperosmolar solutions
- 95% ethanol (ethyl alcohol)

Algorithm for Nodular Thyroid Lesions

1. Ultrasound (US) is used to assess:
    - Number of nodules (solitary vs. multiple)
    - Size
    - Location (cervical vs. cervicomediastinal)
2. Management based on nodule size:
    - Nodules <1 cm: observation
    - Nodules >1–1.5 cm: perform FNAB
3. FNAB results guide further management:
    - Malignant or suspicious lesion: surgical intervention
    - Non-representative material: repeat FNAB
    - Benign nodule with growth: continue monitoring or consider surgery if indicated

To prevent recurrent fluid accumulation in a cyst, it is advisable to inject alcohol into its cavity. If the cyst rapidly refills after drainage, surgical treatment is indicated. Indications for surgery also include:

- Cyst size exceeding 3 cm in diameter
- Thick cyst walls (possibly calcified)
- Irregular internal walls (possible cystadenoma)
- Presence of inclusions within the cavity

Patients with benign changes confirmed by cytology should be monitored. In outpatient practice, many endocrinologists conduct long-term treatment with thyroid hormone preparations for nodular thyroid lesions, especially when TSH levels are elevated.

- If the nodule decreases in size (confirmed by ultrasound monitoring), conservative treatment should be continued.
- Fine-needle aspiration biopsy (FNAB) should be performed at least once a year to reassess cytological findings.
- If the nodule increases in size, surgical intervention is required.

Autoimmune Diseases:

Immunodeficiency states with localized involvement of the thyroid gland include two nosological forms, which differ in clinical manifestations, as well as morphological and immunological characteristics:

- Diffuse toxic goiter
- Autoimmune thyroiditis

Diffuse Toxic Goiter

Diffuse toxic goiter (DTG) is an organ-specific autoimmune disease, characterized by hyperproduction of thyroid hormones and a persistent increase of their levels in the blood serum, accompanied by a uniform, diffuse enlargement of all parts of the thyroid gland. DTG is the most common cause of thyrotoxicosis, accounting for approximately 80% of cases.

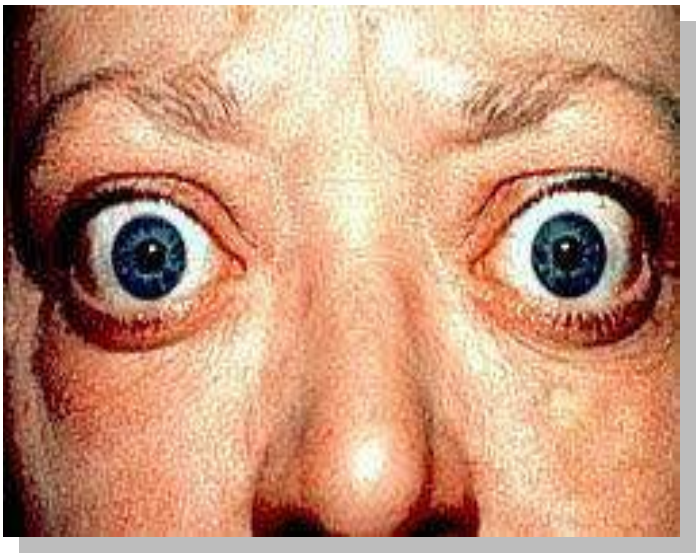
Epidemiology:
The prevalence of DTG depends on numerous factors, including geochemical, demographic, social, environmental, and climatic conditions. Among these, iodine intake has the greatest influence on the frequency of thyroid disorders. The incidence of DTG and other autoimmune thyroid diseases is higher in regions with high iodine content and consumption. On average, the disease occurs in 5–6 cases per 100,000 population per year.

Clinical Presentation:
The main clinical features of DTG are associated with thyrotoxicosis. Early symptoms often include:

- Muscle weakness
- Fatigue
- Irritability
- Distractibility
- Insomnia
- Palpitations

- Shortness of breath
- Tremor of the hands
- Heat intolerance and sweating
- Weight loss
- Frequent stools

Some patients also notice thyroid enlargement or exophthalmos. According to many authors, ophthalmopathy is considered a separate autoimmune condition, primarily affecting the retrobulbar connective tissue and extraocular muscles.



Edema of the retrobulbar connective tissue and extraocular muscles causes protrusion of the eyeball, which may lead to incomplete closure of the palpebral fissures and loss of the protective function of the eyelids. As a result, pain, tearing (lacrimation), and photophobia develop.

As the process progresses, venous outflow becomes impaired, leading to chemosis (edema of the bulbar conjunctiva) and periorbital edema. Compression of the optic nerve results in blurred vision, impaired color perception, and visual field defects. In later stages, fibrosis of the extraocular muscles develops, which manifests clinically as diplopia [11].

Ocular Signs Commonly Assessed in Clinical Practice

- **Oculo-palpebral asynergy** – lagging of the upper eyelid behind the iris during slow downward gaze, leaving a visible white strip of sclera between the upper eyelid and the iris (Graefe's sign); a white scleral strip may also appear during upward gaze (Kocher's sign).
- **Möbius sign** – weakness of convergence.
- **Stellwag's sign** – infrequent (normally 6–8 times per minute) and incomplete blinking.
- **Dalrymple's sign** – abnormally wide palpebral fissures.
- **Jellinek's sign** – hyperpigmentation of the eyelids

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Thyroid Gland Findings in Diffuse Toxic Goiter

On examination of a patient with diffuse toxic goiter (DTG), uniform enlargement of the thyroid gland is notable. The gland may have variable consistency and is typically painless. In some cases, pulsation of the gland may be observed, and vascular bruits can be auscultated over it.

Classification of Goiter According to O. V. Nikolaev (1955)

Degree of Thyroid Enlargement	Physical Characteristics
0.	Thyroid gland is neither visible nor palpable
I.	Thyroid gland is not visible but palpable; the isthmus becomes visible during swallowing
II.	Thyroid gland is visible during swallowing and palpable; the shape of the neck is not altered
III. (“thick neck”).	The thyroid gland is visible and alters the contours of the neck
IV.	Large goiter causing marked deformation of the neck.
V.	Giant goiter with compression of the neck organs.

Approximately 10% of patients already have palpable nodules in the thyroid gland against the background of its diffuse enlargement. The frequency of thyroid nodules is directly proportional to the patient’s age and the duration of the disease. The formation of nodules in the setting of diffuse proliferation of the thyroid epithelium is explained by the uneven nature of hyperplastic processes within the gland.

Histologically, the following are distinguished:

- **Colloid nodules**
- **Papillary and cystopapillary adenomas**
- **Follicular adenomas**
- **Follicular adenomas composed of Hürthle–Askanazy cells**

It should be noted that, according to various authors, the incidence of thyroid cancer in patients with diffuse toxic goiter (DTG) ranges from 0.4% to 18%. The most common malignancies developing in the setting of DTG are follicular and papillary carcinomas.

Nervous System Manifestations in DTG

Symptoms of nervous system involvement include **tremor** of the hands, feet, lips, and tongue. Patients often complain of memory impairment and difficulty concentrating; however, increased but poorly productive

work capacity is frequently observed. Tearfulness, emotional lability, and irritability are common. Characteristic features also include shiny eyes, headaches, and dizziness.

Neurological examination may reveal decreased muscle tone, signs of **myopathy**, reduced or exaggerated **reflexes**, **anisoreflexia**, and other scattered neurological symptoms. Mild cerebellar disturbances may occur, such as static ataxia and intention tremor (fine tremor of the fingers with outstretched arms, closed eyelids, and sometimes the entire body—known as the "telegraph pole" sign).

Cardiovascular Manifestations

Among cardiovascular symptoms, tachycardia is the most characteristic. The degree of tachycardia reflects the severity of the disease. Patients frequently develop atrial fibrillation (reported in 4.4–10.7% of cases). Atrial fibrillation is most commonly detected in patients aged 50–70 years with a long-standing history of thyrotoxicosis.

Elimination of thyrotoxicosis in such patients is often accompanied by persistent restoration of normal sinus rhythm. In the pathogenesis of arrhythmias in DTG, a leading role is played by functional alterations of the atrial conduction system due to **thyrotoxic myocardial dystrophy.**

Other features of thyrotoxicosis include the catabolic syndrome, characterized by progressive weight loss despite increased appetite. In rare cases, weight gain may be observed ("fatty Basedow's disease").

The skin of patients is elastic and warm to the touch. Dryness and brittleness of hair, as well as splitting and fragility of nails, are commonly noted.

Digestive System Manifestations

From the digestive system, patients may experience **dyspeptic disorders, vomiting, frequent bowel movements, and impaired liver function**. **Glucose intolerance** and **hyperglycemia** may occur. A characteristic reaction of the skeletal system is the development of osteoporosis.

As a result of impaired glycoprotein metabolism, edema and induration of the skin with a reddish-bluish discoloration may develop on the anteromedial surfaces of the lower legs (pretibial myxedema, occurring in up to 5% of cases).

Reproductive System:

From the reproductive system, women may develop menstrual irregularities up to **amenorrhea**, **galactorrhea**, and **decreased libido**; in men, **gynecomastia** may occur.

Severity Grades of Thyrotoxicosis

(Baranov G.V., 1956)

Severity	Physical criteria
Mild	Heart rate (HR) 80–100 beats/min, no atrial fibrillation, mild weight loss, slight decrease in work capacity, mild hand tremor
Moderate	HR >100–120 beats/min, increased pulse pressure, no atrial fibrillation, weight loss up to 10 kg, reduced work capacity
Severe	HR >120 beats/min, atrial fibrillation, psychiatric disturbances, dystrophic changes in parenchymal organs, marked weight loss, loss of work capacity

Classification of the Disease

(Developed by the Romanian endocrinologist S. Milcu, 1977)

- **Stage I** – Neurotic stage:
  Initial symptoms of thyrotoxicosis are present; enlargement of the thyroid gland is minimal and barely noticeable.
- **Stage II** – Neurohormonal stage:
  Pronounced manifestations of thyrotoxicosis with a clearly noticeable enlargement of the thyroid gland.
- **Stage III** – Visceropathic stage:
  Organic damage to internal organs is observed.
- **Stage IV** – Dystrophic (cachectic) stage:
  Irreversible changes develop in the body.

Diagnosis of Diffuse Toxic Goiter (DTG)

Laboratory methods play a key role in the diagnosis of DTG. Currently, the “gold standard” for examining patients with DTG includes:

- Ultrasound examination (US) of the thyroid gland
- Measurement of TSH, free T4, and T3 levels in blood plasma

Radionuclide thyroid scintigraphy is used for the differential diagnosis of nodular thyroid lesions (functional autonomy) and retrosternal or intrathoracic goiter.

According to specific indications, additional diagnostic methods may be employed:

- Determination of thyroid-stimulating antibodies (TSAb / TSI)
- Fine-needle aspiration biopsy (FNAB)
- Thyrotropin-releasing hormone (TRH) test

Ultrasound Examination

Ultrasound is a widely available and highly specific diagnostic method. According to literature data, its diagnostic accuracy in detecting nodules within a diffusely hyperplastic thyroid gland approaches 90%. Ultrasound also allows assessment of:

- The degree of diffuse thyroid enlargement (with calculation of thyroid volume)
- Diffuse reduction in parenchymal echogenicity

Hormonal and Functional Tests

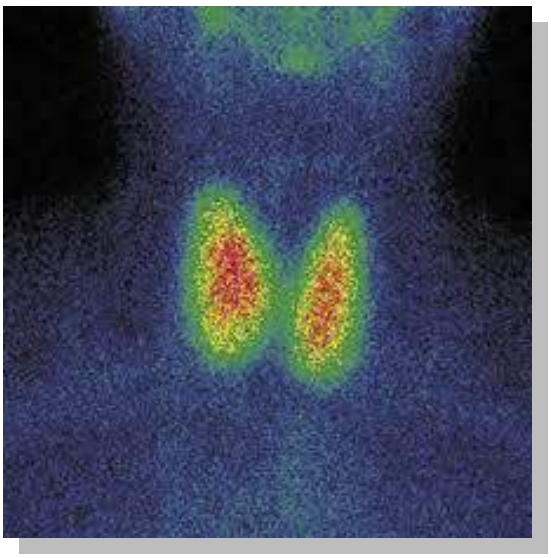
Using radioimmunoassay or enzyme-linked immunosorbent assay (ELISA) methods, it is possible to accurately determine blood levels of substances related to thyroid function.

Diffuse toxic goiter is characterized by:

- Elevated T3 and T4 levels
- Decreased TSH levels

In cases of only mild elevation of T3 and T4 levels, indications may arise for performing a TRH stimulation test. After intravenous administration of thyrotropin-releasing hormone in healthy individuals, serum TSH levels increase by 300–1000% within 20–30 minutes.

When hyperthyroidism is suspected and baseline TSH levels are normal, a negative response to TRH administration confirms the diagnosis of thyrotoxicosis, indicating pituitary suppression by excessive thyroid hormone concentrations.



