

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**  
**Харківський національний медичний університет**

**DISEASES OF ENDOCRINE SYSTEM.  
HYPOTHALAMIC-PITUITARY SYSTEM DISEASES,  
DISTURBANCES OF GROWTH. OBESITY.  
MECHANISM OF ACTION OF HYPOTHALAMIC  
AND PITUITARY HORMONES**

*Methodological recommendations  
for students of IV course*

**ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ.  
ЗАХВОРЮВАННЯ ГІПОТАЛАМО-ГІПОФІЗАРНОЇ  
СИСТЕМИ, ПОРУШЕННЯ РОСТУ. ОЖИРІННЯ.  
МЕХАНІЗМ ДІЇ ГОРМОНІВ ГІПОТАЛАМУСА І ГІПОФІЗА**

*Методичні вказівки  
для студентів IV курсу*

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## **Module №1 “Bases of diagnostics, treatment and prevention of main diseases of the endocrine system”**

### **Topic “Diseases of the hypothalamic-pituitary system. Disturbance of grows. Obesity. Mechanism of action of hormones”**

#### **The purpose:**

1. To study the method of determination of etiologic and pathogenic factors of diseases of the hypothalamic-pituitary system (HPS).
2. To familiarize students with classifications of diseases of HPS.
3. Determination of variants of clinical picture of HPS diseases.
4. Familiarization with the atypical clinical variants of diseases of HPS.
5. Familiarization of students with possible complications of diseases of HPS.
6. Working off the methodology of determination of basic diagnostic criteria of HPS diseases.
7. Planning of patients examination with the diseases of HPS.
8. Analyzing of results of laboratory and instrumental investigations that are used for diagnostics of HPS diseases.
9. Tactic of conducting differential diagnostics of HPS diseases.
10. Technology of grounding and formulation of diagnosis for HPS diseases.
11. Planning of treatment of patients with the HPS diseases.
12. Deontological and psychological features of curation of patients with the disease of HPS.

#### **What a student should know?**

1. Determination of concept of HPS diseases.
2. Epidemiology of HPS diseases.
3. Risk factors of HPS diseases.
4. Mechanism of hormonal and metabolic disorders at the diseases of HPS.
5. Etiology and pathogenesis of HPS diseases.
6. Classification of HPS diseases.
7. Clinical picture of HPS diseases.
8. Polyorganic complications of HPS diseases.
9. Diagnostic criteria of HPS diseases.
10. Choice of method of treatment of HPS diseases.

#### **What a student should be able to do?**

1. To define the risk factors of HPS diseases.
2. To diagnose the HPS disease.
3. To determine the degree of development of the second sexual signs.
4. To define character of polyorganic complications of HPS diseases.
5. To analyze the results of hormonal investigations and functional tests.
6. To estimate the results of ultrasound and roentgenologic investigations HPS.
7. To conduct the differential diagnostics of HPS diseases.

8. Drafting of long-term plan of treatment of HPS diseases and their complications, technology of bringing in of patient to participation in a medical process.
9. Co-operating with contiguous specialists (surgeon, gynecologist, ect.) on the stage of defining of complete diagnosis, choice of method and tactic of treatment and further supervision

### **Content of topic**

#### **ACROMEGALY AND GIGANTISM**

Growth hormone stimulates skeletal and soft tissue growth. GH excess therefore produces gigantism in children (if acquired before epiphyseal fusion) and acromegaly in adults. Both are due to a pituitary tumour in almost all cases. Hyperplasia due to GHRH excess is very rare. Overall incidence is approximately 3–4/million per year and the prevalence is 50–80/million worldwide.

### **Clinical features**

One-third of patients present with changes in appearance, one quarter with visual field defects or headaches; in the remainder the diagnosis is made by an alert observer in another clinic, e.g. GP, diabetic, hypertension, dental, dermatology. Sleep apnoea is common and requires investigation and treatment if there are suggestive symptoms. Sweating, headaches and soft tissue swelling are particularly useful symptoms of persistent growth hormone secretion. Headache is very common in acromegaly and may be severe even with small tumours; it is often improved after surgical cure or with somatostatin analogues.

<b>Symptoms</b>	<b>Signs</b>
Change in appearance	Prominent supraorbital ridge
Increased size of hands/feet	Prognathism
Headaches	Arthropathy
Excessive sweating	Interdental separation
Visual deterioration	Large tongue
Tiredness	Hirsutism
Weight gain	Thick greasy skin
Amenorrhoea oligomenorrhoea in women	Spade-like hands and feet
Galactorrhoea	Tight rings
Impotence or poor libido	Carpal tunnel syndrome
Deep voice	Colonic polyps
Goitre	Visual field defects
Breathlessness Pain/tingling in hands	Galactorrhoea
Polyuria/polydipsia	Hypertension
Muscular weakness	Oedema
Joint pains	Heart failure
	Proximal myopathy
	Glycosuria

## Investigation

**GH levels** may exclude acromegaly if undetectable but a detectable value is non-diagnostic taken alone. Normal adult levels are 1 mU/L for most of the day except during stress or a 'GH pulse'.

■ **A glucose tolerance test** is diagnostic if there is no suppression of GH. Acromegalics fail to suppress GH below 1 mU/L and some show a paradoxical rise; about 25% of acromegalics have a diabetic glucose tolerance test.

■ **IGF-1 levels** are almost always raised in acromegaly – a single plasma level of IGF-1 reflects mean 24-hour GH levels and is useful in diagnosis. A normal IGF-1 together with GH 5 mU/L (2.5 ng/L) may be taken to exclude acromegaly if the diagnosis is clinically unlikely.

■ **Visual field examination** – defects are common, e.g. bitemporal hemianopia.

■ **MRI scan** of pituitary if above tests abnormal. This will almost always reveal the pituitary adenoma.

■ **Pituitary function** – partial or complete anterior hypopituitarism is common.

■ **Prolactin** – mild to moderate hyperprolactinaemia occurs in 30% of patients. In some, the adenoma secretes both GH and prolactin.

## Management and treatment

Untreated acromegaly results in markedly reduced survival. Most deaths occur from heart failure, coronary artery disease and hypertension-related causes. In addition, there is an increase in deaths due to neoplasia, particularly large bowel tumours. Treatment is therefore indicated in all except the elderly or those with minimal abnormalities. The aim of therapy is to achieve a mean growth hormone level below 5 mU/L (or 2.5 ng/L); this has been shown to reduce mortality to normal levels. A normal IGF-1 is also a goal of therapy.

Complete cure is often slow to achieve, if possible at all. Progress can be assessed by monitoring GH and IGF-1 levels.

When present, hypopituitarism should be corrected and concurrent diabetes and/or hypertension should be treated conventionally; both usually improve with treatment of the acromegaly. Some specialist centres advocate regular colonoscopy to detect and remove colonic polyps to reduce the risk of colonic cancer.

■ **Surgery.** Trans-sphenoidal surgery is the appropriate first-line therapy. It will result in clinical remission in a majority of cases (60–90%) with pituitary microadenoma, but in only 50% of those with macroadenoma. Very high pre-operative GH and IGF-1 levels are also poor prognostic markers of surgical cure. Surgical success rates are variable and highly dependent upon experience, and a specialist pituitary surgeon is essential. Transfrontal surgery is rarely required except for massive macroadenomas. There is approximately a 10% recurrence rate.

■ **Pituitary radiotherapy.** External radiotherapy is normally used after pituitary surgery fails to normalize GH levels rather than as primary therapy. It is often combined with medium-term treatment with a somatostatin analogue or a dopamine agonist because of the slow biochemical response to radiotherapy,

which may take 10 years or more and is often associated with hypopituitarism which makes it unattractive in patients of reproductive age. Stereotactic radiotherapy is used in some centres.

■ **Medical therapy.** There are three receptor targets for the treatment of acromegaly, viz. pituitary somatostatin receptors, dopamine (D2) receptors and growth hormone receptors in the periphery.

– **Somatostatin receptor agonists.** Octreotide and lanreotide are synthetic analogues of somatostatin that selectively act on somatostatin receptor subtypes (SST2 and SST5), which are highly expressed in growth-hormone-secreting tumours. These drugs were used as a short-term treatment whilst other modalities become effective, but now are sometimes used as primary therapy. They reduce GH and IGF levels in most patients. Both drugs are typically administered as monthly depot injections and are generally well tolerated but are associated with an increased incidence of gallstones and are expensive.

– **Dopamine agonists.** Dopamine agonists act on D2 receptors and can be given to shrink tumours prior to definitive therapy or to control symptoms and persisting GH secretion; they are probably most effective in mixed growth-hormone-producing (somatotroph) and prolactin-producing (mammotroph) tumours. The doses are bromocriptine 10–60 mg daily or cabergoline 0.5 mg daily (higher than for prolactinomas) which should be started slowly. Given alone they reduce GH to ‘safe’ levels in only a minority of cases – but they are useful for mild residual disease or in combination with somatostatin analogues. Drugs with combined somatostatin and dopamine receptor activity are under development.

– **Growth hormone antagonists.** Pegvisomant (a genetically modified analogue of GH) is a GH receptor antagonist which has its effect by binding to and preventing dimerization of the GH receptor. It does not lower growth hormone levels or reduce tumour size but has been shown to normalize IGF-1 levels in 90% of patients. Its main role at the present time is treatment of patients in whom GH and IGF levels cannot be reduced to safe levels with somatostatin analogues alone, surgery or radiotherapy.

## **HYPOPITUITARISM**

### **Pathophysiology**

Deficiency of hypothalamic releasing hormones or of pituitary trophic hormones can be selective or multiple. Thus isolated deficiencies of GH, LH/FSH, ACTH, TSH and vasopressin are all seen, some cases of which are genetic and congenital and others sporadic and autoimmune or idiopathic in nature.

