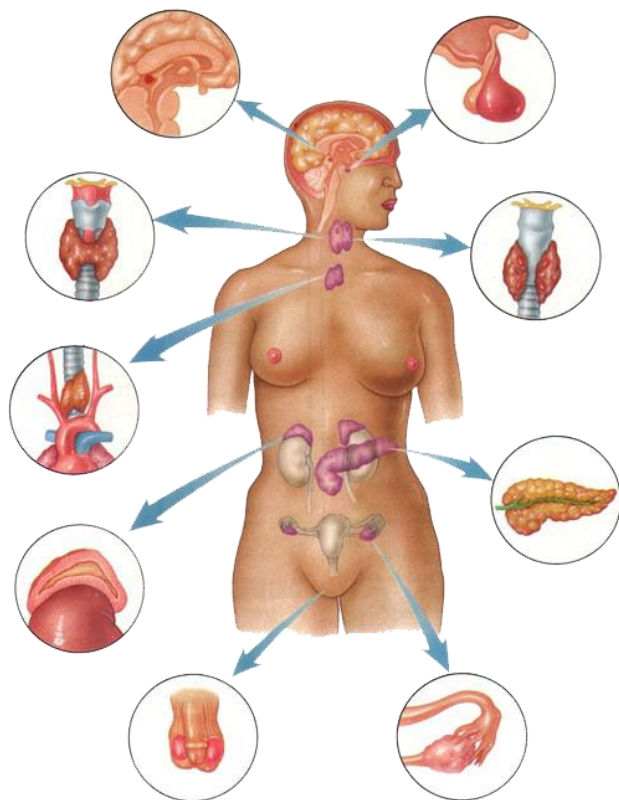




National University of Pharmacy
Department of Pharmacology and Drug Toxicology

Side effects of hormonal drugs

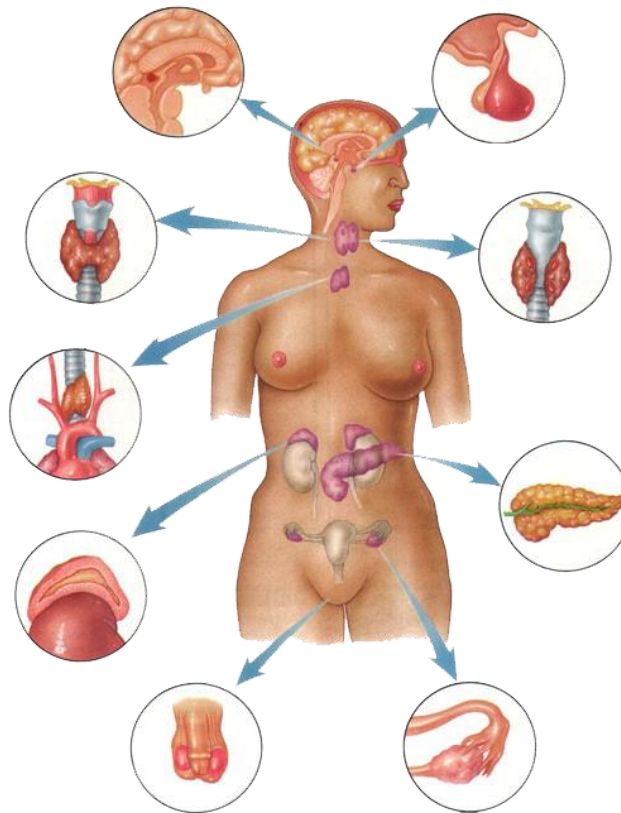


Lecturer: Olga Tovchiga

PhD (pharmacology, pharm.sc.)
ass. prof. of the Department of Pharmacology and
Drug Toxicology

HORMONAL DRUGS

are the medicinal forms of natural hormones or their synthetic analogues used for treatment of diseases