Radioisotope scanning of the thyroid gland makes it possible to determine the location, shape, and size of functionally active thyroid tissue, as well as the presence of nodular lesions within it. For thyroid imaging, thyrotropic radiopharmaceuticals are used, primarily sodium iodide (^{131}I) and technetium-99m pertechnetate (^{99m}Tc-pertechnetate).

When the development of carcinoma on the background of diffuse toxic goiter (DTG) is suspected, a dual-nuclide study is advisable using ^{75}Se-methionine, which is a tumor-tropic radiopharmaceutical.

Diffuse toxic goiter is characterized by enlargement of the thyroid image and uniformly increased radionuclide uptake

The goals of treatment of diffuse toxic goiter (DTG) are elimination of thyrotoxicosis, relief of clinical manifestations of the disease, normalization of laboratory parameters, including achievement of immunological remission.

There are three independent methods for the treatment of thyrotoxicosis:

- **Comprehensive drug (medical) therapy**
- **Surgical treatment**
- **Radioactive iodine therapy**

Antithyroid (thyrostatic) drug therapy may be used as an independent treatment or as preparation for surgical intervention or radioiodine therapy. Conservative treatment of hyperthyroidism is primarily aimed at reducing excessive production of thyroid hormones by inhibiting their synthesis and secretion.

These drugs, known as thyrostatics, include:

- Thionamides: mercazolil, thiamazole, methimazole, carbimazole, propylthiouracil
- Iodides: Lugol's solution, saturated solution of potassium iodide (KI)
- Iodinated contrast agents
- Potassium perchlorate

It has been established that iodide doses exceeding 0.1 mg per kg of body weight suppress intrathyroidal iodine transport and the biosynthesis of thyronines, and also reduce the rate of release of thyroid hormones from the thyroid gland. This is accompanied by a rapid decrease in their serum levels.

However, after achieving a therapeutic effect—which persists for 10–14 days—the thyroid gland subsequently "escapes" from the blockade of thyroid hormone biosynthesis despite continued iodide administration. Therefore, iodine preparations cannot be used long-term as monotherapy.

Currently, iodides are used for preoperative preparation of patients with diffuse toxic goiter, as well as in combination with antithyroid drugs for the treatment of thyrotoxic crisis.

The main agents of conservative therapy for diffuse toxic goiter (DTG) are **imidazole and thiouracil** derivatives, which were introduced into clinical practice by E. Astwood in 1943. Their action consists in inhibiting the synthesis of thyroid hormones by blocking reactions catalyzed by thyroid peroxidase. Since thionamides do not block iodine transport and do not inhibit the release of hormones from their stores, compensation of thyrotoxicosis takes time and in most cases requires 2 to 6 weeks.

Mercazolil (thiamazole) is prescribed at a dose of 30–60 mg/day, with the daily dose divided into four administrations, taking into account the relatively short half-life of

these substances in the blood. Treatment with thiamazole (mercazolil) is usually combined with β-adrenergic blockers (propranolol/anaprilin, atenolol), which help control tachycardia and autonomic symptoms of the disease. β-blockers are withdrawn gradually, most often after 3–4 weeks.

As a euthyroid state is achieved (normalization of clinical manifestations and thyroid hormone levels), the dose of thyrostatics is slowly reduced to a maintenance dose (5–15 mg of thiamazole/mercazolil), combined with the addition of L-thyroxine (50–75 μg/day). To prevent relapses of thyrotoxicosis, maintenance therapy is recommended for 1–2 years.

The incidence of serious adverse effects (agranulocytosis, severe vasculitis, cholestatic jaundice, toxic hepatitis, aplastic anemia, thrombocytopenia) during treatment with mercazolil does not exceed 1%. Minor adverse effects (rash, pruritus, urticaria, fever, arthralgia, gastrointestinal disturbances, loss of taste) occur in approximately 10% of cases.

In some patients receiving long-term thyrostatic therapy, prolonged reduction of thyroid hormone levels in the blood leads to increased TSH secretion, which stimulates thyroid function and results in enlargement of the goiter (goitrogenic effect). To prevent this effect, thyroxine at a dose of 50–75 μg/day is recommended, with the dose adjusted to maintain a euthyroid state.

The drug of choice for radioactive iodine therapy is **the isotope ^{131}I**. When used in therapeutic doses (10–20 mCi), the isotope induces an inflammatory reaction in thyroid tissue, accompanied by cellular necrosis. The ionizing effect of β-particles emitted by ^{131}I, with a tissue penetration range of less than 2 mm, allows localized irradiation of thyroid tissue with minimal impact on surrounding organs.

An unfavorable consequence of radioiodine therapy is considered the development of hypothyroidism in the absolute majority of patients (more than 90%), requiring lifelong hormone replacement therapy.

In women of reproductive age, treatment with radioactive iodine should not be administered earlier than 10 days after the end of the preceding menstruation, which reduces the risk of radiation exposure during conception or early pregnancy. Pregnancy is an absolute contraindication to therapy with ^{131}I.

Starting from the 10th week of intrauterine development, the fetal thyroid gland activates mechanisms for iodine uptake and concentration, and accumulation of ^{131}I is associated with a risk of developing fetal and neonatal hypothyroidism. Another absolute contraindication to the use of ^{131}I is the **lactation** period, since the isotope accumulates in the mammary glands and is excreted into breast milk.

Relative **contraindications** to radioiodine therapy include severe ophthalmopathy, marked enlargement of the thyroid gland, hematopoietic disorders, and young patient age.

Approximately 40% of patients with diffuse toxic goiter (DTG) undergo surgical treatment. As a result of advances in anesthesiologic management, preoperative preparation, and thyroid surgery techniques, postoperative mortality has decreased to fractions of a percent.

Current indications for surgery in diffuse toxic goiter (DTG) include:

- combination of DTG with neoplastic processes of the thyroid gland;
- large goiter (40–45 mL or more) with compression of organs and anatomical structures;
- DTG with a complicated course;
- retrosternal (intrathoracic) location of the goiter;
- recurrence of thyrotoxicosis after surgery when treatment with radioactive iodine is impossible;
- ineffectiveness of antithyroid (thyrostatic) therapy for 1–1.5 years, recurrence of the disease;
- intolerance to antithyroid drugs.

Contraindications to surgical treatment of DTG include: myocardial infarction, stroke, severe DTG with decompensation of vital organ functions (circulatory failure grade III, anasarca, ascites, jaundice, etc.), oncological and infectious diseases, and psychiatric disorders. Inadequate preoperative preparation is also considered a contraindication.

The **surgical method** for treating DTG was proposed in 1884 by J. Mikulicz; the operation consisted of wedge resection of the thyroid gland after ligation of the superior thyroid arteries. It was later modified by A.V. Martynov, who increased the extent of gland resection.
In 1902, T. Kocher developed a radical surgical method, considered classical, consisting of subtotal thyroidectomy after ligation of all four thyroid arteries.
E.S. Drachinsky developed an original surgical technique for DTG, consisting of subfascial subtotal resection of the thyroid gland with preservation of tissue at one of the upper poles of the lobes.
In 1951, O.V. Nikolaev described the technique of subfascial subtotal thyroidectomy with preservation of tissue fragments of 3–4 mL in the tracheoesophageal grooves, which reduces the risk of recurrent laryngeal nerve injury and the incidence of hypoparathyroidism.

The most serious intraoperative and postoperative complication is **bleeding**. The incidence of postoperative bleeding ranges from 0.3 to 5%, averaging about 2%. The frequency of recurrent laryngeal nerve injury during surgery for DTG averages less than 5%, and hypoparathyroidism occurs in 0.5–3% of cases.

The clinical picture develops acutely within the first hours or the first day after surgery and is characterized by a sharp exacerbation of all symptoms of thyrotoxicosis. The earlier the crisis occurs after surgery, the worse the prognosis.

One of the **earliest symptoms** is a rapid rise in body temperature, beginning 6–10 hours after surgery and reaching 40–41°C. The more severe the crisis, the higher the hyperthermia. The patient's face becomes markedly flushed. Hyperthermia is a poor prognostic sign.

Patients develop **mental and motor agitation, dyspnea, and tachycardia** up to 150–200 beats per minute. The pulse is often arrhythmic, and atrial fibrillation is frequently observed. Blood pressure initially rises and then falls. The patient sweats profusely; suffocation and tachypnea with cyanosis appear, along with general weakness and muscular adynamia.

Abdominal pain accompanied by nausea, vomiting, and diarrhea may simulate an "acute abdomen" (the so-called false acute abdomen). Operated patients are restless and experience intense fear of impending death. Urine output decreases, sometimes progressing to anuria.

Another **unfavorable prognostic sign** in thyrotoxic crisis is jaundice, the appearance of which indicates a threat of acute liver failure.

The most dangerous complication of thyrotoxic crisis is cardiovascular failure. Myocardial dystrophy and a marked reduction in myocardial functional reserve, which develop in thyrotoxicosis, are aggravated by hypoxia and pronounced metabolic and microcirculatory disturbances during the crisis. Consequently, more than half of deaths in thyrotoxic crisis are associated with the development of acute cardiovascular failure.

A thyrotoxic crisis usually lasts 1–2 days. In particularly severe forms, death may occur within a few hours. Mortality reaches up to 50%.

Depending on the degree of temperature elevation, heart rate, and neuropsychiatric disturbances, thyrotoxic crisis is classified as:

(classification follows)

Depending on temperature elevation, heart rate, and neuropsychiatric disturbances, thyrotoxic crisis is classified as:

- **Mild**: heart rate < 120 beats/min, body temperature up to 38°C.
- **Moderate**: heart rate 120–140 beats/min, body temperature 38–39°C.
- **Severe**: heart rate > 140 beats/min, body temperature > 39°C.

Management of a thyrotoxic crisis requires immediate intensive care in a specialized ICU. Comprehensive therapy typically includes:

1. **Glucocorticoids**
    - Example: hydrocortisone hemisuccinate
    - Dose: approximately 50–100 mg, depending on severity
    - Route: intravenous drip or intramuscular injection every 3–4 hours
    - Initial dose: 100 mg infused over 30 minutes

2. **Thyrostatics (Antithyroid Drugs)**
    - Preferred: propylthiouracil (PTU), 400–800 mg/day
        - Inhibits thyroid hormone biosynthesis and prevents T4 → T3 conversion
    - Alternative: mercazolil (methimazole) 40–60 mg/day
3. **β-Adrenergic Blockers**
    - Use cautiously due to risk of acute cardiovascular failure
    - Example: propranolol (anaprilin)
        - IV: 1–2 mg slowly
        - Oral: 40–60 mg every 4–6 hours

Detoxification therapy and correction of water-electrolyte imbalances (intravenous infusion volume 3–5 L per day). To correct water-electrolyte disturbances, polyionic solutions, glucose solutions, rheopolyglucin, and hemodez are used under monitoring of acid-base balance and blood potassium levels. As a method of extracorporeal detoxification, plasmapheresis is advisable.

1. Sedative therapy – preference is given to phenobarbital, which accelerates peripheral metabolism and enhances binding of T4 to thyroxine-binding globulin.
2. Correction of cardiovascular insufficiency – low-dose cardiac glycosides and other agents.

Features of Diffuse Toxic Goiter (DTG) in Men

- In men, the disease typically begins after psycho-emotional stress or significant life events, such as the death of close relatives or professional mental stress.
- The most characteristic symptoms in men are palpitations, weight loss, muscle weakness, and rapid fatigue.
- Less commonly than in women, men experience sweating and sleep disturbances.
- Thyroid enlargement is less noticeable in men due to well-developed neck musculature.
- The clinical course of DTG in men is generally more aggressive.
- Nodular formations on the background of DTG in men are more often malignant (thyroid cancer).
- There is a tendency for retrosternal and retrotracheal thyroid locations in men.

These characteristics of DTG in men indicate the need for earlier surgical intervention.

Autoimmune Thyroiditis

Autoimmune thyroiditis (AIT) was first described in 1912 by H. Hashimoto under the name *struma lymphomatosa*, characterized by diffuse infiltration of the thyroid gland by lymphocytes, the formation of specific lymphoid follicles, destruction of epithelial cells, and proliferation of fibrous tissue replacing normal thyroid parenchyma.

It is generally accepted to distinguish the following clinicomorphological variants of chronic thyroiditis:

1. **Hypertrophic thyroiditis (Hashimoto's goiter)**
2. **Atrophic thyroiditis, or primary myxedema**
3. **Fibrosing-infiltrative thyroiditis (Riedel's goiter)**
4. **Postpartum (painless "silent") thyroiditis**

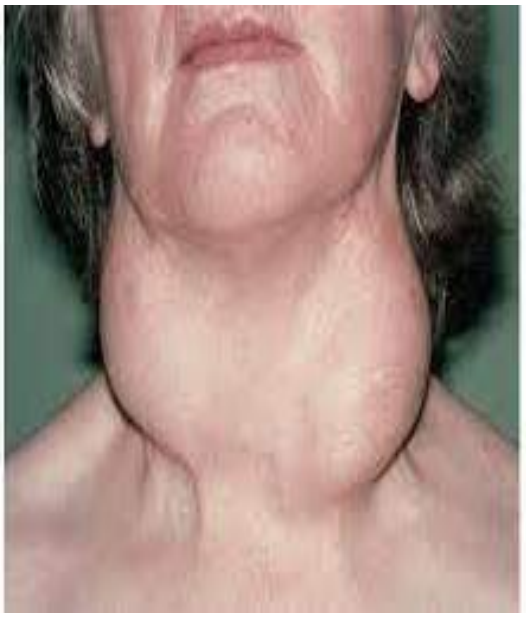
The hypertrophic variant of AIT (Hashimoto's goiter) occurs in nearly 90% of cases, manifesting as progressive enlargement of the thyroid gland and a relatively slowly developing hypothyroidism. The subtlety of clinical signs of thyroid insufficiency is explained by compensatory hypertrophy of the gland. Patients in this group often have a family history of thyroid diseases, associated dyshormonal disorders, and account for 70–75% of all patients with clinically manifest AIT.