Multiple deficiencies usually result from tumour growth or other destructive lesions. There is generally a progressive loss of anterior pituitary function. GH and gonadotrophins are usually first affected. Hyperprolactinaemia, rather than prolactin deficiency, occurs relatively early because of loss of tonic inhibitory control by dopamine. TSH and ACTH are usually last to be affected.

Panhypopituitarism refers to deficiency of all anterior pituitary hormones; it is most commonly caused by pituitary tumours, surgery or radiotherapy. Vasopressin and oxytocin secretion will be significantly affected only if the hypothalamus is involved by a hypothalamic tumour or major suprasellar extension of a pituitary lesion, or if there is an infiltrative/inflammatory process. Posterior pituitary deficiency is rare in an uncomplicated pituitary adenoma.

### **Causes**

**Congenital** (Isolated deficiency of pituitary hormones (e.g. Kallmann's syndrome); POU1F1 (Pit-1), Prop1, HESX1 mutations)

**Infective** (Basal meningitis (e.g. tuberculosis), Encephalitis □ Syphilis □)

**Vascular** (Pituitary apoplexy, □ Sheehan's syndrome (postpartum necrosis), Carotid artery aneurysms)

**Immunological** (Pituitary antibodies)

**Neoplastic** (Pituitary or hypothalamic tumours, Craniopharyngioma, Meningiomas, Gliomas, Pinealoma, Secondary deposits, especially breast Lymphoma)

### **Traumatic**

**Infiltrations** (Sarcoidosis, Langerhans' cell histiocytosis, Hereditary haemochromatosis, Hypophysitis)

**Others** (Radiation damage, Fibrosis Chemotherapy, Empty sella syndrome)

**'Functional'** (Anorexia nervosa, Starvation, Emotional deprivation)

### **Clinical features**

Symptoms and signs depend upon the extent of hypothalamic and/or pituitary deficiencies, and mild deficiencies may not lead to any complaint by the patient. In general, symptoms of deficiency of a pituitary-stimulating hormone are the same as primary deficiency of the peripheral endocrine gland.

- Secondary hypothyroidism and adrenal failure both lead to tiredness and general malaise.
- Hypothyroidism causes weight gain, slowness of thought and action, dry skin and cold intolerance.
- Hypoadrenalism causes mild hypotension, hyponatraemia and ultimately cardiovascular collapse during severe intercurrent stressful illness.
- Gonadotrophin and thus gonadal deficiencies lead to loss of libido, loss of secondary sexual hair, amenorrhoea and erectile dysfunction.
- Hyperprolactinaemia may cause galactorrhoea and hypogonadism.
- GH deficiency causes growth failure in children and impaired well-being in some adults.
- Weight may increase (due to hypothyroidism, see above) or decrease in severe combined deficiency (pituitary cachexia).
- Long-standing panhypopituitarism gives the classic picture of pallor with hairlessness ('alabaster skin').

Particular syndromes related to hypopituitarism are:

**Kallmann's syndrome.** This syndrome is isolated gonadotrophin (GnRH) deficiency.

**Septo-optic dysplasia.** This is a rare congenital syndrome (associated with mutations in the HESX-1 gene) presenting in childhood with a clinical triad of midline forebrain abnormalities, optic nerve hypoplasia and hypopituitarism.

**Sheehan's syndrome** is due to pituitary infarction following postpartum haemorrhage and is rare in developed countries.

**Pituitary apoplexy.** A pituitary tumour occasionally enlarges rapidly owing to infarction or haemorrhage. This may produce severe headache and sudden severe visual loss sometimes followed by acute life-threatening hypopituitarism.

**The 'empty sella' syndrome.** An 'empty sella' is sometimes reported on pituitary imaging. All or most of the sella turcica is devoid of apparent pituitary tissue, but, despite this, pituitary function is usually normal, the pituitary being eccentrically placed and flattened against the floor or roof of the fossa.

### **Treatment**

- Steroid and thyroid hormones are essential for life. Both are given as oral replacement drugs, as in primary thyroid and adrenal deficiency, aiming to restore the patient to clinical and biochemical normality and levels are monitored by routine hormone assays. **NB** Thyroid replacement should not commence until normal glucocorticoid function has been demonstrated or replacement steroid therapy initiated, as an adrenal 'crisis' may otherwise be precipitated.
- Sex hormones are replaced with androgens and oestrogens, both for symptomatic control and to prevent long-term problems related to deficiency (e.g. osteoporosis).
- When fertility is desired, gonadal function is stimulated directly by human chorionic gonadotrophin, purified or biosynthetic gonadotrophins, or indirectly by pulsatile **gonadotrophin-releasing** hormone (GnRH – also known as luteinizing hormone-releasing hormone, LHRH); all are expensive and time-consuming and should be restricted to specialist units.
- GH therapy is given in the growing child, under the care of a paediatric endocrinologist. In adult GH deficiency, GH therapy also produces improvements in body composition, work capacity and psychological well-being, together with reversal of lipid abnormalities associated with a high cardiovascular risk, and this may result in significant symptomatic benefit in some cases.
- Glucocorticoid deficiency may mask impaired urine concentrating ability, diabetes insipidus only becoming apparent after steroid replacement.



## GROWTH FAILURE: SHORT STATURE

When children or their parents complain of short stature, particular attention should focus on:

- intrauterine growth retardation, weight and gestation at birth
- possible systemic disorders – any system, but especially small bowel disease
- evidence of skeletal, chromosomal or other congenital abnormalities
- endocrine status – particularly thyroid
- dietary intake and use of drugs, especially steroids for asthma
- emotional, psychological, family and school problems.

School, general practitioner, clinic and home records of height and weight should be obtained if possible to allow growth-velocity calculation. If unavailable, such data must be obtained prospectively.

A child with normal growth velocity is unlikely to have significant endocrine disease and the commonest cause of short stature in this situation is pubertal or ‘constitutional’ delay. However, low growth velocity without apparent systemic cause requires further investigation. Sudden cessation of growth suggests major physical disease; if no gastrointestinal, respiratory, renal or skeletal abnormality is apparent, then a cerebral tumour or hypothyroidism is likeliest.

Consistently slow-growing children require full endocrine assessment. Around the time of puberty, where constitutional delay is clearly shown and symptoms require intervention, then very-low-dose sex steroids in 3- to 6-month courses will usually induce acceleration of growth.

### Investigations

Systemic disease having been excluded, perform:

- **Thyroid function tests** – serum TSH and free T4 to exclude hypothyroidism.
- **GH status.** Basal levels are of little value, though urinary GH measurements may prove to be of some value in screening. Dynamic tests include the GH response to insulin (the ‘gold standard’), glucagon, arginine, exercise and clonidine. Tests should only be performed in centres experienced in their use and interpretation. Normal responses depend on test and GH assay used.
- **Blood levels of IGF-1 (insulin-like growth factor-1) and IGF-BP3 (binding protein 3)** may provide evidence of GH undersecretion.
- **Assessment of bone age.** Non-dominant hand and wrist X-rays allow assessment of bone age by comparison with standard charts.

**Karyotyping in females.** Turner’s syndrome is associated with short stature. It is thought that this is due to a defect in the short stature homeobox (SHOX) gene which has a role in non-GH mediated growth.

### Treatment

Systemic illness should be treated and primary hypothyroidism treated with levothyroxine. For GH insufficiency, recombinant GH (somatropin) is given as nightly injections in doses of 0.17–0.35 mg/kg per week. Treatment is expensive

and should be supervised in expert centres. Human GH (collected from pituitaries) was previously used but was withdrawn as cases of Creutzfeldt–Jakob disease were reported.

GH treatment in so-called ‘short normal’ children has not been shown to produce any worthwhile increase in final height. In Turner’s syndrome large doses of GH are effective in increasing final height, especially in combination with appropriate very-low-dose oestrogen replacement. Familial cases of resistance to GH owing to an abnormal GH receptor (Laron-type dwarfism) are well described. They are very rare but may respond to therapy with synthetic IGF-1.

## **DIABETES INSIPIDUS**

### **Clinical Characteristics**

Decreased secretion or action of arginine vasopressin (AVP), also known as antidiuretic hormone, usually manifests as Diabetes Insipidus (DI), a syndrome characterized by the production of abnormally large volumes of dilute urine. The 24-h urine volume is  $>50$  mL/kg body weight and the osmolarity is  $<300$  mosmol/L. The polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence. It is also associated with thirst and a commensurate increase in fluid intake (polydipsia). Clinical signs of dehydration are uncommon unless fluid intake is impaired.

### **Etiology**

Deficient secretion of AVP can be primary or secondary. The primary form usually results from agenesis or irreversible destruction of the neurohypophysis and is variously referred to as neurohypophyseal DI, pituitary DI, or central DI. It can be caused by a variety of congenital, acquired, or genetic disorders but almost half the time it is idiopathic. The genetic form of neurohypophyseal DI is usually transmitted in an autosomal dominant mode and is caused by diverse mutations in the coding region of the AVP–neurophysin II (or AVP-NPII) gene. The AVP deficiency and DI develop several months to several years after birth and appear to result from selective degeneration of AVP-producing magnocellular neurons, probably caused by accumulation of misfolded precursor. A primary deficiency of plasma AVP can also result from increased metabolism by an N-terminal aminopeptidase produced by the placenta. It is referred to as gestational DI since the signs and symptoms manifest during pregnancy and usually remit several weeks after delivery. However, a subclinical deficiency in AVP secretion can often be demonstrated in the nonpregnant state, indicating that damage to the neurohypophysis may also contribute to the AVP deficiency. Secondary deficiencies of AVP result from inhibition of secretion by excessive intake of fluids. They are referred to as primary polydipsia and can be divided into three subcategories. One of them, called dipsogenic DI, is characterized by

inappropriate thirst caused by a reduction in the "set" of the osmoregulatory mechanism. It sometimes occurs in association with multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, or multiple sclerosis but is often idiopathic. The second subtype, called psychogenic polydipsia, is not associated with thirst, and the polydipsia seems to be a feature of psychosis. The third subtype, which may be referred to as iatrogenic polydipsia, results from recommendations to increase fluid intake for its presumed health benefits. Primary deficiencies in the antidiuretic action of AVP result in nephrogenic DI. They can be genetic, acquired, or caused by exposure to various drugs. Secondary deficiencies in the antidiuretic response to AVP result from polyuria per se. They are caused by washout of the medullary concentration gradient and/or suppression of aquaporin function. They usually resolve 24–48 h after the polyuria is corrected but often complicate interpretation of acute tests commonly used for differential diagnosis.