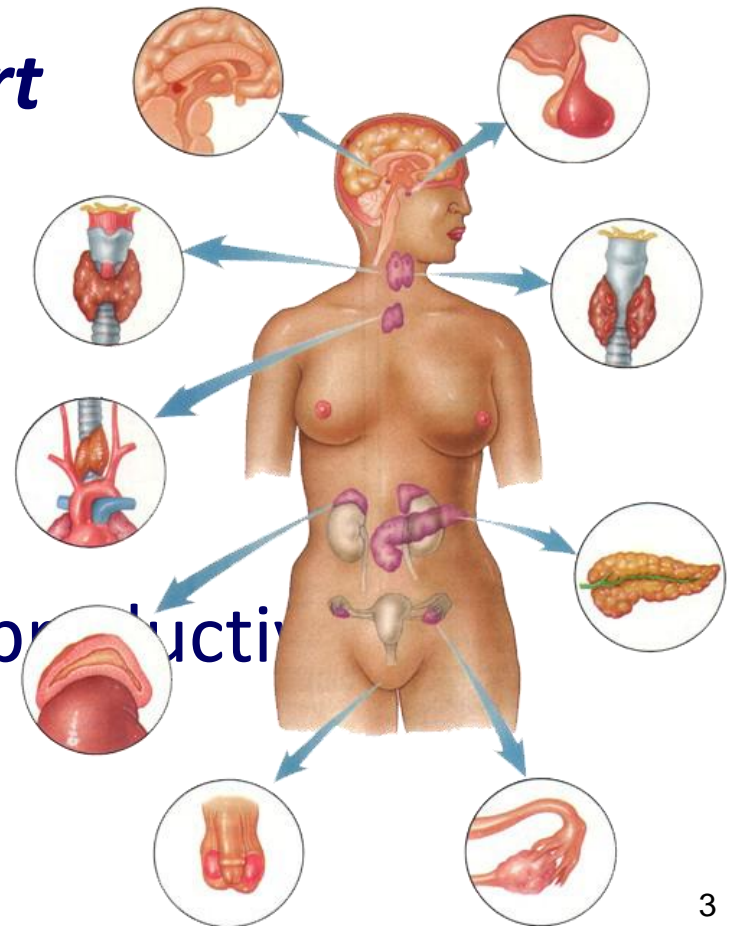
ENDOCRINE SYSTEM

• *Central part*

- ✓ Hypothalamus
- ✓ Hypophysis (pituitary gland)
- ✓ Pineal body (epiphysis)

• *Peripheral part*

- ✓ Thyroid gland
- ✓ Parathyroid gland
- ✓ Thymus
- ✓ Adrenal glands
- ✓ Pancreatic gland
- ✓ Gonadal glands of the reproductive system



STAGES OF ENDOCRINE SYSTEM RESPONSE

STIMULUS



Hypothalamus

Releasing Hormone
(Release-Inhibiting Hormone)



Pituitary

Stimulating Hormone



Gland
Hormone



Target

CLASSIFICATION OF HORMONES BY CHEMICAL STRUCTURE

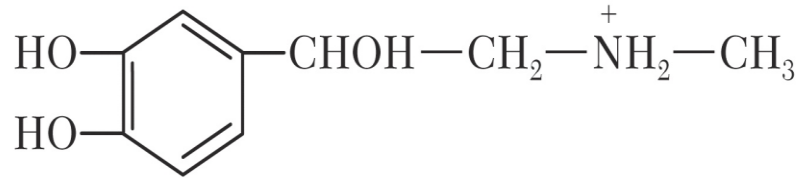
1. Derivatives of amino acids

- **Amines:**

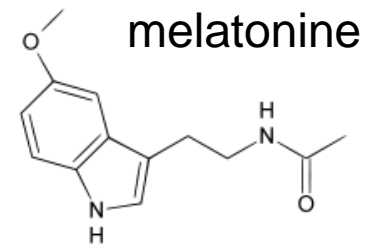
- epinephrine (adrenaline)
- melatonin

- **Iodothyronines:**

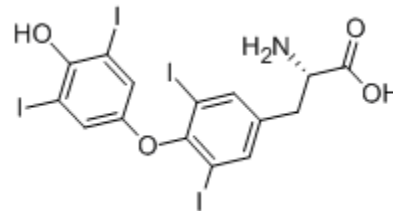
- L-thyroxine
- triiodothyronine



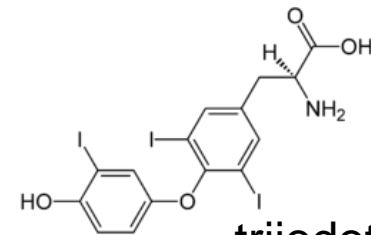
Epinephrine
(an amine)