The **atrophic** form of AIT is observed in approximately 12–18% of patients and often presents as nodular goiter with slowly developing hypothyroidism and atrophy of thyroid epithelium. Immune deficiency syndromes associated with chronic thyroidopathies—such as systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, vitiligo, chronic active hepatitis, glomerulonephritis, etc.—are most frequently seen in patients of this group.

Fibrosing-infiltrative thyroiditis, despite its aggressive clinical course, does not have a distinctive morphological pattern. Proliferation of connective tissue in the thyroid stroma with moderate lymphocyte and plasma cell infiltration, on the background of colloid nodules of normal structure, is nonspecific and occurs in the early stages of almost all autoimmune thyroidopathies.

Clinical manifestations of chronic thyroiditis are nonspecific. Hormone production deficiency develops gradually, and by the time patients seek medical attention for local changes, most are in a state of euthyroidism or subclinical hypothyroidism. Thyroid enlargement determines the most frequent complaints: a feeling of discomfort or pressure in the neck area.

Riedel's chronic fibrous thyroiditis is an extremely rare pathology (0.5% of all thyroid gland diseases). The condition presents with progressive and invasive proliferation of the organ's connective tissue, leading to the development of tracheo-obstructive syndrome. The thyroid gland becomes nodular and has a stony hard consistency. The involvement may be unilateral or bilateral. It more commonly affects women of middle and older age groups.



Postpartum Thyroiditis

Postpartum thyroiditis occurs in 5–10% of women after pregnancy. The onset of the disease usually falls between 8–12 weeks postpartum and is characterized by mild hyperplasia and firming of the thyroid gland against a background of transient hypothyroidism.

A distinctive feature of this form is the change in thyroid functional activity, with transition from hypofunction to hyperthyroidism, followed by spontaneous recovery. Persistent hypothyroidism is rare, but approximately half of women develop thyroid insufficiency within 10 years after childbirth.

A unique early clinical variant (about 10% of AIT patients) is transient (up to six months) mild thyrotoxicosis, sometimes called "Hashitoxicosis", more common in the hypertrophic form of the disease and characterized by symptoms of thyroid hyperfunction. This is often misdiagnosed as diffuse toxic goiter (Graves' disease). It is linked to damage to some thyroid follicles or temporary production of thyroid-stimulating antibodies. Patients in this category typically have a short disease history and are younger in age.

Diagnostic Criteria for Autoimmune Thyroiditis (AIT)

The gold standard for diagnosing autoimmune thyroid syndromes is the presence of a combination of the following:

- Primary hypothyroidism
- Diffuse enlargement of the thyroid gland (more than 25 mL in men, 18 mL in women)
- High, diagnostically significant levels of autoantibodies against thyroid tissue
- Characteristic ultrasonographic signs of autoimmune thyroid involvement

If one or more of these criteria are missing, the diagnosis of AIT is considered probable but not definitive. Fine-needle aspiration biopsy of the thyroid is generally not recommended unless a nodular formation is detected on ultrasound.

Thyroid Hormone Assessment

Thyroid function is assessed by measuring:

- Free and total thyroxine (T4)
- Free and total triiodothyronine (T3)
- Thyroid-stimulating hormone (TSH) in peripheral blood
- A TSH concentration of 0.2–5 mIU/L is considered normal.
- TSH > 5 mIU/L with normal free T4 indicates subclinical hypothyroidism.
- Elevated TSH with low T4 confirms manifest hypothyroidism.

Assessment of Thyroid Autoimmunity

Clinically relevant antibodies include:

- Anti-thyroid peroxidase (TPO) antibodies
- Anti-thyroglobulin (TG) antibodies
- TSH receptor antibodies
- Patients with chronic thyroiditis typically have high titers of anti-TPO and anti-TG antibodies.
- Some patients with the atrophic form may also have anti-TSH receptor antibodies.

Ultrasound Diagnosis of Autoimmune Thyroiditis (AIT)

Ultrasound (US) is a non-invasive and simple diagnostic method with a sensitivity of 60–75% and specificity of 70–75%. Supplementing traditional US with color Doppler mapping increases diagnostic value up to 85%.

The most characteristic echographic sign of AIT is:

- Diffuse decreased echogenicity of the thyroid gland, caused by the formation of lymphoid-plasmacytic infiltrates in the parenchyma.
- Sometimes small, irregular hyperechoic inclusions are detected, likely due to the formation of fibrotic zones in the gland tissue.

Changes in thyroid size are another important diagnostic criterion:

- Hypertrophy occurs in 80% of cases.
- Reduced thyroid volume is observed in 15% of patients.
- A common additional sign of chronic inflammation is thickening of the thyroid isthmus.

Treatment Concepts for Chronic Thyroiditis

Current treatment approaches are primarily symptomatic, due to the secondary nature of organ changes.

- Immunomodulation via plasmapheresis, laser photomodification, or medications is of limited pathogenetic rationale.
- Corticosteroids and cytostatics have a high risk of side effects and complications.

A more rational approach is dynamic monitoring and correction of thyroid homeostasis.

1. **Manifest Hypothyroidism**
    - Defined by elevated TSH and decreased T4.
    - Indication for levothyroxine replacement therapy at 1.6–1.8 µg/kg body weight/day until TSH normalizes.
2. **Subclinical Hypothyroidism**
    - Defined by elevated TSH with normal T4.
    - Dynamic monitoring with hormone level assessment every 3–4 months.
    - If subclinical hypothyroidism is diagnosed during pregnancy, levothyroxine therapy is indicated.

Effect of Replacement Therapy:

- Stabilizes progressive thyroid enlargement.
- About one-third of patients may experience some regression of goiter, likely due to reduced TSH stimulation.
- If cardiac symptoms appear, correct cardiovascular disturbances and temporarily adjust thyroid medication dose.

Treatment of Hashitoxicosis:

- Preferred drug: Methimazole (Mercazole).
- Mechanism: accelerates iodide elimination from follicular epithelium and suppresses thyrocyte enzymatic activity, reducing T4 synthesis.
- Also has immunosuppressive effects, reducing antibody production by T-lymphocytes.

Dosage:

- Mild hyperthyroidism: 10–20 mg/day
- Moderate hyperthyroidism: 30–40 mg/day
- Once euthyroidism is achieved, gradually reduce to 5–10 mg/day as maintenance.

Duration:

- Usually at least 1 year.
- Recurrence after discontinuation requires repeat courses of therapy.

Radioactive iodine therapy is not recommended for patients with hashitoxicosis.

Surgical Treatment of Patients with Autoimmune Thyroiditis (AIT)

Surgical intervention in patients with AIT is currently rarely used and has limited indications.

- The primary indication for surgery is progressive AIT with compression of the trachea or superior vena cava due to a hypertrophied thyroid gland.
- These patients are most often elderly with a long-standing history of the disease.
- Prolonged conservative management in such cases carries the risk of asphyxia and hemorrhagic strokes, while surgeries performed emergently for life-threatening indications tend to have poorer immediate and long-term outcomes.

Absolute indications for surgery include the **first signs of compression syndrome**:

- Voice changes
- Dyspnea on exertion
- Discomfort when swallowing solid food
- Headaches
- The surgery of choice for AIT today is subtotal thyroidectomy.
- Smaller-volume interventions often lead to recurrence of compression syndrome.

Surgery may also be necessary in patients with **Hashitoxicosis** in cases of:

- Intolerance to antithyroid drugs
- Development of granulocytopenia
- Persistent, recurrent thyrotoxicosis despite methimazole therapy

Important: Management of patients with thyrotoxic AIT should remain as conservative as possible, because surgery accelerates the development of thyroid hormone deficiency and the need for lifelong replacement therapy.

Rare Forms of Thyroiditis

- Subacute thyroiditis, first described in 1904 by De Quervain ("granulomatous" or "pseudotuberculous" thyroiditis), is a very rare condition.
- Among patients with thyroid pathology, subacute thyroiditis occurs in only 0.01–0.05%.
- Women are affected more frequently than men.

Morphological Changes in Granulomatous Thyroiditis

- The disease is characterized by degenerative-dystrophic changes in the follicular epithelium on a background of stromal proliferation with the formation of granulomas containing multinucleated giant cells.
- The etiology is generally considered viral, although the exact causative agents have not been definitively identified.

Clinical Course

- De Quervain's thyroiditis usually develops 1–4 weeks after an acute viral infection, such as upper respiratory infections, mumps, infectious mononucleosis, or measles.
- Symptoms often resemble an acute viral infection: malaise, chills, muscle pain, low-grade fever, sometimes high fever.

Local Changes

- Painful enlargement of a thyroid lobe with radiation of pain to the ears, occiput, or jaw
- Erythema of overlying skin
- Mild neck edema
- A notable feature is localized involvement—usually one lobe or the isthmus.
- Regional lymph nodes are usually intact.
- Follicular epithelial destruction and the release of thyroid hormones into circulation can sometimes cause mild thyrotoxicosis.

Diagnosis

- Diagnosis is challenging due to the rarity of the disease and lack of specific symptoms.
- Laboratory findings often include:
    - Markedly elevated ESR (50–70, sometimes up to 100 mm/h)
    - Leukocytosis with lymphocytosis
- Thyroid hormone studies may show mildly elevated T3 and T4, as well as thyroglobulin.
- Transient increases in antithyroid antibodies are possible.
- Ultrasound typically shows diffuse increased echogenicity due to parenchymal edema, with hypoechoic areas corresponding to epithelial destruction.
- Cytology reveals "pseudogiant multinucleated cells" amidst epithelioid cells, macrophages, and lymphocytes. Occasionally, Hurthle-Askanazy cells may be observed.

Treatment

- Therapy is strictly conservative.
- Glucocorticoids are the mainstay, at high doses (0.5–1.0 mg/kg/day), with gradual tapering.

- NSAIDs and antihistamines are used additionally.
- In cases of significant thyrotoxicosis, β-blockers are recommended.
- The total duration of therapy is usually 1–3 months.

Acute (Suppurative) Thyroiditis

- Acute thyroiditis is a rare bacterial disease of the thyroid gland.
- It is usually secondary, occurring in the presence of chronic infection foci such as tonsillitis, sinusitis, pneumonia, furunculosis, etc.
- The infection spreads predominantly via the lymphatic system.

Clinical Features

- Onset is acute, with symptoms of purulent intoxication.
- Local changes include:
  - Enlargement of the thyroid
  - Erythema of overlying skin
  - Severe pain radiating to the ear, occiput, or lower jaw
  - Firm consistency of the gland, softening in areas of purulent necrosis
- Cervical lymph nodes are enlarged and tender.
- A specific symptom is severe pain on swallowing.

Diagnosis

- Diagnosis is primarily clinical.
- Laboratory and instrumental studies are nonspecific.
- Blood tests typically show a pattern of purulent bacterial inflammation: elevated ESR, pronounced leukocytosis with a shift to the left (band neutrophils).
- Ultrasound reveals diffuse heterogeneity of thyroid tissue with decreased echogenicity in the affected area.
- If parenchymal necrosis forms an abscess, ultrasound detects a cystic formation with fluid content.

Complications

- Dangerous complications include rupture of the abscess into the trachea or esophagus.
- Spontaneous drainage into the mediastinum can lead to mediastinitis.

Treatment

- Before abscess formation, therapy is conservative:
  - Intensive antibacterial therapy
  - Desensitization and detoxification therapy

- Drugs stimulating antibacterial immunity may be useful

- If an abscess forms, surgical intervention is indicated, following the principles of purulent surgery: opening and drainage of the abscess.

Preparation for Surgery. Standard Thyroid Resection

- **Position** of the Patient on the Operating Table
  During thyroid surgery, the patient is placed horizontally on the operating table, lying on the back, with a pillow placed under the shoulders and the head extended backward**.**
  The horizontal position promotes venous filling of the neck veins, thereby reducing the risk of air embolism**.**
- **Anesthesia**
  At present, endotracheal anesthesia is the generally accepted method for thyroid surgery.
  Its advantages include a reduced risk of air embolism and prevention of tracheal collapse in cases of tracheomalacia.
- **Surgical Approach**
  As is well known, the operation begins with a skin incision.
  The **Kocher collar incision** provides the best surgical access and the most favorable cosmetic outcome.
- This **incision** is made in a **curved** (arc-shaped) manner between the two sternocleidomastoid muscles, along a natural skin crease of the neck, 1–2 transverse fingers above the suprasternal notch**.**
- In cases of **large goiters**, the skin incision is placed slightly higher for cosmetic reasons, so that excess skin from the upper portion of the incision does not overhang the lower part (O. V. Nikolaev).
- The length of the incision does not depend on cosmetic considerations, since the ends of the incision heal well and are barely noticeable; only the central portion of the scar tends to deform.
  The incision line is additionally marked with **transverse scratch marks** (Fig. 1) to align the wound edges accurately at the end of surgery, ensuring optimal healing.