### **Investigation and Differential Diagnosis**

When symptoms of urinary frequency, enuresis, nocturia, and/or persistent thirst are present, a 24-h urine should be collected on an ad libitum fluid intake. If the volume exceeds 50 mL/kg per day (3500 mL in a 70-kg man), polyuria is present. If the osmolality is  $>300$  mosmol/L, the polyuria is due to a solute diuresis and the patient should be evaluated for glucosuria or other less common causes of excessive solute excretion. However, if the 24-h urine osmolality is  $<300$  mosmol/L, the patient has a water diuresis and should be evaluated further to determine which type of DI is present.

In differentiating between the various types of DI, the history, physical examination, and routine laboratory tests may be helpful but are rarely sufficient because few, if any, of the findings are pathognomonic. Except in the rare patient who is clearly dehydrated under basal conditions of ad libitum fluid intake, this evaluation should begin with a fluid deprivation test. To minimize patient discomfort, avoid excessive dehydration, and maximize the information obtained, the test should be started in the morning and water balance should be monitored closely with hourly measurements of body weight, plasma osmolality and/or sodium concentration, and urine volume and osmolality.

If fluid deprivation does not result in urine concentration (osmolality  $> 300$  mosmol/L, specific gravity  $>1.010$ ) before body weight decreases by 5% or plasma osmolality/sodium exceed the upper limit of normal, the patient has severe pituitary or severe nephrogenic DI. These disorders can usually be distinguished by administering desmopressin (DDAVP, 0.03 g/kg SC or IV) and repeating the measurement of urine osmolality 1–2 h later. An increase of  $>50\%$  indicates severe pituitary DI, whereas a smaller or absent response is strongly suggestive of nephrogenic DI.

If fluid deprivation results in concentration of the urine, the differential diagnosis is more difficult because the patient can have either partial pituitary DI, partial nephrogenic DI, or a form of primary polydipsia. In this situation, the change in urine osmolarity after the administration of desmopressin does not differentiate the possible disorders because the responses are variable and overlap in the three types of DI. The best way to differentiate between them is to measure plasma or urine AVP before and during the fluid deprivation test and analyze the results in relation to the concurrent plasma or urine osmolarity. This approach invariably differentiates partial nephrogenic DI from partial pituitary DI and primary polydipsia. It also differentiates partial pituitary DI from primary polydipsia if the hormone is measured when plasma osmolarity or sodium is clearly above the normal range. The requisite level of hypertonic dehydration may be difficult to produce by fluid deprivation alone when the urine is concentrated. Therefore, it is usually necessary to infuse hypertonic (3%) saline at a rate of 0.1 mL/kg per min while continuing the fluid deprivation and repeat the AVP measurements as soon as plasma osmolarity rises to  $>300$  mosmol/L ( $\text{Na}^+ >145$  mmol/L). This endpoint is usually reached within 30–120 min.

The differential diagnosis of DI may also be facilitated by MRI of the pituitary and hypothalamus. In most healthy adults and children, the posterior pituitary emits a hyperintense signal in T1-weighted mid-sagittal images. This "bright spot" is almost always present in patients with primary polydipsia but is invariably absent or abnormally small in patients with pituitary DI. It is usually also small or absent in nephrogenic DI presumably because of high secretion and turnover of vasopressin. Thus, a normal bright spot virtually excludes pituitary DI, is against nephrogenic DI, and strongly suggests primary polydipsia. Lack of the bright spot is less helpful, however, because it is absent not only in pituitary and nephrogenic DI but also in some normal persons and in patients with empty sella who do not have DI.

The other way to distinguish between the three basic types of DI is to closely monitor the effects of antidiuretic therapy on changes in water balance.

## **Treatment**

The signs and symptoms of uncomplicated pituitary DI can be eliminated completely by treatment with desmopressin (DDAVP), a synthetic analogue of AVP. It acts selectively at V2 receptors to increase urine concentration and decrease urine flow in a dose-dependent manner. It is also more resistant to degradation than AVP and has a three- to fourfold longer duration of action. Desmopressin (DDAVP) can be given by IV or SC injection, nasal inhalation, or oral tablet. The doses required to completely control pituitary DI vary widely, depending on the patient and the route of administration. However, they usually range from 1–2 g qd or bid by injection, 10–20 g bid or tid by nasal

spray, or 100–400 g bid or tid orally. The onset of action is rapid, ranging from as little as 15 min after injection to 60 min after oral administration. When given in doses sufficient to completely normalize urinary osmolality and flow, desmopressin produces a slight (1–3%) increase in total-body water and a commensurate decrease in plasma osmolality and sodium concentration that rapidly eliminate thirst and polydipsia. Consequently, water balance is maintained and hyponatremia does not develop unless the patient has an associated abnormality in the osmoregulation of thirst or ingests/receives excessive amounts of fluid for some other reason. Fortunately, thirst is usually normal in patients with pituitary DI, and the other causes of excessive intake can usually be eliminated by educating the patient about the risks of drinking for reasons other than thirst. Therefore, desmopressin can usually be given safely in doses sufficient to maintain a completely normal urine output without subjecting the patient to the inconvenience and discomfort of allowing intermittent escape to prevent water intoxication.

Primary polydipsia cannot be treated safely with desmopressin. It inhibits the polyuria but, unlike pituitary DI, does not eliminate the urge to drink. Therefore, it almost always produces water intoxication within 24–48 h. Iatrogenic polydipsia can often be corrected by patient counseling, but there is no effective treatment for either psychogenic or dipsogenic DI.

The symptoms and signs of nephrogenic DI are not affected by treatment with desmopressin but may be reduced by treatment with a thiazide diuretic and/or amiloride in conjunction with a low-sodium diet. Inhibitors of prostaglandin synthesis (e.g., indomethacin) are also very effective in some patients.

## CUSHING'S DISEASE (ACTH-Producing Adenoma)

### **Etiology and Prevalence**

Pituitary corticotrope adenomas account for 70% of patients with endogenous causes of Cushing's disease. However, it should be emphasized that iatrogenic hypercortisolism is the most common cause of cushingoid features. Ectopic tumor ACTH production, cortisol-producing adrenal adenomas, adrenal carcinoma, and adrenal hyperplasia account for the other causes; rarely, ectopic tumor CRH production is encountered.

ACTH-producing adenomas account for about 10–15% of all pituitary tumors. Because the clinical features of Cushing's disease often lead to early diagnosis, most ACTH-producing pituitary tumors are relatively small microadenomas. However, macroadenomas are also seen, and some ACTH-secreting adenomas are clinically silent. Cushing's disease is 5–10 times more common in women than in men. These pituitary adenomas exhibit unrestrained ACTH secretion, with resultant hypercortisolemia. However, they retain partial suppressibility in the presence of high doses of administered glucocorticoids, providing the basis

for dynamic testing to distinguish pituitary and nonpituitary causes of Cushing's syndrome.

### **Presentation and Diagnosis**

The diagnosis of Cushing's disease presents two great challenges: (1) to distinguish patients with pathologic cortisol excess from those with physiologic or other disturbances of cortisol production; and (2) to determine the etiology of cortisol excess.

Typical features of chronic cortisol excess include thin, fragile skin, central obesity, hypertension, plethoric moon facies, purple striae and easy bruisability, glucose intolerance or diabetes mellitus, gonadal dysfunction, osteoporosis, proximal muscle weakness, signs of hyperandrogenism (acne, hirsutism), and psychological disturbances (depression, mania, and psychoses). Hematopoietic features of hypercortisolism include leukocytosis, lymphopenia, and eosinopenia. Immune suppression includes delayed hypersensitivity. The protean manifestations of hypercortisolism make it challenging to decide which patients mandate formal laboratory evaluation. Certain features make pathologic causes of hypercortisolism more likely—these include characteristic central redistribution of fat, thin skin with striae and bruising, and proximal muscle weakness. In children and in young females, early osteoporosis may be particularly prominent. The primary cause of death is cardiovascular disease, but infections and risk of suicide are also increased.

Rapid development of features of hypercortisolism associated with skin hyperpigmentation and severe myopathy suggests an ectopic source of ACTH. Hypertension, hypokalemic alkalosis, glucose intolerance, and edema are also more pronounced in these patients. Serum potassium levels  $<3.3$  mmol/L are evident in ~70% of patients with ectopic ACTH secretion but are seen in  $<10\%$  of patients with pituitary-dependent Cushing's syndrome.

### **Laboratory Investigation**

The diagnosis of Cushing's disease is based on laboratory documentation of endogenous hypercortisolism. Measurements of 24-h urine free cortisol (UFC) is a precise and cost-effective screening test. Alternatively, the failure to suppress plasma cortisol after an overnight 1-mg dexamethasone suppression test can be used to identify patients with hypercortisolism. As nadir levels of cortisol occur at night, elevated midnight samples of cortisol are suggestive of Cushing's disease. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syndrome. Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion compared to those with pituitary ACTH-secreting adenomas.

However, extensive overlap of ACTH levels in these two disorders precludes using ACTH to make the distinction. Instead, dynamic testing, based on differential sensitivity to glucocorticoid feedback, or ACTH stimulation in response to corticotropin releasing hormone (CRH) or cortisol reduction is used to discriminate ectopic versus pituitary sources of excess ACTH. Very rarely, circulating CRH levels are elevated, reflecting ectopic tumor-derived secretion of CRH and often ACTH.

Most ACTH-secreting pituitary tumors are <5 mm in diameter, and about half are undetectable by sensitive MRI. The high prevalence of incidental pituitary microadenomas diminishes the ability to distinguish ACTH-secreting pituitary tumors accurately by MRI.

### Inferior Petrosal Venous Sampling

Because pituitary MRI with gadolinium enhancement is insufficiently sensitive to detect small (<2 mm) pituitary ACTH-secreting adenomas, bilateral inferior petrosal sinus ACTH sampling before and after CRH administration may be required to distinguish these lesions from ectopic ACTH-secreting tumors that may have similar clinical and biochemical characteristics. Simultaneous assessment of ACTH concentrations in each inferior petrosal vein and in the peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at baseline and 2, 5, and 10 min after intravenous ovine CRH (1 g/kg) injection. An increased ratio (>2) of inferior petrosal: peripheral vein ACTH confirms pituitary Cushing's syndrome. After CRH injection, peak petrosal:peripheral ACTH ratios of 3 confirm the presence of a pituitary ACTH-secreting tumor. The sensitivity of this test is >95%, with very rare false-positive results. False-negative results may be encountered in patients with aberrant venous drainage. Petrosal sinus catheterizations are technically difficult, and about 0.05% of patients develop neurovascular complications. The procedure should not be performed in patients with hypertension or in the presence of a well-visualized pituitary adenoma on MRI.

### Treatment

Selective transsphenoidal resection is the treatment of choice for Cushing's disease. The remission rate for this procedure is ~80% for microadenomas but <50% for macroadenomas. After successful tumor resection, most patients experience a postoperative period of symptomatic ACTH deficiency that lasts for up to 12 months. This usually requires low-dose cortisol replacement, as patients experience steroid withdrawal symptoms as well as having a suppressed HPA axis. Biochemical recurrence occurs in approximately 5% of patients in whom surgery was initially successful.

When initial surgery is unsuccessful, repeat surgery is sometimes indicated, particularly when a pituitary source for ACTH is well documented. In older

patients, in whom issues of growth and fertility are less important, hemi- or total hypophysectomy may be necessary if a discrete adenoma is not recognized. Pituitary irradiation may be used after unsuccessful surgery, but it cures only about 15% of patients. Because radiation is slow and only partially effective in adults, steroidogenic inhibitors are used in combination with pituitary irradiation to block the adrenal effects of persistently high ACTH levels.

Ketoconazole, an imidazole derivative antimycotic agent, inhibits several P450 enzymes and effectively lowers cortisol in most patients with Cushing's disease when administered twice daily (600–1200 mg/d). Elevated hepatic transaminases, gynecomastia, impotence, gastrointestinal upset, and edema are common side effects. Metyrapone (2–4 g/d) inhibits 11-hydroxylase activity and normalizes plasma cortisol in up to 75% of patients. Side effects include nausea and vomiting, rash, and exacerbation of acne or hirsutism. Mitotane (o, p'-DDD; 3–6 g/d orally in four divided doses) suppresses cortisol hypersecretion by inhibiting 11-hydroxylase and cholesterol side-chain cleavage enzymes and by destroying adrenocortical cells. Side effects of mitotane include gastrointestinal symptoms, dizziness, gynecomastia, hyperlipidemia, skin rash, and hepatic enzyme elevation. It may also lead to hypoaldosteronism. Other agents include aminoglutethimide (250 mg tid), trilostane (200–1000 mg/d), cyproheptadine (24 mg/d), and IV etomidate (0.3 mg/kg per hour). Glucocorticoid insufficiency is a potential side effect of agents used to block steroidogenesis.

The use of steroidogenic inhibitors has decreased the need for bilateral adrenalectomy. Removal of both adrenal glands corrects hypercortisolism but may be associated with significant morbidity and necessitates permanent glucocorticoid and mineralocorticoid replacement. Adrenalectomy in the setting of residual corticotrope adenoma tissue predisposes to the development of Nelson's syndrome, a disorder characterized by rapid pituitary tumor enlargement and increased pigmentation secondary to high ACTH levels. Radiation therapy may be indicated to prevent the development of Nelson's syndrome after adrenalectomy.

## OBESITY

In a world where food supplies are intermittent, the ability to store energy in excess of what is required for immediate use is essential for survival. Fat cells, residing within widely distributed adipose tissue depots, are adapted to store excess energy efficiently as triglyceride and, when needed, to release stored energy as free fatty acids for use at other sites. This physiologic system, orchestrated through endocrine and neural pathways, permits humans to survive starvation for as long as several months. However, in the presence of nutritional abundance and a sedentary lifestyle, and influenced importantly by genetic endowment, this system increases adipose energy stores and produces adverse health consequences.



Although not a direct measure of adiposity, the most widely used method to gauge obesity is the body mass index (BMI), which is equal to weight/height<sup>2</sup> (in kg/m<sup>2</sup>). Other approaches to quantifying obesity include anthropometry (skin-fold thickness), densitometry (underwater weighing), CT or MRI, and electrical impedance. Using data from the Metropolitan Life Tables, BMIs for the midpoint of all heights and frames among both men and women range from 19–26 kg/m<sup>2</sup>; at a similar BMI, women have more body fat than men. Based on data of substantial morbidity, a BMI of 30 is most commonly used as a threshold for obesity in both men and women. Large-scale epidemiologic studies suggest that all-cause, metabolic, cancer, and cardiovascular morbidity begin to rise (albeit at a slow rate) when BMIs are 25, suggesting that the cut-off for obesity should be lowered. Most authorities use the term overweight (rather than obese) to describe individuals with BMIs between 25 and 30. A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention, especially in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

The distribution of adipose tissue in different anatomic depots also has substantial implications for morbidity. Specifically, intraabdominal and abdominal subcutaneous fat have more significance than subcutaneous fat present in the buttocks and lower extremities. This distinction is most easily made clinically by determining the waist-to-hip ratio, with a ratio >0.9 in women and >1.0 in men being abnormal. Many of the most important complications of obesity, such as insulin resistance, diabetes, hypertension, hyperlipidemia, and hyperandrogenism in women, are linked more strongly to intraabdominal and/or upper body fat than to overall adiposity. The mechanism underlying this association is unknown but may relate to the fact that intraabdominal adipocytes are more lipolytically active than those from other depots. Release of free fatty acids into the portal circulation has adverse metabolic actions, especially on the liver. Whether adipokines and cytokines secreted by visceral adipocytes play an additional role in systemic complications of obesity is an area of active investigation.

### Physiologic Regulation of Energy Balance

Substantial evidence suggests that body weight is regulated by both endocrine and neural components that ultimately influence the effector arms of energy intake and expenditure. This complex regulatory system is necessary because even small imbalances between energy intake and expenditure will ultimately have large effects on body weight. For example, a 0.3% positive imbalance over 30 years would result in a 9-kg weight gain. This exquisite regulation of energy balance cannot be monitored easily by calorie-counting in relation to physical activity. Rather, body weight regulation or dysregulation depends on a complex interplay of hormonal and neural signals. Alterations in stable weight by forced overfeeding or food deprivation induce physiologic changes that

resist these perturbations: with weight loss, appetite increases and energy expenditure falls; with overfeeding, appetite falls and energy expenditure increases. This latter compensatory mechanism frequently fails, however, permitting obesity to develop when food is abundant and physical activity is limited. A major regulator of these adaptive responses is the adipocyte-derived hormone leptin, which acts through brain circuits (predominantly in the hypothalamus) to influence appetite, energy expenditure, and neuroendocrine function (see below).

Appetite is influenced by many factors that are integrated by the brain, most importantly within the hypothalamus. Signals that impinge on the hypothalamic center include neural afferents, hormones, and metabolites. Vagal inputs are particularly important, bringing information from viscera, such as gut distention. Hormonal signals include leptin, insulin, cortisol, and gut peptides. Among the latter are ghrelin, which is made in the stomach and stimulates feeding, and peptide YY (PYY) and cholecystokinin, which are made in the small intestine and signal to the brain through direct action on hypothalamic control centers and/or via the vagus nerve. Metabolites, including glucose, can influence appetite, as seen by the effect of hypoglycemia to induce hunger; however, glucose is not normally a major regulator of appetite. These diverse hormonal, metabolic, and neural signals act by influencing the expression and release of various hypothalamic peptides [e.g., neuropeptide Y (NPY), Agouti-related peptide (AgRP), -melanocyte-stimulating hormone (-MSH), and melanin-concentrating hormone (MCH)] that are integrated with serotonergic, catecholaminergic, endocannabinoid, and opioid signaling pathways (see below). Psychological and cultural factors also play a role in the final expression of appetite. Apart from rare genetic syndromes involving leptin, its receptor, and the melanocortin system, specific defects in this complex appetite control network that influence common cases of obesity are not well defined.

Energy expenditure includes the following components: (1) resting or basal metabolic rate; (2) the energy cost of metabolizing and storing food; (3) the thermic effect of exercise; and (4) adaptive thermogenesis, which varies in response to chronic caloric intake (rising with increased intake). Basal metabolic rate accounts for ~70% of daily energy expenditure, whereas active physical activity contributes 5–10%. Thus, a significant component of daily energy consumption is fixed.