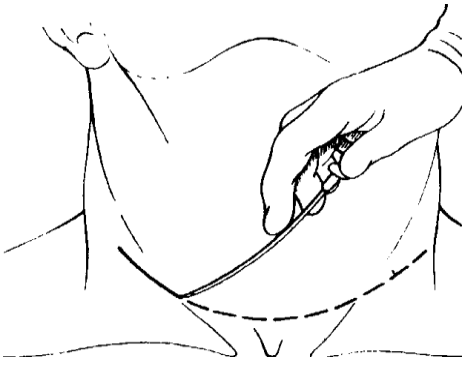


Fig. 1. Strumectomy. 1. Marking of the skin incision line.

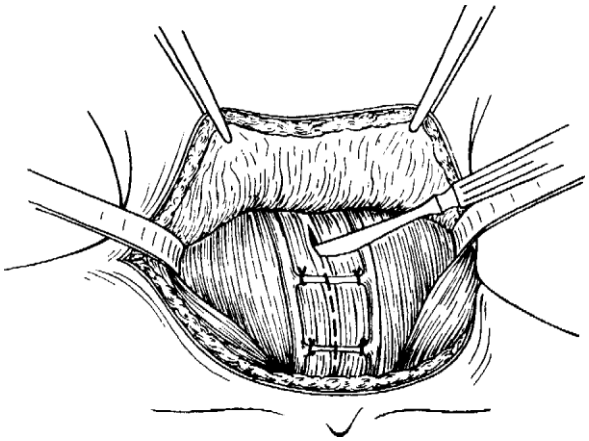


Fig. 2. Strumectomy. II. Separation along the midline of the infrahyoid muscles.

- **Dissection of Soft Tissues**

With a single movement of the scalpel, the skin, platysma, and subcutaneous tissue are incised down to the superficial fascia.

The upper flap, consisting of skin, platysma, and subcutaneous fat, is retracted upward and dissected from the fascial base using wide transverse movements.
Bleeding in this layer is minimal, as blood vessels are located mainly within the adipose tissue and beneath the fascia.

The upper flap is dissected up to the upper border of the thyroid cartilage and fixed with several sutures to sterile drapes covering the patient's face.

Next, the lower flap is dissected from the fascial base, retracting the skin together with the platysma and subcutaneous fat downward to the suprasternal notch.

Thus, despite the seemingly small transverse incision, excellent exposure of the goiter is achieved without transverse division of the strap muscles of the neck.

- **Exposure of the Thyroid Gland**

Along the midline, from top to bottom down to the suprasternal notch, the fascia and anterior neck muscles are incised and separated from the central portion of the thyroid cartilage.

The incision is deepened until the capsule of the thyroid gland is reached, which has a shiny surface with a pearly sheen (Fig. 2).

From the midline incision, the fascial–muscular flaps are gently retracted using blunt hooks, or the anterior surface of the thyroid gland is exposed with a swab (tupfer).

Through this approach, goiters of even large size can be adequately resected.
There is no need to transect the strap (infrahyoid) muscles transversely, since a large goiter significantly stretches these muscles, thereby creating sufficient space for dissection and mobilization of the thyroid gland.

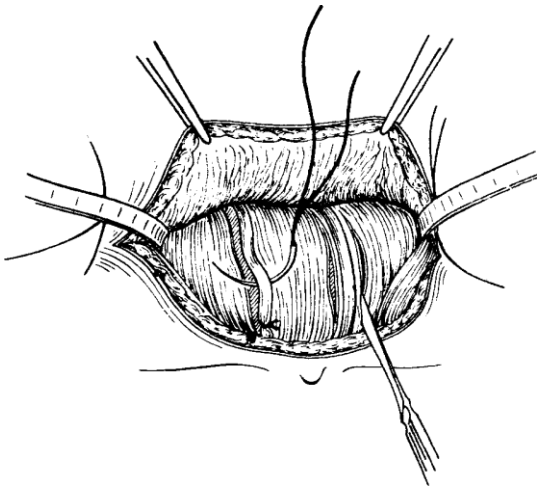
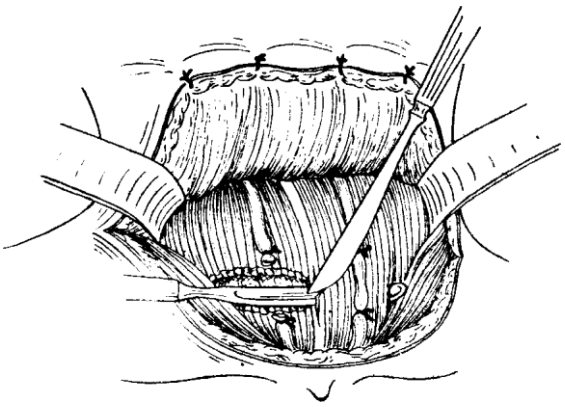


Fig. 3. Strumectomy. III. Identification and ligation of both anterior jugular veins.



Fig, 4 Strumectomy. IV. Transverse division of the infrahyoid muscles.

Sometimes, in order to obtain wider exposure, it becomes necessary to perform a transverse incision of the strap (broad) muscles of the neck. For this purpose, the veins of the anterior surface of the neck, running from above downward beneath the fascia, are first divided between two ligatures (Fig. 3). The muscles are lifted over the thyroid gland and divided transversely within the limits of the skin incision (Fig. 4). The sternocleidomastoid muscle is neither incised nor divided; it can be adequately retracted with hooks.

After mobilization of the thyroid gland, its size, shape, and structure are assessed. The surgeon passes the index finger around its lateral and posterior surfaces, evaluating its consistency. Care must be taken not to injure the veins located in the loose connective tissue.

After this examination, a decision is made regarding which side and how much thyroid tissue should be resected. The main stages of this important surgical procedure are:

- **dislocation** of the thyroid gland from its bed;
- **ligation** and **division** of the superior thyroid artery and vein;

- **intracapsular subtotal wedge** resection of the thyroid tissue;
- **suturing** of the remaining thyroid tissue and the capsule.

During resection of the thyroid tissue, the inferior thyroid artery is ligated and divided intracapsularly. This is because extracapsular ligation may injure the recurrent laryngeal nerve, which ascends between the branches of the inferior thyroid artery.

• Dislocation of the thyroid gland from its bed

If both lobes of the gland are affected by the pathological process, the operation is begun on the right lobe, retracting the strap muscles laterally with blunt hooks. The posterior surface of the gland is palpated with a finger, and the gland is bluntly dislocated from its bed. If the finger enters the correct plane, it advances through loose, easily separable, almost avascular connective tissue. These and subsequent maneuvers are greatly facilitated by placing a deep suture of thick thread through the thyroid tissue. A gauze swab (tupfer) is attached to this thread, and the thread is grasped with a clamp (Fig. 5). With this traction suture, the gland can be rotated in the required direction. A particular advantage of this “stay suture” is that it can sometimes be used to draw down a deeply located and poorly accessible superior pole. If necessary, a series of 3–4 such stay sutures may be placed in different parts of the goiter, allowing extraction of various portions from depth.

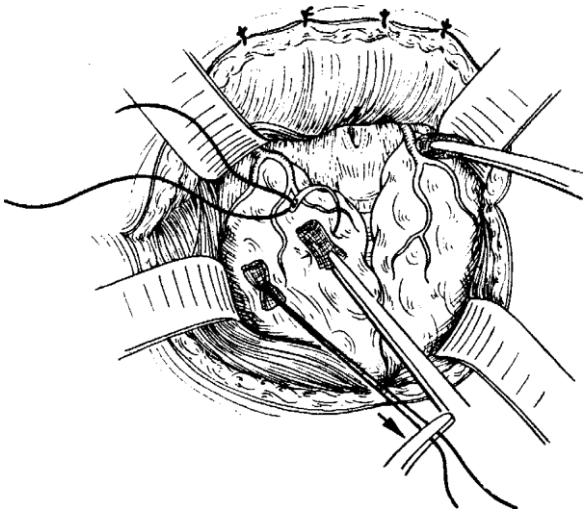


Fig. 5. Strumectomy, Stage V.

Placement of two stay sutures (“holders”) and dissection of the superior pole.

By forcefully retracting the strap muscles of the neck laterally with hooks, the surgeon passes a finger beneath the thyroid gland and gradually dislocates it from its bed. The middle portion of the thyroid lobe is usually delivered without significant difficulty. However, mobilization of the superior and inferior poles in cases of large goiters presents considerable challenges.

The superior pole of the gland is drawn downward using the stay suture (“holder”), while loose connective tissue is displaced from it with a blunt dissecting swab. This

exposes the branching superior thyroid artery and vein entering the substance of the superior pole of the gland.

- **Ligation and division of the superior thyroid artery and vein**

The superior thyroid artery and vein are dissected with a dissector over a sufficiently long segment so that, after ligation, a stump of at least 2 cm remains distal to the ligature. The central portion of the vessels is transfixed and tied with two ligatures (Fig. 6), after which the vessels are divided. The central vascular stump retracts and disappears deep into the wound. The superior pole of the goiter is grasped with a clamp and pulled downward, continuing the dislocation of the gland from its bed, into which a gauze tampon is placed.

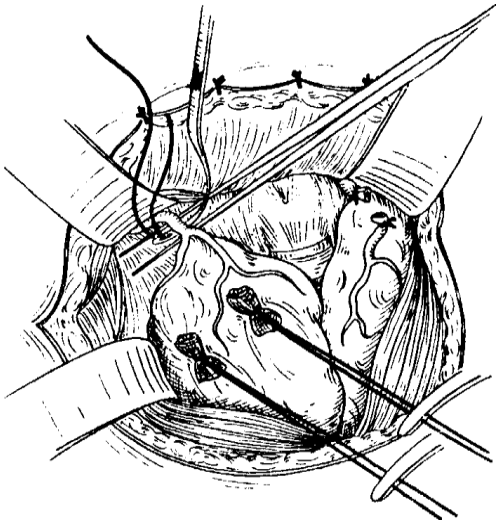
Usually, only after this maneuver is it possible to completely deliver the superior pole of the goiter. For this purpose, the assistant shifts the retractors downward, widening this part of the wound. A finger is then passed along the capsule of the gland downward toward the inferior pole, isolating and dislocating it outward from the wound (Fig. 7). These maneuvers are facilitated by traction on the stay sutures (“holders”). A tampon is placed at the bottom of the wound.

If difficulties arise during mobilization of the goiter, they should not be forced; instead, the cause of these difficulties should be identified.

The goiter may be fixed by a flat, markedly developed Kocher’s vein running along its lateral surface (Fig. 8). It can be quickly identified using a blunt dissecting swab introduced into the loose connective tissue surrounding the capsule of the goiter; with this swab, the capsule should be gently retracted medially. This vein must be divided after prior ligation. Kocher’s vein drains directly into the internal jugular vein, and therefore it must be handled with great care.

Exteriorization of the inferior pole of the goiter may be difficult in cases where the lobe fixing the goiter has a retrovisceral (retrotracheal, rarely retroesophageal) or retrosternal position.

In such cases, the following approach is used: the retrovisceral lobe is transfixed with a stay suture (“holder”) and elevated, then bluntly dissected, separating the lobe from the surrounding tissues while avoiding their injury. A substernal nodule, if it does not extend beyond the angle of the sternum, can—by blunt finger dissection behind the sternum—be delivered outward with greater or lesser difficulty, even if its diameter reaches 6–8 cm. If substernal dissection is performed in the correct tissue plane, there is no risk of bleeding, since this retrosternal portion is supplied with blood from the neck rather than from the mediastinum.



Strumectomy, Stage VI. Ligation of the superior thyroid artery.

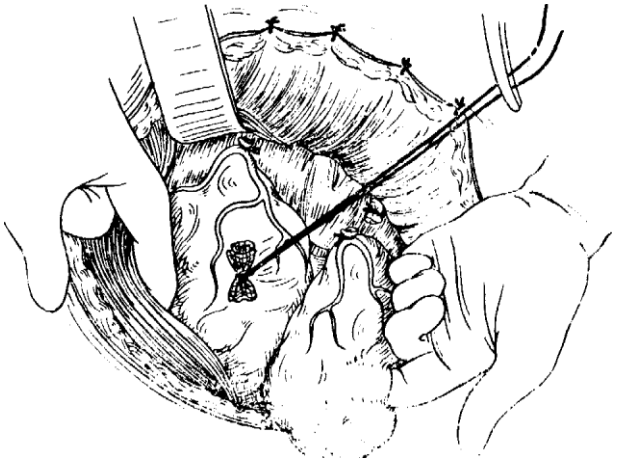


Fig. 7. Strumectomy, Stage VII. Digital dislocation (delivery) of the inferior pole of the gland.