Genetic models in mice indicate that mutations in certain genes (e.g., targeted deletion of the insulin receptor in adipose tissue) protect against obesity, apparently by increasing energy expenditure. Adaptive thermogenesis occurs in brown adipose tissue (BAT), which plays an important role in energy metabolism in many mammals. In contrast to white adipose tissue, which is used to store energy in the form of lipids, BAT expends stored energy as heat. A mitochondrial uncoupling protein (UCP-1) in BAT dissipates the hydrogen

ion gradient in the oxidative respiration chain and releases energy as heat. The metabolic activity of BAT is increased by a central action of leptin, acting through the sympathetic nervous system, which heavily innervates this tissue. In rodents, BAT deficiency causes obesity and diabetes; stimulation of BAT with a specific adrenergic agonist (3 agonist) protects against diabetes and obesity. Although BAT exists in humans (especially neonates), its physiologic role is not yet established. Homologues of UCP-1 (UCP-2 and -3) may mediate uncoupled mitochondrial respiration in other tissues.

### **The Adipocyte and Adipose Tissue**

Adipose tissue is composed of the lipid-storing adipose cell and a stromal/vascular compartment in which cells including preadipocytes and macrophages reside. Adipose mass increases by enlargement of adipose cells through lipid deposition, as well as by an increase in the number of adipocytes. Obese adipose tissue is also characterized by increased numbers of infiltrating macrophages. The process by which adipose cells are derived from a mesenchymal preadipocyte involves an orchestrated series of differentiation steps mediated by a cascade of specific transcription factors. One of the key transcription factors is peroxisome proliferator-activated receptor (PPAR), a nuclear receptor that binds the thiazolidinedione class of insulin-sensitizing drugs used in the treatment of type 2 diabetes.

Although the adipocyte has generally been regarded as a storage depot for fat, it is also an endocrine cell that releases numerous molecules in a regulated fashion. These include the energy balance–regulating hormone leptin, cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6, complement factors such as factor D (also known as adipsin), prothrombotic agents such as plasminogen activator inhibitor I, and a component of the blood pressure regulating system, angiotensinogen. Adiponectin, an abundant adipose-derived protein whose levels are reduced in obesity, enhances insulin sensitivity and lipid oxidation and it has vascular protective effects, whereas resistin and RBP4, whose levels are increased in obesity, may induce insulin resistance. These factors, and others not yet identified, play a role in the physiology of lipid homeostasis, insulin sensitivity, blood pressure control, coagulation, and vascular health, and are likely to contribute to obesity-related pathologies.

### **Etiology of Obesity**

Though the molecular pathways regulating energy balance are beginning to be illuminated, the causes of obesity remain elusive. In part, this reflects the fact that obesity is a heterogeneous group of disorders. At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuroendocrine and metabolic systems that regulate energy intake, storage,

and expenditure, it has been difficult to quantitate all the relevant parameters (e.g., food intake and energy expenditure) over time in human subjects.

### Role of Genes versus Environment

Obesity is commonly seen in families, and the heritability of body weight is similar to that for height. Inheritance is usually not Mendelian, however, and it is difficult to distinguish the role of genes and environmental factors. Adoptees more closely resemble their biologic than adoptive parents with respect to obesity, providing strong support for genetic influences. Likewise, identical twins have very similar BMIs whether reared together or apart, and their BMIs are much more strongly correlated than those of dizygotic twins. These genetic effects appear to relate to both energy intake and expenditure.

Whatever the role of genes, it is clear that the environment plays a key role in obesity, as evidenced by the fact that famine prevents obesity in even the most obesity-prone individual. In addition, the recent increase in the prevalence of obesity in the United States is far too rapid to be due to changes in the gene pool. Undoubtedly, genes influence the susceptibility to obesity in response to specific diets and availability of nutrition. Cultural factors are also important—these relate to both availability and composition of the diet and to changes in the level of physical activity. In industrial societies, obesity is more common among poor women, whereas in underdeveloped countries, wealthier women are more often obese. In children, obesity correlates to some degree with time spent watching television. Although the role of diet composition in obesity continues to generate controversy, it appears that high-fat diets may promote obesity, especially when combined with diets rich in simple (as opposed to complex) carbohydrates.

Additional environmental factors may contribute to the increasing obesity prevalence. Both epidemiologic correlations and experimental data suggest that sleep deprivation leads to increased obesity. Less well supported in humans are potential changes in gut flora with capacity to alter energy balance and a possible role for obesigenic viral infections.

For many years obesity in rodents has been known to be caused by a number of distinct mutations distributed through the genome. Most of these single-gene mutations cause both hyperphagia and diminished energy expenditure, suggesting a physiologic link between these two parameters of energy homeostasis. Identification of the *ob* gene mutation in genetically obese (*ob/ob*) mice represented a major breakthrough in the field. The *ob/ob* mouse develops severe obesity, insulin resistance, and hyperphagia, as well as efficient metabolism (e.g., it gets fat even when ingesting the same number of calories as lean litter mates). The product of the *ob* gene is the peptide leptin, a name derived from the Greek root *leptos*, meaning thin. Leptin is secreted by adipose cells and acts primarily through the hypothalamus. Its level of production provides an index of adipose energy stores. High leptin levels decrease food intake and increase

energy expenditure. Another mouse mutant, db/db, which is resistant to leptin, has a mutation in the leptin receptor and develops a similar syndrome. The OB gene is present in humans and expressed in fat. Several families with morbid, early-onset obesity caused by inactivating mutations in either leptin or the leptin receptor have been described, thus demonstrating the biologic relevance of leptin in humans. The obesity in these individuals begins shortly after birth, is severe, and is accompanied by neuroendocrine abnormalities. The most prominent of these is hypogonadotropic hypogonadism, which is reversed by leptin replacement. Central hypothyroidism and growth retardation are seen in the mouse model, but their occurrence in leptin-deficient humans is less clear. To date, there is no evidence to suggest that mutations or polymorphisms in the leptin or leptin receptor genes play a prominent role in common forms of obesity.

### **Other Specific Syndromes Associated with Obesity**

#### **Cushing's Syndrome**

Although obese patients commonly have central obesity, hypertension, and glucose intolerance, they lack other specific stigmata of Cushing's syndrome. Nonetheless, a potential diagnosis of Cushing's syndrome is often entertained. Cortisol production and urinary metabolites (17OH steroids) may be increased in simple obesity. Unlike in Cushing's syndrome, however, cortisol levels in blood and urine in the basal state and in response to corticotropin-releasing hormone (CRH) or ACTH are normal; the overnight 1-mg dexamethasone suppression test is normal in 90%, with the remainder being normal on a standard 2-day low-dose dexamethasone suppression test. Obesity may be associated with excessive local reactivation of cortisol in fat by 11-hydroxysteroid dehydrogenase 1, an enzyme that converts inactive cortisone to cortisol.

#### **Hypothyroidism**

The possibility of hypothyroidism should be considered, but it is an uncommon cause of obesity; hypothyroidism is easily ruled out by measuring thyroid-stimulating hormone (TSH). Much of the weight gain that occurs in hypothyroidism is due to myxedema.

#### **Insulinoma**

Patients with insulinoma often gain weight as a result of overeating to avoid hypoglycemic symptoms. The increased substrate plus high insulin levels promote energy storage in fat. This can be marked in some individuals but is modest in most.

## **Craniopharyngioma and Other Disorders Involving the Hypothalamus**

Whether through tumors, trauma, or inflammation, hypothalamic dysfunction of systems controlling satiety, hunger, and energy expenditure can cause varying degrees of obesity. It is uncommon to identify a discrete anatomic basis for these disorders. Subtle hypothalamic dysfunction is probably a more common cause of obesity than can be documented using currently available imaging techniques. Growth hormone (GH), which exerts lipolytic activity, is diminished in obesity and is increased with weight loss. Despite low GH levels, insulin-like growth factor (IGF) I (somatomedin) production is normal, suggesting that GH suppression is a compensatory response to increased nutritional supply.

### **Pathogenesis of Common Obesity**

Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Thus, identifying the etiology of obesity should involve measurements of both parameters. However, it is nearly impossible to perform direct and accurate measurements of energy intake in free-living individuals, and the obese, in particular, often underreport intake. Measurements of chronic energy expenditure have only recently become available using doubly labeled water or metabolic chamber/rooms. In subjects at stable weight and body composition, energy intake equals expenditure. Consequently, these techniques allow assessment of energy intake in free-living individuals. The level of energy expenditure differs in established obesity, during periods of weight gain or loss, and in the pre- or postobese state. Studies that fail to take note of this phenomenon are not easily interpreted.

There is continued interest in the concept of a body weight "set point." This idea is supported by physiologic mechanisms centered around a sensing system in adipose tissue that reflects fat stores and a receptor, or "adipostat," that is in the hypothalamic centers. When fat stores are depleted, the adipostat signal is low, and the hypothalamus responds by stimulating hunger and decreasing energy expenditure to conserve energy. Conversely, when fat stores are abundant, the signal is increased, and the hypothalamus responds by decreasing hunger and increasing energy expenditure. The recent discovery of the ob gene, and its product leptin, and the db gene, whose product is the leptin receptor, provides important elements of a molecular basis for this physiologic concept (see above).

### **The Status of Food Intake in Obesity**

This question has stimulated much debate, due in part to the methodologic difficulties inherent in determining food intake. Many obese individuals believe that they eat small quantities of food, and this claim has often been supported by the results of food intake questionnaires. However, it is now established that average energy expenditure increases as individuals get more obese, due primarily to the fact that metabolically active lean tissue mass increases with obesity.

Given the laws of thermodynamics, the obese person must therefore eat more than the average lean person to maintain their increased weight. It may be the case, however, that a subset of individuals who are predisposed to obesity have the capacity to become obese initially without an absolute increase in caloric consumption.

### The State of Energy Expenditure in Obesity

The average total daily energy expenditure is higher in obese than lean individuals when measured at stable weight. However, energy expenditure falls as weight is lost, due in part to loss of lean body mass and to decreased sympathetic nerve activity. When reduced to near-normal weight and maintained there for a while, (some) obese individuals have lower energy expenditure than (some) lean individuals. There is also a tendency for those who will develop obesity as infants or children to have lower resting energy expenditure rates than those who remain lean.

The physiologic basis for variable rates of energy expenditure (at a given body weight and level of energy intake) is essentially unknown. A mutation in the human 3-adrenergic receptor may be associated with increased risk of obesity and/or insulin resistance in certain (but not all) populations. Homologues of the BAT uncoupling protein, named UCP-2 and UCP-3, have been identified in both rodents and humans. UCP-2 is expressed widely, whereas UCP-3 is primarily expressed in skeletal muscle. These proteins may play a role in disordered energy balance. One newly described component of thermogenesis, called nonexercise activity thermogenesis (NEAT), has been linked to obesity. It is the thermogenesis that accompanies physical activities other than volitional exercise, such as the activities of daily living, fidgeting, spontaneous muscle contraction, and maintaining posture. NEAT accounts for about two-thirds of the increased daily energy expenditure induced by overfeeding. The wide variation in fat storage seen in overfed individuals is predicted by the degree to which NEAT is induced. The molecular basis for NEAT and its regulation is unknown.

### Leptin in Typical Obesity

The vast majority of obese persons have increased leptin levels but do not have mutations of either leptin or its receptor. They appear, therefore, to have a form of functional "leptin resistance." Data suggesting that some individuals produce less leptin per unit fat mass than others or have a form of relative leptin deficiency that predisposes to obesity are at present contradictory and unsettled. The mechanism for leptin resistance, and whether it can be overcome by raising leptin levels, is not yet established. Some data suggest that leptin may not effectively cross the blood-brain barrier as levels rise. It is also apparent from animal studies that leptin signaling inhibitors, such as SOCS3 and PTP1b, are involved in the leptin-resistant state.

## **Pathologic Consequences of Obesity**

Obesity has major adverse effects on health. Obesity is associated with an increase in mortality, with a 50–100% increased risk of death from all causes compared to normal-weight individuals, mostly due to cardiovascular causes. Obesity and overweight together are the second leading cause of preventable death in the United States, accounting for 300,000 deaths per year. Mortality rates rise as obesity increases, particularly when obesity is associated with increased intraabdominal fat (see above). Life expectancy of a moderately obese individual could be shortened by 2–5 years, and a 20- to 30-year-old male with a BMI >45 may lose 13 years of life. It is also apparent that the degree to which obesity affects particular organ systems is influenced by susceptibility genes that vary in the population.

### **Insulin Resistance and Type 2 Diabetes Mellitus**

Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and diminishing with weight loss. Insulin resistance is more strongly linked to intraabdominal fat than to fat in other depots. The molecular link between obesity and insulin resistance in tissues such as fat, muscle, and liver has been sought for many years. Major factors under investigation include: (1) insulin itself, by inducing receptor downregulation; (2) free fatty acids, known to be increased and capable of impairing insulin action; (3) intracellular lipid accumulation; and (4) various circulating peptides produced by adipocytes, including the cytokines TNF- and IL-6, RBP4, and the "adipokines" adiponectin and resistin, which are produced by adipocytes, have altered expression in obese adipocytes, and are capable of modifying insulin action. Despite nearly universal insulin resistance, most obese individuals do not develop diabetes, suggesting that the onset of diabetes requires an interaction between obesity-induced insulin resistance and other factors that predispose to diabetes, such as impaired insulin secretion. Obesity, however, is a major risk factor for diabetes, and as many as 80% of patients with type 2 diabetes mellitus are obese. Weight loss and exercise, even of modest degree, are associated with increased insulin sensitivity and often improve glucose control in diabetes.

### **Reproductive Disorders**

Disorders that affect the reproductive axis are associated with obesity in both men and women. Male hypogonadism is associated with increased adipose tissue, often distributed in a pattern more typical of females. In men >160% ideal body weight, plasma testosterone and sex hormone-binding globulin (SHBG) are often reduced, and estrogen levels (derived from conversion of adrenal androgens in adipose tissue) are increased. Gynecomastia may be seen. However, masculinization, libido, potency, and spermatogenesis are preserved



in most of these individuals. Free testosterone may be decreased in morbidly obese men whose weight is >200% ideal body weight.

Obesity has long been associated with menstrual abnormalities in women, particularly in women with upper body obesity. Common findings are increased androgen production, decreased SHBG, and increased peripheral conversion of androgen to estrogen. Most obese women with oligomenorrhea have the polycystic ovarian syndrome (PCOS), with its associated anovulation and ovarian hyperandrogenism; 40% of women with PCOS are obese. Most nonobese women with PCOS are also insulin-resistant, suggesting that insulin resistance, hyperinsulinemia, or the combination of the two are causative or contribute to the ovarian pathophysiology in PCOS in both obese and lean individuals. In obese women with PCOS, weight loss or treatment with insulin-sensitizing drugs often restores normal menses. The increased conversion of androstenedione to estrogen, which occurs to a greater degree in women with lower body obesity, may contribute to the increased incidence of uterine cancer in postmenopausal women with obesity.

### Cardiovascular Disease

The Framingham Study revealed that obesity was an independent risk factor for the 26-year incidence of cardiovascular disease in men and women [including coronary disease, stroke, and congestive heart failure (CHF)]. The waist/hip ratio may be the best predictor of these risks. When the additional effects of hypertension and glucose intolerance associated with obesity are included, the adverse impact of obesity is even more evident. The effect of obesity on cardiovascular mortality in women may be seen at BMIs as low as 25. Obesity, especially abdominal obesity, is associated with an atherogenic lipid profile; with increased low-density lipoprotein (LDL) cholesterol, very low density lipoprotein, and triglyceride; and with decreased high-density lipoprotein cholesterol and decreased levels of the vascular protective adipokine adiponectin. Obesity is also associated with hypertension. Measurement of blood pressure in the obese requires use of a larger cuff size to avoid artifactual increases. Obesity-induced hypertension is associated with increased peripheral resistance and cardiac output, increased sympathetic nervous system tone, increased salt sensitivity, and insulin-mediated salt retention; it is often responsive to modest weight loss.

### Pulmonary Disease

Obesity may be associated with a number of pulmonary abnormalities. These include reduced chest wall compliance, increased work of breathing, increased minute ventilation due to increased metabolic rate, and decreased functional residual capacity and expiratory reserve volume. Severe obesity may be associated with obstructive sleep apnea and the "obesity hypoventilation syndrome" with attenuated hypoxic and hypercapnic ventilatory responses. Sleep apnea can be

obstructive (most common), central, or mixed and is associated with hypertension. Weight loss (10–20 kg) can bring substantial improvement, as can major weight loss following gastric bypass or restrictive surgery. Continuous positive airway pressure has been used with some success.

## **Gallstones**

Obesity is associated with enhanced biliary secretion of cholesterol, supersaturation of bile, and a higher incidence of gallstones, particularly cholesterol gallstones. A person 50% above ideal body weight has about a sixfold increased incidence of symptomatic gallstones. Paradoxically, fasting increases supersaturation of bile by decreasing the phospholipid component. Fasting-induced cholecystitis is a complication of extreme diets.

## **Cancer**

Obesity in males is associated with higher mortality from cancer, including cancer of the esophagus, colon, rectum, pancreas, liver, and prostate; obesity in females is associated with higher mortality from cancer of the gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries. Some of the latter may be due to increased rates of conversion of androstenedione to estrone in adipose tissue of obese individuals. It was recently estimated that obesity accounts for 14% of cancer deaths in men and 20% in women in the United States.

## **Bone, Joint, and Cutaneous Disease**

Obesity is associated with an increased risk of osteoarthritis, no doubt partly due to the trauma of added weight bearing and joint malalignment. The prevalence of gout may also be increased. Among the skin problems associated with obesity is acanthosis nigricans, manifested by darkening and thickening of the skin folds on the neck, elbows, and dorsal interphalangeal spaces. Acanthosis reflects the severity of underlying insulin resistance and diminishes with weight loss. Friability of skin may be increased, especially in skin folds, enhancing the risk of fungal and yeast infections. Finally, venous stasis is increased in the obese.

## **Treatment**

### **Dietary control**

This largely depends on a reduction in calorie intake. The most common diets allow a daily intake of approximately 4200 kJ (1000 kcal), although this may need to be nearer 6300 kJ (1500 kcal) for someone engaged in physical work. Very low calorie diets are also advocated by some, usually over shorter periods of time, but unless they are accompanied by changes in lifestyle, weight regain is likely. Patients must realize that prolonged dieting is necessary for large amounts of fat to be lost. Furthermore, a permanent change in eating habits is

required to maintain the new low weight. It is relatively easy for most people to lose the first few kilograms, but long-term success in moderate obesity is poor, with an overall success rate of no more than 10%. Many dietary regimens aim to produce a weight loss of approximately 1 kg per week. Weight loss will be greater initially owing to accompanying protein and glycogen breakdown and consequent water loss. After 3–4 weeks, further weight loss may be very small because only adipose tissue is broken down and there is less accompanying water loss.

Patients must understand the principles of energy intake and expenditure, and the best results are obtained in educated, well-motivated patients. Constant supervision by healthcare professionals, by close relatives or through membership of a slimming club helps to encourage compliance. It is essential to establish realistic aims. A 10% weight loss, which is regarded by some as a 'success' (see Table 5.14) is a realistic initial aim.

An increase in exercise will increase energy expenditure and should be encouraged – provided there is no contraindication – since weight control is usually not achieved without exercise. The effects of exercise are complex and not entirely understood. However, exercise alone will usually produce little long-term benefit. On the other hand there is evidence to suggest that in combination with dietary therapy, it can prevent weight being regained. In addition, regular exercise (30 min daily) will improve general health.