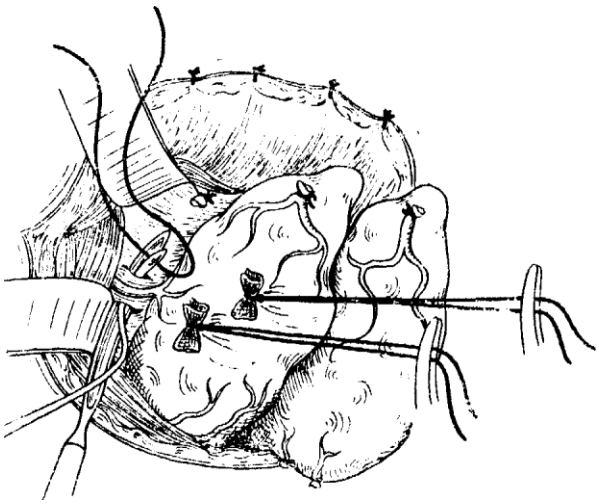


Fig. 8. Strumectomy, Stage VIII. Ligation of the lateral Kocher vein that hinders dislocation of the gland.

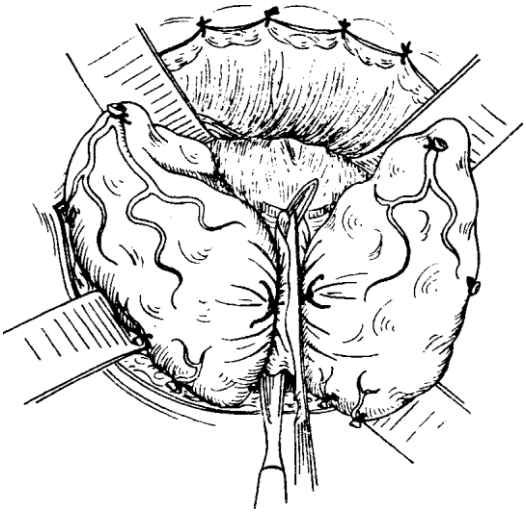


Fig. 9. Strumectomy, Stage IX. Transection of the thyroid isthmus.

By pulling on the “stay” suture and continuing the dissection, the retrosternal nodule is carefully mobilized and brought out from behind the sternum. The force applied to extract the nodule from behind the sternum should not be excessive, in order to avoid tearing the capsule or detaching the nodule. It is not uncommon to successfully extract substernal nodules whose cross-sectional size exceeds that of the thoracic inlet.

A midline sternotomy is performed in cases where the goiter extends beyond the sternal notch, is fixed behind the sternum, and cannot be mobilized. Sternotomy is also indicated in the event of severe substernal bleeding in the mediastinum, when a calcified substernal nodule is densely adherent to surrounding tissues, or when a nodule detaches and slips deeper into the mediastinum. Sternotomy allows for rapid and safe resolution of these potentially dangerous, complicated situations. Bleeding control and removal of the nodular lower pole of the gland are performed simply and safely.

After mobilizing and bringing out the entire right lobe of the thyroid from the wound, a gauze pad is placed in its bed, and the same steps are performed on the left lobe.

Once both lobes are mobilized and delivered from the wound, the isthmus is dissected. The pretracheal fascia above and below the isthmus, which connects the upper and lower edges of the isthmus to the trachea, is transected transversely with a scalpel. A Kocher probe or dissector is inserted between the isthmus and the trachea from below upward, and the isthmus is divided into two halves (Fig. 9). This completely frees the anterior surface of the trachea from thyroid tissue. After this, the upward-extending pyramidal lobe is removed; if left in place, it may hypertrophy, and the recurrent portion could reappear in the midline of the neck.

- ## Intracapsular Subtotal Wedge Resection of Thyroid Tissue

After fully mobilizing both lobes of the thyroid and bringing them into the surgical field, the final stage of the operation is performed — resection of thyroid tissue. The planned line of resection is marked at the level of clamps placed along it. Extreme care

must be taken to avoid injury to the recurrent laryngeal nerve and the parathyroid glands (Figs. 10 and 11).

The thyroid lobe is held with the left hand so that four fingers are positioned on its posterior surface and the thumb lies anteriorly. The gland is lifted and slightly stretched, and a wedge resection of the thyroid tissue is performed. The depth of the incision is controlled with the left-hand fingers along the line indicated by the clamps.

The thyroid capsule, especially on the lateral and posterior surfaces, is left intact, because the structures essential for normal function — the recurrent laryngeal nerve and the parathyroid glands — lie external to the capsule. The scalpel is used intracapsularly only, leaving a layer of thyroid parenchyma on the capsule with a thickness sufficient to protect these critical structures.

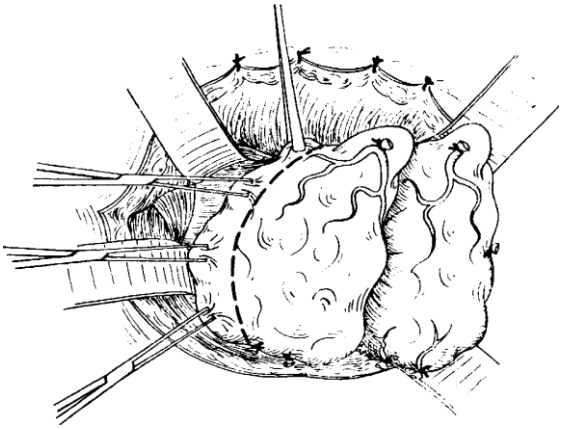


Fig. 10. Strumectomy, X. Marking the Resection Line on the Lateral Surface of the Thyroid

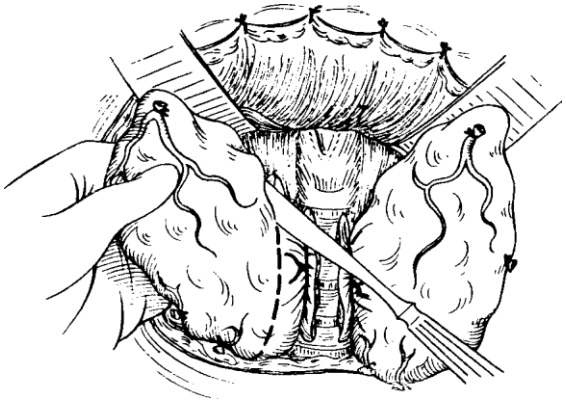


Fig. 11. Strumectomy, XI. Marking the Resection Line on the Medial Surface of the Thyroid

- **Suturing of the Thyroid Tissue**

The lateral walls of the thyroid lobe, formed after the wedge resection, are tightly approximated so that no residual cavity remains between them. They are connected using either interrupted or continuous catgut sutures. The outer wall is grasped only by the edge of the capsule (Fig. 12), taking care not to damage any structures located posterior to it.

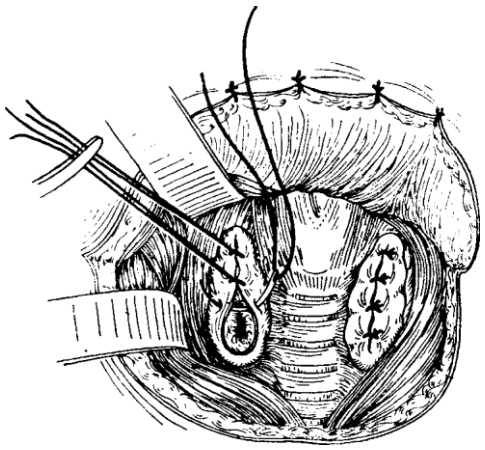


Fig. 12. Strumectomy, XII. Suturing of the thyroid capsule on both sides

After carefully suturing the remaining thyroid tissue, the beds of both lobes are inspected. Complete hemostasis is ensured. At this stage, the anesthesiologist provides increased ventilation with elevated airway pressure. This measure is aimed at checking for any bleeding from remaining unligated veins or from veins where the ligature may have slipped.

If hemostasis is confirmed to be adequate, a thin, soft drain is inserted through a small skin incision above the sternal notch using forceps or a clamp (Fig. 13).

The patient’s head is returned to the neutral position, and the neck muscles and dissected platysma are restored with interrupted sutures using fine catgut (Fig. 14).

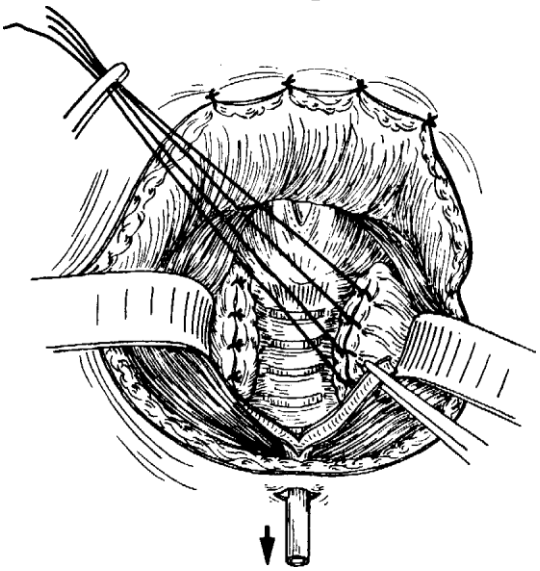
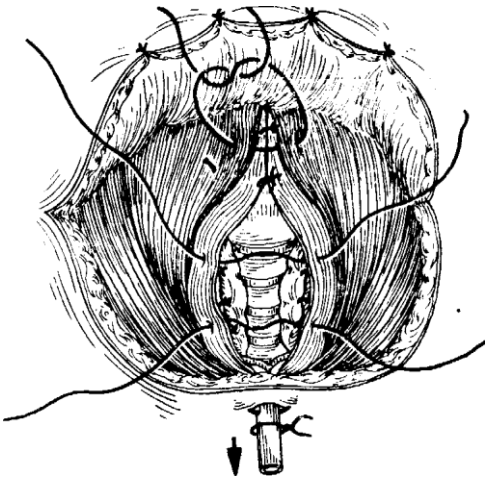


Fig. 13. Strumectomy, XIII. Placement of a V-shaped (or two separate) drain into the thyroid bed



.Fig. 14. Strumectomy, XIV. Closure of the two layers of the platysma and other neck muscles

The platysma and other dissected neck muscles are sutured in two layers. The skin incision is closed with staples or atraumatic sutures, followed by a dressing with a polyethylene cover to prevent contamination from oral secretions. After surgery, the patient requires lifelong thyroid hormone replacement therapy to prevent hypothyroidism and reduce the risk of recurrence.

- **Enucleation**

Enucleation of a cyst or nodule in the thyroid gland is technically straightforward. This procedure is undertaken when one or several enlarged nodules or degeneratively altered cysts are found in an otherwise normal-sized and structurally normal thyroid. Adenomas causing thyrotoxicosis can also be safely enucleated.

Enucleation should only be performed after complete exposure of the thyroid and careful intraoperative revision. It is important to note that in 25–30% of cases, the preoperative diagnosis may differ from the diagnosis established during surgery.

- **Enucleation Technique:**

The affected lobe of the thyroid gland is exposed following the principles described earlier. Blood vessels running over the cyst or nodule are ligated on both sides, and the thyroid capsule is incised between the ligatures. The lobe is then brought out of its bed.

The nodule is pushed from the posterior surface toward the anterior side and enucleated with scissors through the opening in the capsule (Fig. 15). Any bleeding vessels in its bed are ligated. The wound cavity is sutured, with the edges turned inward to prevent residual space.

Removal of an adenoma located near the pole of the gland or deeper within its tissue can often be accompanied by significant bleeding. In such cases, Bay and Zuckschwerdt recommend a technique that minimizes blood loss: the arteries supplying the lobe from which the nodule is being removed are carefully identified and vascular clamps are applied to them (Fig. 16).

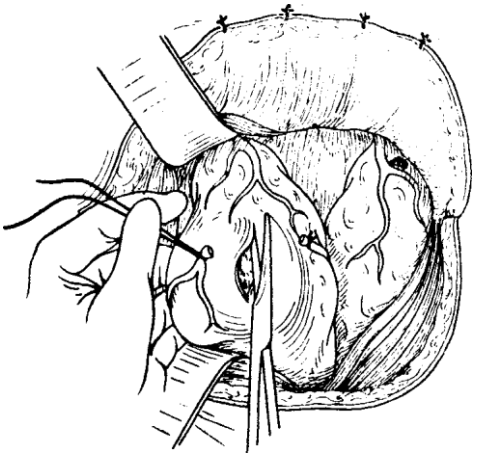


Fig. 15. Enucleation of a Thyroid Adenoma

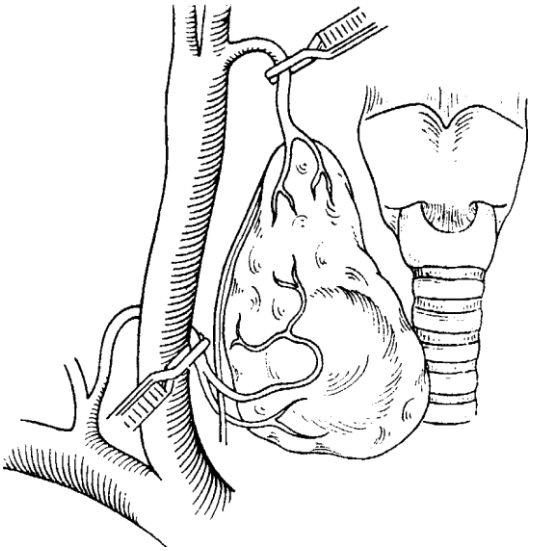


Fig. 16. Ischemization of the thyroid gland by temporary occlusion of its feeding arteries

- **Recurrence of a goiter in the pyramidal lobe of the thyroid gland**

The operation for recurrent goiter in the pyramidal lobe begins with the excision of the old skin scar. If dense adhesions are expected within the old scar that complicate surgical access, the incision should be made at a new site, above the previous one.

The vessels supplying the pyramidal lobe are highly variable. Ligation and division of these vessels are more important than parenchymal resection. The pyramidal lobe can extend through the thyrohyoid membrane up to the base of the tongue. Total resection is not necessary; ligation of the small arteries feeding the pyramidal lobe parenchyma is sufficient.

Recurrence may also occur from the upper pole of the thyroid gland. Such a recurrence can result from a portion of the upper pole left during the first operation, along with a

branch of the superior thyroid artery that was not ligated. In this case, it is necessary to locate this artery, carefully dissect it, ligate it, and resect the upper pole. If the recurrent goiter is located near the thyroid cartilage, care must be taken before ligating and dividing its vessels to ensure the superior laryngeal nerve is not included in the ligature (Fig. 17). Injury to this nerve is generally safe but may cause an undesirable change in voice.

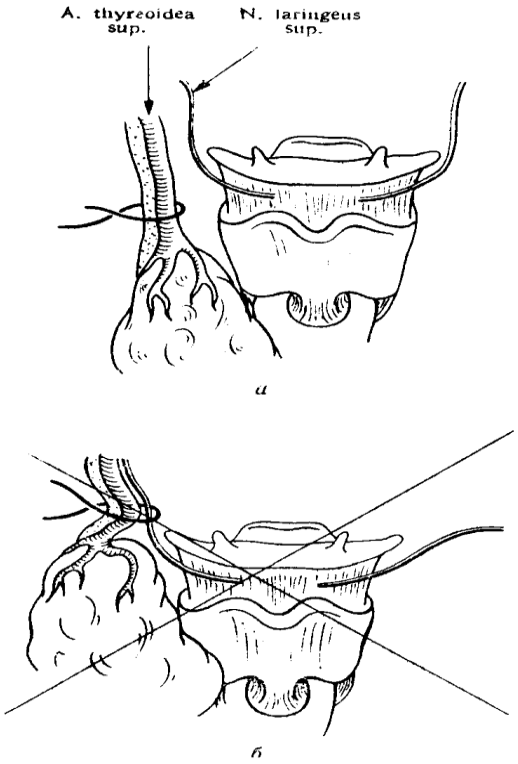


Fig.17. Surgery for recurrent goiter, 1. The superior laryngeal nerve must not be ligated (a, b)

Recurrence of goiter in the lateral lobe of the thyroid gland
Recurrence of goiter in the lateral lobe of the thyroid gland is rare if the initial surgery was performed correctly. Such recurrence may result from insufficient radicality of the initial procedure. Significant scar tissue from the first surgery can make a repeat operation very difficult, severely altering the normal anatomical relationships in the area.

There are two approaches for removing the recurrent goiter:

1. Extracapsular dissection first, followed by intracapsular resection – similar to the technique used in the initial operation.
2. Intracapsular resection from the start – performing the resection entirely within the capsule from the outset.

The choice between these techniques depends on the specific circumstances of the case and the operating surgeon’s experience with each approach in the given surgical setting.

- **Extracapsular Resection of Recurrent Goiter in the Lateral Thyroid Lobe**

Extracapsular resection of a recurrent goiter in the lateral lobe of the thyroid generally does not present major difficulties if the appropriate tissue plane can be identified and

the remaining thyroid lobe tissue mobilized. However, even with ideal dissection in the correct plane, special caution is required.

Scar tissue from the previous surgery can distort normal anatomical relationships, including the internal jugular vein and the recurrent laryngeal nerve. These structures may be located in completely unexpected positions, making them vulnerable to accidental injury by the scalpel (Fig. 18).

If the internal jugular vein is damaged under these conditions, a direct vascular suture is often unreliable. A more secure approach is to ligate the vein above and below the site of injury.

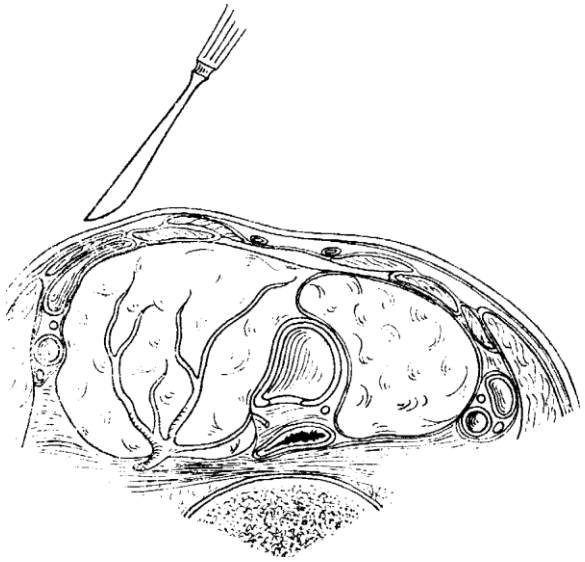


Figure 18 – Surgery for Recurrent Goiter, II.

Due to altered anatomical relationships from prior surgery, various complications can arise.

Changes in the course and location of the recurrent laryngeal nerve can often be inferred from the position of the inferior thyroid artery. If branches of this artery extend far anteriorly toward the lower pole of the lobe, it is likely that the recurrent nerve runs nearby.

However, when significant anatomical distortions make orientation difficult, to prevent potential nerve injury, it is recommended to switch to an intracapsular resection (Fig. 19).

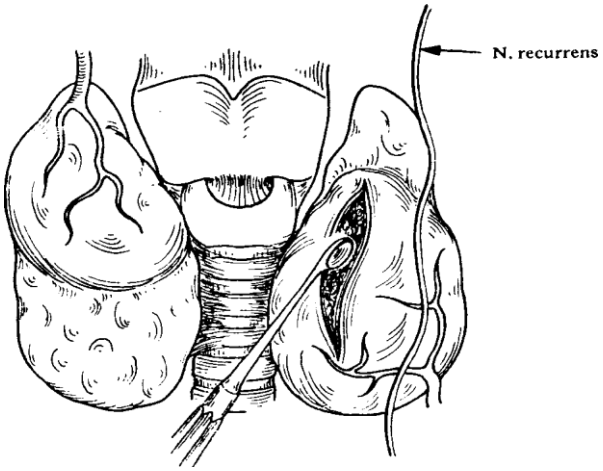


Fig. 19. Surgery for recurrent goiter, III. Contraction of the thyroid after ligation of its feeding Artery (right lobe) and intracapsular removal of thyroid parenchyma (left lobe).

This surgical approach is considered a forced or last-resort option, but it eliminates the risk of the previously noted injuries. Intra-capsular removal of altered thyroid parenchyma is performed using scissors or a sharp spoon, down to the inner surface of the capsule. This approach is complicated by significant parenchymal bleeding during tissue removal. This bleeding can be prevented by ligating the inferior thyroid artery at the Fuchsig, Keminger, or De Quervain points.

In any thyroid surgery, whether it is a primary operation or a procedure for recurrent goiter, it is important to remember that 80% of the gland’s blood supply comes from four arteries (two on each side): the superior and inferior thyroid arteries.

- The superior thyroid artery is the first branch of the external carotid artery.
- The inferior thyroid artery arises from the subclavian artery via the thyrocervical trunk, approximately a transverse finger above the clavicle, posterior to the internal jugular vein and lateral to the vertebral artery. The inferior thyroid artery ascends, passing behind the common carotid artery, turns medially, and reaches the lower-lateral surface of the thyroid gland.

If sudden severe bleeding occurs, especially if the source is the stump of a large vessel deep in the wound, one should not attempt to control it blindly by clamping the entire mass of poorly visualized and insufficiently differentiated tissue. Blind clamping may result in serious collateral injury to nearby structures.

Instead, the bleeding site should be compressed manually or tamponaded, and the main supplying vessel (superior or inferior thyroid artery) should be identified and ligated outside the bleeding area.

Postoperative Recurrent Goiter

Postoperative recurrent goiter (PRG) is one of the main reasons for unsatisfactory results after surgical treatment of benign thyroid diseases. PRG is a collective term describing the appearance of pathological thyroid symptoms in patients who have previously undergone thyroid surgery.

One of the key goals of thyroid surgery is to prevent recurrences. Over recent decades, according to various authors, the rate of recurrence has ranged from 3% to 7%.

Diagnosis of PRG is not always straightforward:

- Palpation is often uninformative, especially in early or small recurrences.
- Accurate assessment requires integration of clinical, laboratory, radioisotope, ultrasound, and radiologic findings to determine the functional activity of the recurrent goiter and its topographic-anatomical relationships with adjacent neck structures.

Factors influencing PRG occurrence, according to V.M. Sedov and colleagues, include:

1. Surgeon's qualification and experience in thyroid surgery,
2. Extent of thyroid tissue removed (adequacy of the operation),
3. Individual patient characteristics,
4. Morphological structure of the goiter,
5. Time elapsed since surgery,
6. Postoperative hormonal therapy.

Most authors distinguish between **"false" and "true" recurrences**:

- False recurrences occur early after surgery (within the first few months) due to leaving pathologically altered thyroid tissue during an inadequate intraoperative revision.
- True recurrences develop later (more than 1 year after surgery) in previously normal thyroid tissue under the influence of the same factors that caused the primary disease.

Recurrent toxic goiter refers to the reappearance of thyrotoxicosis symptoms that were present before surgery, with thyroid enlargement considered a major sign.

- A true recurrence in diffuse toxic goiter is defined as:
    - The patient achieved euthyroid status after the initial surgery,
    - Then, after some time, thyrotoxicosis reappears.

- False recurrence occurs when thyrotoxicosis symptoms never fully disappeared after surgery, i.e., euthyroid status was not achieved.

Recurrent Adenomatous (Nodular) Goiter

A recurrent adenomatous (nodular) goiter is defined as the reappearance of nodules in the operated lobe during the postoperative period. These nodules may be detected clinically during examination or through special instrumental diagnostic methods, such as:

- Radioisotope scanning
- Ultrasound scanning
- Indirect thyrolymphography

Some authors also include the appearance of nodules in the previously unoperated lobe under the concept of recurrent nodular goiter.

Unlike recurrent toxic goiter, a recurrent nodular endemic goiter may not affect thyroid function and can remain clinically silent.

Causes of recurrence:

- Excess thyroid parenchyma left behind during the initial surgery,
- Previously undetected proliferating nodules.

In such cases, the patient is considered “under-operated” and leaves the surgery with a potential risk of recurrence. According to several studies, false recurrences occur in more than 50% of patients operated on for recurrent goiter. In a small percentage of cases, a recurrent goiter may also develop after radical surgery if compensatory hyperplasia of the remaining tissue progresses into pathology.

Timing of recurrence:

- False recurrences are usually detected immediately or shortly after surgery.
- True recurrences occur later, after several months or even years.

Different authors define temporal criteria for recurrence:

- False recurrence: within 2–6 months, up to 1 year, or 2–3 years.
- True recurrence: after 6 months, or 2–3 years postoperatively.

Mechanisms of development remain unclear, and consequently, there is no standardized preventive strategy for recurrence.

True recurrences of diffuse toxic goiter are particularly challenging: literature suggests that even after a radical operation, hyperplasia may reappear in thyroid tissue at any unfavorable moment in life.
Contributing factors to recurrence may include:

- Persistence of primary etiopathogenetic mechanisms,
- Incompleteness of the initial surgery,

- Transformation of one type of goiter into another,
- Morphological type of the goiter,
- Presence of adenomatous tissue surrounding nodules,
- Inadequate postoperative hormone replacement therapy.

Some authors consider that a possible cause of true recurrences of diffuse toxic goiter in the long term is the presence of a pathological inhibitory focus in the cerebral cortex, which induces excitation in the subcortical structures, along with pathological changes in the nuclei and conducting pathways of the autonomic nervous system.