The diet should contain adequate amounts of protein, vitamins and trace elements. A diet of 4200 kJ (1000 kcal) per day should be made up of more than 50 g protein, approximately 100 g of carbohydrate, and 40 g of fat. The carbohydrate should be in the form of complex carbohydrates such as vegetables and fruit rather than simple sugars. Alcohol contains 29 kJ/g (7 kcal/g) and should normally be discouraged. It can be substituted for other foods in the diet, but it often reduces the willpower. With a varied diet, vitamins and minerals will be adequate and supplements are not necessary.

A balanced diet, attractively presented, is of much greater value and safer than any of the slimming regimens often advertised in magazines.

Most obese people oscillate in weight; they often regain the lost weight, but many manage to lose weight again. This 'cycling' in bodyweight may play a role in the development of coronary artery disease.

A wide range of diets are available, including low-fat or low-carbohydrate diets, and some suit certain individuals better than others. The following general statements can be made about them.

- All low-calorie diets produce loss of bodyweight and fat, irrespective of dietary composition. Short-term weight loss is faster on low-carbohydrate diets, as a result of greater loss of body water, which is regained after the end of dietary therapy.

- Very low-fat diets are often low in vitamins E, B<sub>12</sub>, and zinc. Very low-carbohydrate diets may be nutritionally inadequate, and may lead to deficiencies.
- Low-fat diets decrease LDL triglycerides and increase HDL, whereas low-carbohydrate diets produce a greater decrease in HDL and triglyceride, with no change in LDL.
- There are some potential long-term concerns with low-carbohydrate diets (high in fat and protein), including increased risk of osteoporosis, renal stones and atheroma (due to high saturated fat, high trans fat and cholesterol and the lack of fruits, vegetables and whole grains), but long-term studies are lacking.
- Low-energy-density diets, often bulky and rich in fibre and complex carbohydrates, may be more satiating but they are often less palatable than high-energy-dense diets which may affect long-term compliance.■
- Liquids, e.g. soft drinks, appear to be less satiating than solid foods.■
- A recent study has shown that Mediterranean and low-carbohydrate diets are as effective as a low-fat diet for weight loss.

## Behavioural modification

The aim of behavioural modification is to encourage the patient to take personal responsibility for changing lifestyle, which will determine dietary habits and physical activity. Family therapy may also be useful, especially when it involves obese children. It can be time-consuming and expensive. Cognitive behavioural therapy is even more time-consuming and expensive.

## Drug therapy

Drugs can be used in the short term (up to 3 months) as an adjunct to the dietary regimen, but they do not substitute for strict dieting.

Centrally acting drugs:

- Drugs acting on both serotonergic and noradrenergic pathways, e.g. sibutramine, tesofensine.
- Cannabinoid-1 receptor blockers, e.g. rimonabant (now withdrawn due to depression/suicide risk), acting on the endocannabinoid system.
- Drugs acting on the noradrenergic pathways do suppress appetite but all have been withdrawn in the UK because of cardiovascular side-effects.

Peripherally acting drugs:

Orlistat is an inhibitor of pancreatic and gastric lipases. It reduces dietary fat absorption and aids weight loss. Weight regain occurs after the drug is stopped. It has been used continuously in a large-scale trial for up to 2 years. The patients complain of diarrhoea during treatment and to avoid this take a low-fat diet resulting in weight loss.

Incretins. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are being used in type 2 diabetes mellitus. They suppress appetite

and are being used in obesity. A systematic review of long-term pharmacotherapy concluded that there was a paucity of long-term studies with antiobesity agents, and that in weight loss trials of 1-year duration, orlistat and sibutramine appear to be only modestly effective in promoting weight loss (2.7 and 4.3 kg greater weight loss respectively than the control group). Rimonabant produces a greater weight loss (6.7 kg at 1 year compared to a control group) in addition to hypocaloric dieting but it can produce anxiety and severe depression; it does not have FDA approval. Other randomized trials show that a combination of lifestyle modification and pharmacotherapy (sibutramine) produces greater weight loss than either treatment alone.

## Surgical treatment

Surgery is used in some cases of morbid obesity (BMI 40 kg/m<sup>2</sup>) or patients with a BMI 35 kg/m<sup>2</sup> and obesity-related complications, after conventional medical treatments have failed. A variety of gastrointestinal surgical procedures have been used. They fall into two main groups:

- restrictive procedures, which restrict the ability to eat
- malabsorptive procedures, which reduce the ability to absorb nutrients. A systematic analysis of bariatric surgical procedures concluded that, in comparison to non-surgical treatments, they produced significantly more weight loss (23–37 kg), which was maintained to 8 years and associated with improvement in quality of life and co-morbidities.
- Roux-en-Y gastric bypass. This procedure incorporates both restrictive and malabsorptive elements (gastrojejunostomy). This procedure, like other malabsorptive procedures, may result in nutrient deficiencies requiring careful long-term follow-up.
- Bilio-pancreatic diversion (including the duodenal switch variation). This is another malabsorptive procedure that requires long-term evaluation.
- Laparoscopic adjustable gastric banding. This is a restrictive procedure, in which a band is placed around the upper stomach to produce a small proximal pouch and a large distal remnant. It has a perioperative mortality of <0.5%, and results in loss of about 60% (43–78%) of the excess weight after 3 years, although longer-term follow-up studies are required. Laparoscopic adjustable gastric banding has been reported to produce greater weight loss and fewer side effects (e.g. vomiting) and operative revisions than vertical banded gastroplasty.
- Liposuction. The removal of large amounts of fat by suction (liposuction) does not deal with the underlying problem and weight regain frequently occurs. There is no reduction in cardiovascular risk factors.

## Prevention

Preventing obesity must always be the goal because most obese people find it difficult to maintain any weight loss they have managed to achieve. All health professionals must be aware of the dangers of obesity and encourage children, young as well as older adults, from gaining too much weight. A small gain each year over a long period produces an obese individual for whom treatment is difficult. Public health policies should consider creation of public places to encourage physical activity and fitness, education about the benefits of losing weight or not gaining it through healthy eating and physical activity, and changes in food composition (alternatives to high-fat, high-energy-dense foods). The present obesity epidemic has resulted from lifestyle changes, and so it is appropriate to promote lifestyle changes, not only as the first line therapy for most overweight and obese individuals, but also in the prevention of overweight and obesity. Lifestyle modification would involve changes in the amount of time watching television and using computers, use of bicycle paths, dietary changes, and educational activities of patients and public, parents and children. All the specific therapies discussed above, including pharmacotherapy, should be part of a package that involves lifestyle modification.

### Control of initial level of knowledge's

**Task 1.** Hypothalamic-pituitary insufficiency is more frequent due to disturbances of:

- a) *hypothalamic areas;*
- b) *hypophysis;*
- c) *cortex of cerebrum.*

**Task 2.** What symptoms characterize the Simmond's disease?

- a) *muscular weakness; 0-pains in muscles;*
- b) *pigmentation of skin;*
- c) *acute diminishing of body mass;*
- d) *low arterial blood pressure;*
- e) *all above.*

**Task 3.** Which preparations is it expedient to use for patients with Simmond's disease?

- a) *cortizole;*
- b) *thyrotropine;*
- c) *chorionic gonadotropin;*
- d) *hormones of thyroid;*
- e) *sexual hormones;*
- f) *all above.*

**Task 4.** Sheehan's disease on clinical motion differs from a hypothalamic-pituitary cachexia:

- a) *absence of considerable loss of mass of body;*
- b) *violation of function of sexual glands is less expressed;*
- c) *all above.*

**Task 5.** What disturbances of carbohydrate exchange characterize hypopituitarism?

- a) *hypoglycemia;*
- b) *the reduced sensitiveness to insulin;*
- c) *the reduced tolerance to the carbohydrates;*
- d) *all above.*

**Task 6.** What is the pathogenic base of nervous form of Diabetes insipidus?

- a) *resistance of receptors to the action of antidiuretic hormone;*
- b) *kidney pathology;*
- c) *sufficient products of antidiuretic hormone;*
- d) *all above.*

**Task 7.** What are the most frequent etiologic factors of development of nervous form Diabetes insipidus?

- a) *tumor of brain;*
- b) *trauma of skull;*
- c) *tubulopathy;*
- d) *acute and chronic infections;*
- e) *all above.*

**Task 8.** Wich symptoms are not peculiar for Diabetes insipidus?

- a) *polydipsia;*
- b) *polyuria;*
- c) *dysuria;*
- d) *insomnia.*

**Task 9.** What diseases should be considered in differential diagnostics of Diabetes insipidus?

- a) *diabetes mellitus;*
- b) *hyperparathyrosis;*
- c) *psychogenic polydipsia;*
- d) *chronic pyelonephritis;*
- e) *all above.*

**Task 10.** Wich from these signs are characteristic for Nelson`s syndrome?

- a) *chronic adrenal insufficiency;*
- b) *hyperpigmentation of skin;*
- c) *tumors of the hypophysis;*
- d) *all above.*

**Task 11.** At the Nelson`s syndrome develops the disturbance of:

- a) *day's rhythm of ACTH secretion;*
- b) *mechanism of back connection of adjusting of secretion ACTG;*
- c) *both mechanisms of regulation.*

**Task 12.** How does the level of somatotrophic hormone change in healthy person in reply to loading glucose?

- a) *any changes;*
- b) *grow up;*
- c) *sink down;*
- d) *develops two-phase reaction.*

**Task 13.** What consequences do the hyperproducts of somatotropin lead to in adult person?

- a) *to development of acromegaly;*
- b) *to development of tallness;*
- c) *to development of gigantism;*
- d) *all above.*

**Task 14.** What are the consequences of the hyperproducts of somatotropin for children?

- a) *development of gigantism;*
- b) *development of acromegaly;*
- c) *all above.*

**Task 15.** To what consequences do the hyperproducts of somatotropin lead to in teenagers (before closing of epiphysal areas of growth)?