Many other **factors** may also contribute to disease recurrence, including:

- **Dysfunction between the pituitary gland and the thyroid gland,**
- **Disruption of mutual regulation in hormone production between the pituitary and thyroid,**
- **Insufficient iodine content in the environment,**
- **Disorders of iodine metabolism in the body.**

One cause of thyrotoxicosis recurrence is the influence of the gonads on the thyroid gland and functional disorders of the endocrine system in women. Thyrotoxicosis and its recurrences are more common in women than in men. Periods such as puberty, pregnancy, childbirth, and various disturbances in endocrine organ interactions can trigger the disease. In 33.3% of patients with toxic goiter, there is a history of gynecological disorders. The onset of the disease often coincides with pregnancy or the beginning of the climacteric period.

The occurrence of true recurrences of diffuse toxic goiter has also been associated by some researchers with the appearance of antithyroid antibodies in the serum. These antibodies, reacting with thyroid antigens, may cause damage to the surface of cells in the operated thyroid. Unfortunately, the role of these antibodies in the postoperative period of diffuse toxic goiter is still poorly studied. Typically, surgery is accompanied by a reduction or disappearance of thyrotropic antibodies, but within a year, these antibodies are detected in 20% of patients.

The mechanism of nodule formation in the thyroid gland is complex and largely unclear. Traditionally, several theories exist, based on factors that reduce the secretory activity of the thyroid gland:

- Iodine deficiency in water and food,
- Consumption of goitrogenic foods and medications,
- Disruption of enzymatic processes in thyroid hormone synthesis.

When iodine intake is insufficient to maintain euthyroidism, the production of the less iodinated but biologically more active hormone, triiodothyronine (T3), increases, while the content of thyroxine (T4)—the main thyroid hormone—decreases. Via feedback

mechanisms, TSH secretion rises, leading to an increase in the number of thyrocytes. Persistently elevated or fluctuating TSH levels result in changes ranging from diffuse hyperplasia to multinodular goiter.
Some authors believe that the main cause of recurrence is the progressive enlargement of the residual thyroid tissue; the greater the hormonal deficit, the more intense the regeneration and the higher the risk of recurrence.
Other authors consider that recurrence of nodular goiter can result from:

- **insufficient preoperative evaluation,**
- **inadequate attention to diagnostic data during surgery,**
- **insufficient revision of the residual thyroid tissue,**
- **inadequate postoperative management,**
- **morphological features of the thyroid tissue in multinodular goiter.**

However, the majority of researchers consider the primary cause of goiter recurrence to be the non-radical nature of the first operation, including leaving the upper poles, isthmus, pyramidal lobe, retrotracheal and retroesophageal segments—i.e., failure to adhere to the principle of subtotal resection, as well as the development of postoperative hypothyroidism, which triggers a thyrotropic stimulatory mechanism via feedback, among other factors.
Thus, regardless of the type of goiter, the rate of disease recurrence remains high according to the literature. Despite recent advances in endocrinology, modern diagnostic methods, and improved surgical techniques, it is still not possible to significantly reduce the recurrence rate.
The insufficient study of this issue has led to the absence of a universally accepted classification of thyroid disease recurrences. Based on the analysis of etiopathogenesis and morphological studies, the following classification of recurrent goiter was proposed (Romanchishen A.F. et al., 1996):

1. **Continued growth** of residual tissue: adenomas, nodular colloid goiters, thyroid cancer, or regional metastases of thyroid cancer.
2. **Recurrence of previous thyroid disease:**
    - diffuse toxic and euthyroid forms of goiter,
    - nodular forms of goiter,
    - thyroid cancer.
3. Combination of several previous diseases.
4. New diseases in the **thyroid remnant**:
    - diffuse forms of goiter,
    - nodular forms of goiter,
    - thyroid cancer in the remnant after surgery for another disease,
    - combination of several new diseases.
5. **Combination of new disease and recurrence of a previous disease.**

Surgical Treatment of Recurrent Goiter

The highest risk of recurrence is observed in patients with multinodular goiter. According to various studies, this group constitutes 50–70% of all patients undergoing repeat thyroid surgery. Recurrences are more frequent after inadequate operations, such as conservative resections or simple enucleation of nodules.

The surgical strategy for recurrent goiter remains a subject of debate.

- According to V.M. Sedov et al., indications for repeat surgery in recurrent diffuse toxic goiter (DTG) include:
  - Large goiter size,
  - Compression of surrounding organs and tissues,
  - Contraindications to thyrostatic therapy.
- I.S. Breido suggests that in cases of recurrent nodular goiter, surgery is indicated only if nodules appear on the side of the previous intervention. For recurrence in an previously unoperated lobe, surgery is generally not recommended.
- Some authors advocate a more aggressive approach, recommending surgery for all cases of adenomatous recurrent goiter, while others suggest conservative management if there are no life-threatening indications.

There is also evidence suggesting that patients with recurrent goiter represent a high-risk group for thyroid cancer, which partially explains the aggressive surgical approach for these patients.

Technical considerations:

- Surgery for postoperative recurrent goiter is technically challenging and requires a highly skilled surgeon.
- Repeat thyroid operations are often atypical and demand individualized planning.
- The technical difficulties arise from:
  - Extensive scar tissue from previous surgery,
  - Unusual direction of recurrence growth,
  - Altered topographic and anatomical relationships in the neck (vessels, nerves, trachea, larynx, parathyroids, residual thyroid tissue).

Summary:

- Surgery remains the main method of radical treatment for thyroid diseases.
- The choice of surgical method for postoperative toxic and nontoxic recurrent goiter remains complex and unresolved, due to relatively high complication rates and suboptimal outcomes.
- Additionally, thyroid cancer is not uncommon in patients with recurrent goiter, further complicating management decisions.

Surgical Treatment of Recurrent Toxic Goiter

Some authors believe that a 3-month course of medication is sufficient to establish criteria for remission. However, most specialists consider medication therapy primarily as preoperative preparation for patients with postoperative recurrence of diffuse toxic goiter (DTG).

The goal of preoperative preparation is to:

- Reduce or eliminate manifestations of thyrotoxicosis,
- Normalize impaired functions of various organs and systems,
- Correct relative glucocorticoid deficiency.

Some authors recommend radioactive iodine for preoperative preparation. However, this carries risks, including hypothyroidism after treatment and potential genetic damage, particularly in young patients.

Key points of preoperative preparation:

- Mainly involves inorganic iodine-containing medications.
- If iodine is not tolerated, beta-blockers and corticosteroids are used successfully.
- Special attention is given to patients' psychological vulnerability, often increased due to previous surgery and comorbid conditions.
- The preparation aims to reduce thyrotoxicosis, stabilize neuropsychological function, and normalize organ function.

Anesthesia:

- The most commonly used method for surgery in recurrent DTG is local anesthesia combined with neuroleptanalgesia.
    - Local anesthetic blocks reflexogenic zones and allows hydraulic tissue dissection, facilitating technically challenging and atypical procedures.
- However, most endocrine surgeons prefer general anesthesia with endotracheal intubation, arguing that it:
    - Frees the patient from awareness during surgery,
    - Provides optimal operating conditions,
    - Does not increase the risk of recurrent laryngeal nerve injury, contrary to some surgeons' concerns.

Surgical approach:

- Subtotal thyroidectomy is the most common procedure for recurrent DTG.
- To prevent postoperative hypothyroidism, especially in recurrent cases, recent trends include increasing the amount of thyroid tissue left in situ, deviating from the classical Nikolaev technique.

Surgical Treatment of Recurrent Euthyroid Goiter

Currently, there are many publications on the destruction of cystic and nodular thyroid lesions under ultrasound guidance with favorable results. Sclerosing agents that have been proposed include tetradecyl sulfate, tetracycline, hydroxy-polyethoxyoctadecane, hyperosmolar solutions, and 95% ethanol (ethyl alcohol). This method was proposed in 1990 by Livraghi as an alternative to surgical treatment and radioactive iodine therapy.

The surgical strategy for recurrent goiter remains controversial. According to I.S. Breydo (1998), surgery for recurrent nodular goiter is indicated only if nodules develop on the side of the previous operation. For recurrence of adenomatous goiter in a previously unoperated lobe, he recommends avoiding surgery.

Some authors adopt a more aggressive approach, considering the presence of postoperative adenomatous recurrent goiter as an indication for surgery in all cases. Other researchers recommend against surgical intervention for benign postoperative recurrent goiter in the absence of life-threatening indications.

Technical considerations:

- Surgery for postoperative recurrent goiter is technically challenging and requires a highly skilled surgeon.
- Repeat operations are often atypical and require individual planning.
- Technical difficulties arise due to scar tissue from previous surgery, unusual growth direction of the recurrence, and changes in the anatomical relationships of neck structures—vessels, nerves, trachea, larynx, parathyroid glands, and thyroid remnants.

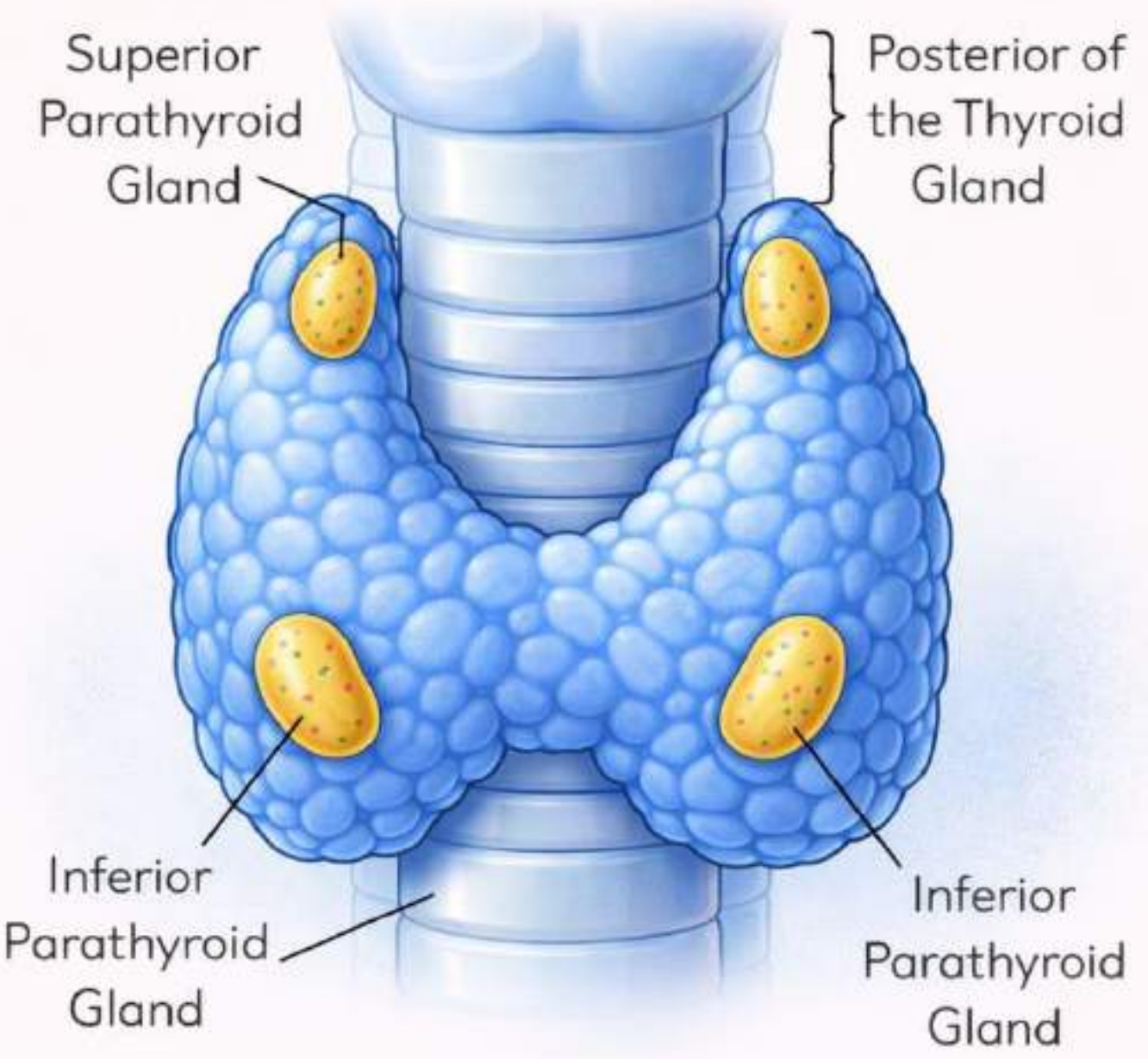
Extent of surgery:

- Many surgeons consider it sufficient to remove the nodular formations while preserving as much of the macroscopically normal thyroid tissue as possible, which often helps prevent postoperative hypothyroidism.
- Some authors recommend subtotal thyroidectomy for recurrent multinodular goiter.
- Others believe that for bilateral multinodular goiter, total thyroidectomy is necessary.

Postoperative outcomes and complications:

- Laryngeal nerve injury occurs in 0.9% to 5.9% of cases, sometimes requiring tracheostomy.
- Bleeding during or after surgery occurs in 1.5% to 2.7% of cases.
- Postoperative thyrotoxic reactions occur in 0.5% to 7.5% or more of cases.
- Parathyroid gland injury can cause postoperative tetany in 0.5% to 0.9% of patients.

Parathyroid Gland



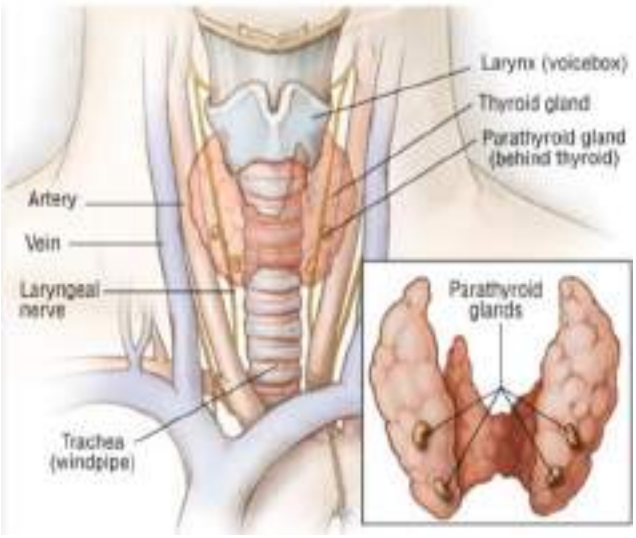
Parathyroid Gland Diseases and Surgery

Embryology and Anatomy of the Parathyroid Glands

- The parathyroid glands originate from the branchial pouches.
- The superior parathyroid glands develop from the 4th branchial pouch, while the inferior parathyroid glands arise from the 3rd branchial pouch.

- Number of Glands:

- Typically, there are 4 parathyroid glands (about 80% of cases).
- In about 13% of cases, there are more than 4 glands; in 5% of cases, there are 3 or fewer glands; and in another 5% of cases, there are 6 glands.



- Location:

- The location of the superior parathyroid glands is more consistent. In 80% of cases, they are found near the cricoid cartilage level, typically located on the posterior aspect of the thyroid gland, in the middle to upper region.
- The location of the inferior parathyroid glands is less consistent. They are generally found within a 2 cm diameter circle centered at the junction of the inferior laryngeal nerve and the inferior thyroid artery. However, they can vary in location and may be found in places such as the thymus, upper mediastinum, pericardium, or paraesophageal groove. Approximately 2% are intrathyroidal.

- Cellular Composition:

- The parathyroid glands consist of several types of cells, including:
  - **Chief Cells:** These cells secrete parathyroid hormone (PTH).
  - **Oxyphil Cells**: Acidophilic cells that are more abundant in older individuals.
  - **Clear Cells:** Cells that contain a large amount of glycogen, giving them a clear appearance.

Hyperparathyroidism

- Definition: Hyperparathyroidism is the condition where the parathyroid glands are overactive.

- Classification: It can be classified as primary, secondary, or tertiary.

• Primary Hyperparathyroidism

- Pathophysiology: In primary hyperparathyroidism, there is an increased secretion of parathyroid hormone (PTH) from pathological parathyroid glands.

- Clinical Presentation:

- Characterized by elevated PTH and calcium levels with low phosphate levels.
- It is the most common cause of hypercalcemia in the general population.
- Among hospitalized patients, it is the second most common cause of hypercalcemia after cancer.
- Commonly seen in 0.1% to 0.3% of the population.
- It is four times more common in women and its incidence increases with age, particularly in postmenopausal women.
- Most cases of primary hyperparathyroidism are sporadic.
- It can also occur in association with hereditary syndromes such as MEN1 (Multiple Endocrine Neoplasia type 1), MEN2A, isolated familial hyperparathyroidism, and jaw tumor syndrome.

MEN 1 (Wermer Syndrome, PPP)

- Parathyroid: Hyperparathyroidism is the earliest and most common manifestation of MEN 1, often presenting before the age of 40.

- Pituitary Adenoma: Frequently presents as prolactinoma.

- Pancreatic Islet Cell Tumor: Gastrinoma is the most common.

• Etiology of Primary Hyperparathyroidism

- Exact Cause: The exact cause is often unknown.

- Low-dose Radiation Exposure: There is an association with low-dose radiation exposure, typically manifesting 30-40 years after exposure.

- Familial Predisposition: Genetic factors may play a role in some cases.

- Diet: Certain diets may be associated with the condition.

- Intermittent Sunlight Exposure: May be related to the development of primary hyperparathyroidism.

- Aging and Kidney Function: Decreased renal function and calcium leakage with advancing age may contribute.

- Lithium Therapy: Lithium treatment is known to be associated with increased PTH levels and mild hypercalcemia.

- **Pathogenesis**

- Single Gland Disease: About 80% of cases are due to a single parathyroid adenoma.

- Multiple Gland Disease: In 15-20% of cases, multiple gland involvement (hyperplasia or multiple adenomas) occurs.

- Parathyroid Cancer: About 1% of cases are related to parathyroid carcinoma.

- **Clinical Manifestations**

- Symptomatology: Most patients are minimally symptomatic or asymptomatic. However, detailed questioning often reveals non-specific symptoms such as fatigue, polyuria, polydipsia, nocturia, bone and joint pain, constipation, anorexia, nausea, itching, depression, and memory loss.

- Renal Complications:

- Renal symptoms or some degree of kidney dysfunction are present in most patients.

- The most severe clinical consequences of primary hyperparathyroidism are often kidney-related.

- Kidney stones occur in approximately 25-30% of cases.

- Other renal complaints include polyuria, polydipsia, and nocturia.

- Hypertension:

- Occurs frequently, in about 50% of cases, and is more common in elderly patients.

- It is related to the degree of renal dysfunction and is the symptom least likely to improve after parathyroidectomy.

- Bone Disease:

- Overt bone disease is rare (5-15% of cases).

- Bone pain, tenderness, and pathological fractures are uncommon, whereas osteopenia and osteoporosis are more frequent.

- Osteitis fibrosa cystica is very rare.

- Brown tumors and bone cysts may be present.

- The extent of bone damage correlates with alkaline phosphatase levels.

- Neurological, Psychiatric, and Neuromuscular Symptoms:

- Patients may exhibit a range of neurological or psychiatric disorders, from depression and anxiety to psychosis or coma.

- Symptoms such as muscle fatigue, weakness, and exhaustion, especially in the proximal muscles, may also develop.

- Gastrointestinal Symptoms:

- Increased incidence of peptic ulcers, pancreatitis, and gallstones.

- Pancreatitis is generally seen only in patients with severe hypercalcemia (calcium levels above 12.5 mg/dL).

• Diagnosis

- Laboratory Findings:

- Diagnosis is made by elevated calcium and serum intact PTH (iPTH) levels.

- About half of the patients have low serum phosphate levels.

- Approximately 60% have increased 24-hour urinary calcium excretion (>200 mg/day).

- In benign familial hypocalciuric hypercalcemia, 24-hour urinary calcium excretion is distinctly low (<100 mg/day).

- Chloride levels are elevated, and mild hyperchloremic metabolic acidosis may be present in 80% of cases.

- A chloride/phosphate ratio >33 is diagnostic.

- Alkaline phosphatase is elevated in 10-40% of patients.

- Normocalcemic Primary Hyperparathyroidism:

- Conditions that may cause normocalcemia in primary hyperparathyroidism include:

- Vitamin D deficiency

- Hypoalbuminemia

- Excessive hydration

- High dietary phosphate intake

- Imaging:

- Routine radiological investigations often do not detect bone lesions in most patients.

- Imaging is recommended only for patients with elevated alkaline phosphatase levels.

- Advanced cases with severe hypercalcemia may show characteristic findings of osteitis fibrosa cystica on X-rays.

- Skull X-rays may reveal a "pepper pot" appearance due to cortical bone erosion.

- Hand X-rays may show subperiosteal resorption, particularly in the middle and distal phalanges.

- Bone mineral densitometry studies are increasingly used to assess the impact of primary hyperparathyroidism on bone and have become the standard method for diagnosing osteoporosis in these patients.

Physical Examination: A palpable neck mass in a patient with primary hyperparathyroidism suggests either parathyroid cancer or a thyroid nodule, as parathyroid tumors are generally not palpable.

• Treatment

- Surgery is recommended if the patient is symptomatic or younger than 50 years old.

- Asymptomatic Patients:

- Asymptomatic primary hyperparathyroidism is defined by the absence of common symptoms and findings associated with bone, kidney, gastrointestinal, or neuromuscular issues.

- Asymptomatic patients with primary hyperparathyroidism can be managed with observation rather than immediate surgery.

- However, some of these patients may eventually require surgical treatment.

Indications for Surgery in Asymptomatic Primary Hyperparathyroidism

- Significant Hypercalcemia: Calcium levels greater than 1 mg/dL above the normal range.

- Decreased Glomerular Filtration Rate (GFR): GFR less than 60 ml/min.

- Reduced Bone Mineral Density: A decrease in bone mineral density (measured in the lumbar spine, hip, or distal radius) by more than 2.5 standard deviations from normal bone mass (T-score < -2.5).

- Inability to Ensure Close Monitoring: When close follow-up is not feasible.

- Age Below 50 Years.

Surgical Treatment

- Single Adenoma: The treatment is solitary parathyroidectomy.

- Multiple Adenomas: If two or three parathyroid glands are enlarged, the enlarged glands are removed. Therefore, it is essential to visualize and evaluate all four parathyroid glands during standard surgical treatment.

- Multiglandular Hyperplasia: If all glands are enlarged, subtotal parathyroidectomy (removal of 3.5 glands) or total parathyroidectomy with autotransplantation is performed.

Secondary Hyperparathyroidism

- In secondary hyperparathyroidism, PTH levels are elevated, but this is due to chronic stimulation of the parathyroid glands caused by decreased serum calcium levels.

- The primary cause of the low serum calcium is usually kidney disease. However, it can also develop due to insufficient calcium or vitamin D intake or malabsorption.

- The parathyroid glands undergo chief cell hyperplasia.

- Patients are generally hypocalcemic or normocalcemic.

- Accompanying hyperphosphatemia further increases PTH secretion. Intact PTH (iPTH) levels, which normally range from 10-65 pg/mL, often rise to 500-1500 pg/mL.

- In patients with chronic kidney failure, significant alkaline phosphatase elevation and itching are warning signs.

- The skeletal changes in secondary hyperparathyroidism are similar to those in primary hyperparathyroidism, with the key difference being that ectopic calcifications are much more common in secondary hyperparathyroidism.

- The initial treatment for secondary hyperparathyroidism is medical.

- Dietary phosphate intake is restricted, and oral phosphate binders are given to treat hyperphosphatemia.

- Calcium and vitamin D replacement therapy is administered.

- Calcimimetic drugs may be used to reduce plasma PTH levels.

Surgical Indications in Secondary Hyperparathyroidism:

- Persistent bone pain and itching despite maximal medical therapy.

- Calcium-phosphate product > 70.

- Calcium > 11 mg/dL with very high PTH levels.

- Calciphylaxis:

  - A severe complication of secondary hyperparathyroidism that can affect extremities and be life-threatening.

- Characterized by painful, purplish extremities.

- Frequently becomes necrotic, leading to non-healing ulcers, gangrene, sepsis, and death.

- Progressive renal osteodystrophy:

- Patients with soft tissue calcification and tumoral calcinosis.

- Localization studies are not necessary.

- Since all glands are hyperplastic, bilateral neck exploration is required.

- Subtotal parathyroidectomy or total parathyroidectomy with forearm autotransplantation is performed.

Tertiary Hyperparathyroidism:

- Tertiary hyperparathyroidism develops due to the autonomy of the chief cell hyperplasia seen in secondary hyperparathyroidism.

- Surgical intervention is indicated if symptomatic disease is present or if autonomous PTH secretion persists for more than a year following a successful kidney transplant.

Complications of Parathyroidectomy:

- Vocal cord paralysis due to recurrent laryngeal nerve injury.

- Hypoparathyroidism:

- Both complications are considered permanent if they persist for more than 6 months.

Hypoparathyroidism is usually temporary, resulting from impaired glandular blood supply, and permanent cases are rare.

Hypoparathyroidism:

- Most common cause: Thyroid surgery, especially total thyroidectomy.

- Hypoparathyroidism can also develop after parathyroid surgery, such as the removal of a parathyroid adenoma or after subtotal parathyroidectomy or total parathyroidectomy with forearm autotransplantation in patients with hyperplasia.

- Distinguishing hypoparathyroidism from "**hungry bone syndrome**":

- Hungry bone syndrome: Occurs after parathyroidectomy when calcium shifts back into the bones, leading to hypocalcemia.

- Commonly seen in patients with kidney disease and severe bone disease, where calcium is deposited in the bones after surgery.

- **Laboratory findings in hypoparathyroidism**:

- Low serum calcium levels.

- High phosphorus levels.

- Low PTH levels.

- **Pseudohypoparathyroidism**: Characterized by resistance to PTH in target organs.

-Lab findings:Low calcium.High phosphorus.High PTH levels.

- Hungry bone syndrome: Both calcium and phosphorus levels are low, but PTH levels are normal.

- DiGeorge syndrome: A congenital condition where the parathyroid glands may be absent.

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