- a) *to development of acromegaly;*
- b) *to development of tallness;*
- c) *to development of gigantism;*
- d) *all above.*

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
B	C	D	C	C	C	A	C	E	D	C	C	A	A	B

### **Control of eventual level of knowledge's**

**Task 1.** Pathology of what part of the neuro-endocrine system does take place at Simmond's disease?

- a) hypothalamus;*
- b) adenohypophysis;*
- c) primary defeat of peripheral endocrine glands;*
- d) secondary hypofunction of peripheral endocrine glands.*

**Task 2.** What reasons do lie in basis of development of hypopituitarism?

- a) traumatic damages of head;*
- b) neuroinfections;*
- c) inflammatory diseases;*
- d) circulatory ischemic necrosis of the hypophysis.*

**Task 3.** What is the reason of development of Sheehan's syndrome?

- a) septic embolism;*
- b) neuroinfection;*
- c) tumor of hypophysis;*
- d) circulatory ischemic necrosis.*

**Task 4.** What is the clinical display of somatotropine insufficiency?

- a) low growth;*
- b) cachexy;*
- c) hypogonadism;*
- d) decrease of muscular mass;*
- e) all above.*

**Task 5.** What are the clinical signs of corticotrophin insufficiency?

- a) arterial hypertension;*
- b) hyperpigmentation of skin;*
- c) reduced arterial pressure;*
- d) muscular hypotony;*
- e) all above.*

**Task 6.** What changes in the analysis of blood do take place at Simmond's disease?

- a) anemia;*
- b) leukocytosis;*
- c) leucopenia;*
- d) eosinopenia.*

**Task 7.** What biochemical indexes of blood most characterize the Simmond's disease?

- a) hyperglycemia;*
- b) inclination to hypoglycemia;*
- c) hyperpotassiumaemia;*
- d) hypersodiumaemia;*
- e) hypernatremia;*
- d) hypokalemia.*

**Task 8.** What laboratory indexes are the characteristic for partial hypopituitarism with insufficiency of secretion of thyrotropine?

- a) decrease of speeds of conducting on nervous fibers;*
- b) negative test with thyroliberine;*
- c) diabetic type of curve during conducting of test of tolerance to glucose.*

**Task 9.** Which investigations are recommended for differential diagnostics of primary and secondary hypogonadism?

- a) large dexamethasone test;*
- b) test with chorionic gonadotropin;*
- c) determining of level of LH, FSH;*
- d) determining of excretion 17 – OCS;*
- e) determining of level of hormones of sexual glands.*



**Task 10.** What tests must be conducted for an estimation the function of hypophysis?

- a) *dexamethasone test*; c) *thyrotropine test*; e) *gonadoliberine test*.  
b) *metopirone test*; d) *thyroliberine test*;

**Task 11.** In what cases the convalescence of patient with Diabetes insipidus is possible?

- a) *in case of development of disease after cerebral trauma*;  
b) *in case of development of disease on a background of neuroinfection*;  
c) *in both cases*.

**Task 12.** At nephrogenic Diabetes insipidus a sensitiveness to vasopressin is:

- a) *promoted*; b) *is stored*; c) *absent*.

**Task 13.** What from the noted preparations do reduce the secretion of vasopressin?

- a) *oxytocine*; c) *alcohol*; e) *all is higher marked*.  
b) *glucocorticoids*; d) *noradrenaline*;

**Task 14.** What functional tests are used in diagnostics of Diabetes insipidus ?

- a) *with clophelinum*; c) *with dexamethasone*;  
b) *with hypothiazidum*; d) *with limitation of liquid*.

1	2	3	4	5	6	7	8	9	10	11	12	13	14
B	D	D	A	C	C	B	B	C	B	C	C	B	D

### Tests

**Task 1.** Wich medicinal preparations is it expedient to use for treatment of Diabetes insipidus?

- a) *analogs of arginine-vasopressin*; d) *miscleronum*;  
b) *pituitrinum*; e) *clophelinum*;  
c) *hypothyazidum*; f) *all above*.

**Task 2.** What are the changes in lymphoid tissue in patients with Cushing`s disease?

- a) *plenty of androgens*; d) *promoted disintegration of albumens*;  
b) *plenty of glucocorticoids*; d) *all above*.  
c) *plenty of corticotrophin*;

**Task 3.** What does distinguish the endocrine-exchange of hypothalamic syndrome in patients with Cushing`s disease?

- a) *less expressed symptoms of hypocorticism*;  
b) *osteoporosis*;  
c) *positive "small dexamethasone test"*;  
d) *all above*.

**Task 4.** If a large dexamethasone test is positive, it is more credible for:

- a) *Cushing`s disease*; c) *ACTH is an ectopic syndrome*;  
b) *glucosteroma*; d) *virilising hyperplasia of adrenal glands*.

**Task 5.** Wich from preparations do diminish a secretion of ACTH in patients with Cushing`s disease?

- a) *parlodel*; c) *chloditane*; e) *rezerpinum*;  
b) *metopirone*; d) *ciproheptadinum*; f) *all above*.

**Task 6.** Function of adrenal cortex at patients with acromegaly is:

- a) *normal*;  
b) *promoted*;  
c) *reduced*;  
d) *at first normal, and then on the measure of multiplying the term of disease can go down*.

**Task 7.** Wich functions of hypophysis do suffer at hypophysal nanism:

- a) *thyrotrophic*; b) *adrenocorticotrophic*; c) *gonadotrophic*.

**Task 8.** At nanism of Larone patients have a secretion of STH:

- a) *not broken*; b) *reduced*; c) *promoted*.

**Task 9.** What are the clinical features of hypothalamic forms of obesity?

- a) *slow increase of body mass*; c) *even distributing fat tissue*;  
b) *vegetative disturbances*; d) *dysplastic obesity*.

**Task 10.** How does the basal secretion of growth hormone change in children with obesity?

- a) *increase*; b) *decrease*; c) *any changes*.

**Task 11.** What does stipulate polyphagia in patients with obesity?

- a) *increase concentrations of endorphins*;  
b) *hyperinsulinism*;  
c) *all above*.

1	2	3	4	5	6	7	8	9	10	11
A	C	C	A	D	D	A	A	B	B	C

### Questions of controls

1. Acromegaly. Etiology and pathogenesis. Clinic. Diagnostics and differential diagnostics. Treatment.

2. Cushing`s disease. Etiology and pathogenesis. Classification. Clinic. Diagnostics and differential diagnostics. Treatment.

3. Hypopituitarism. Etiology and pathogenesis. Clinic. Diagnostics and differential diagnostics. Treatment.

4. Diabetes insipidus. Etiology and pathogenesis. Clinic. Diagnostics and differential diagnostics. Treatment.

5. Hypopituitarism with overwhelming somatotrophic insufficiency (hypophysal nanism). Classification. Etiology and pathogenesis. Clinic. Diagnostics and differential diagnostics. Treatment.

6. Hypophysal gigantism. Etiology and pathogenesis. Clinic. Diagnostics and differential diagnostics. Treatment.

7. Obesity. Etiology and pathogenesis. Classification. Clinic. Diagnostics. Treatment. Children`s and teenagers` obesity.

### **Practical tasks to the theme 9**

1. To define the risk factors of HPS diseases, the possible etiologic factors of disease; retrospectively to set the initial signs of disease, estimate adequacy of applied diagnostic measures; to set pharmacological anamnesis; to define the basic stages of motion of disease.
2. To ground the diagnosis of diseases of HPS.
3. To characterize the complications of HPS diseases.
4. To estimate the results of clinic-laboratory and instrumental investigations.
5. To define the stage of obesity in HPS diseases.
6. To conduct the differential diagnosis of diseases of HPS.

### **Further reading:**

1. Davidson. Internal medicine / Davidson. – 2007. – 1252 p.
2. Concise pathology. – Paracrama Chandrasoma Cl[ve. R Tailor. – Prentice Hall International Inc. – 2004. – 1040 p
3. Harrison Internal medicine. 2005. – 1365 p.
4. Dwarfism: Medical and Psychosocial Aspects of Profound Short Stature. Betti M, Aelson. 2005. –368 p.
5. Endocrinology and metabolism / ed. by Pinchera. – London : McGraw Hill Int., 2001. – 811 p.
6. Handbook of Physiology. Section 7: Endocrine system. Volume III: Endocrine regulation of Water and electrolyte balance / ed. by J.C. S. Fray. – Oxford University press, 2000. – 750 p.
7. Textbook of endocrine physiology / ed. by J.E. Griffin, S.R. Ojeda. – 4-th ed. – Oxford University press, 2000. – 490 p.
8. Skodur Mario. Thyroid Disorders / Mario Skodur, Jesse B. Wilder. – Cleveland Clinic Press, 2006. – 224 p.

*Навчальне видання*

**ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ.  
ЗАХВОРЮВАННЯ ГІПОТАЛАМО-ГІПОФІЗАРНОЇ  
СИСТЕМИ, ПОРУШЕННЯ РОСТУ. ОЖИРІННЯ.  
МЕХАНІЗМ ДІЇ ГОРМОНІВ ГІПОТАЛАМУСА І ГІПОФІЗА**

***Методичні вказівки  
для студентів IV курсу***

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**DISEASES OF ENDOCRINE SYSTEM.  
HYPOTHALAMIC-PITUITARY SYSTEM DISEASES,  
DISTURBANCES OF GROWTH. OBESITY.  
MECHANISM OF ACTION OF HYPOTHALAMIC  
AND PITUITARY HORMONES**

***Methodological recommendations  
for students of IV course***