melatonin



L-thyroxine



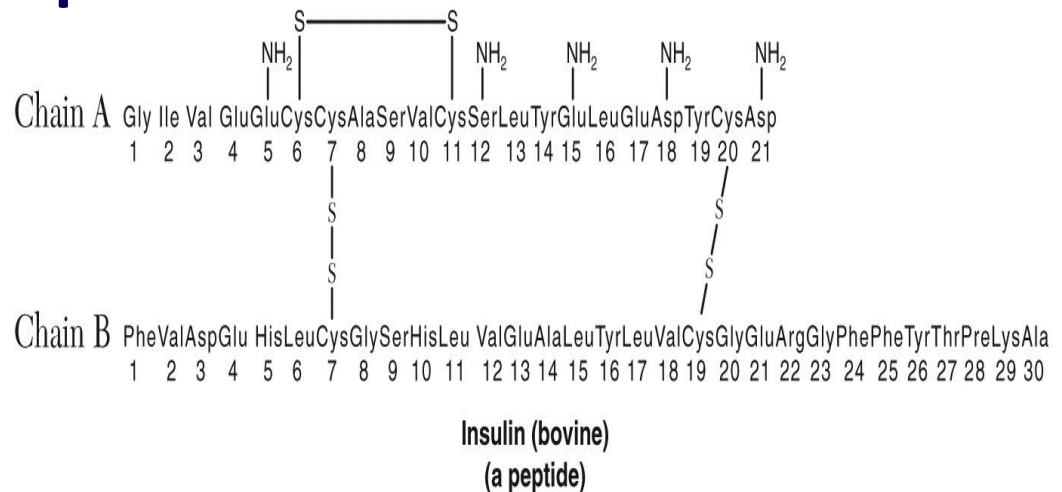
triiodothyronine

They are synthesized from a single amino acid, thyroid hormones from tyrosine
epinephrine from tyrosine, melatonin from tryptophan

CLASSIFICATION OF HORMONES BY CHEMICAL STRUCTURE

2. Peptides

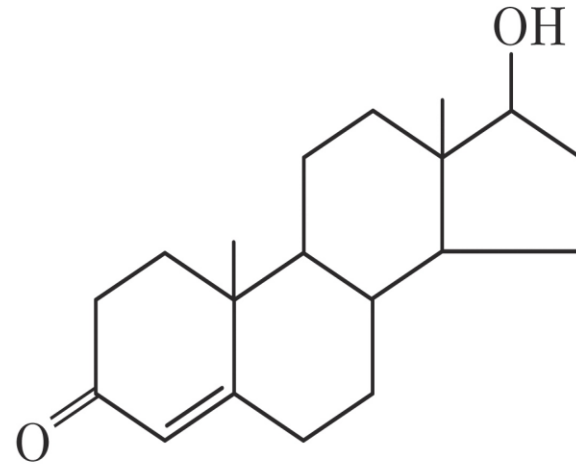
- corticotropin
- somatotropin
- menopaustic gonadotropin
- chorionic gonadotropin
- oxytocin
- vasopressin
- calcitonin
- parathyroidin
- insulin



CLASSIFICATION OF HORMONES BY CHEMICAL STRUCTURE

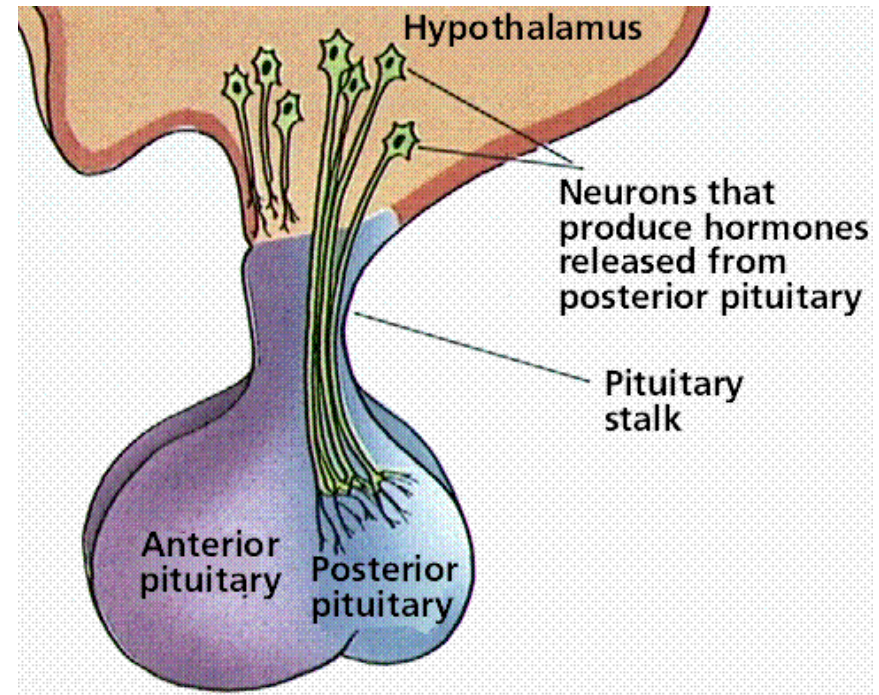
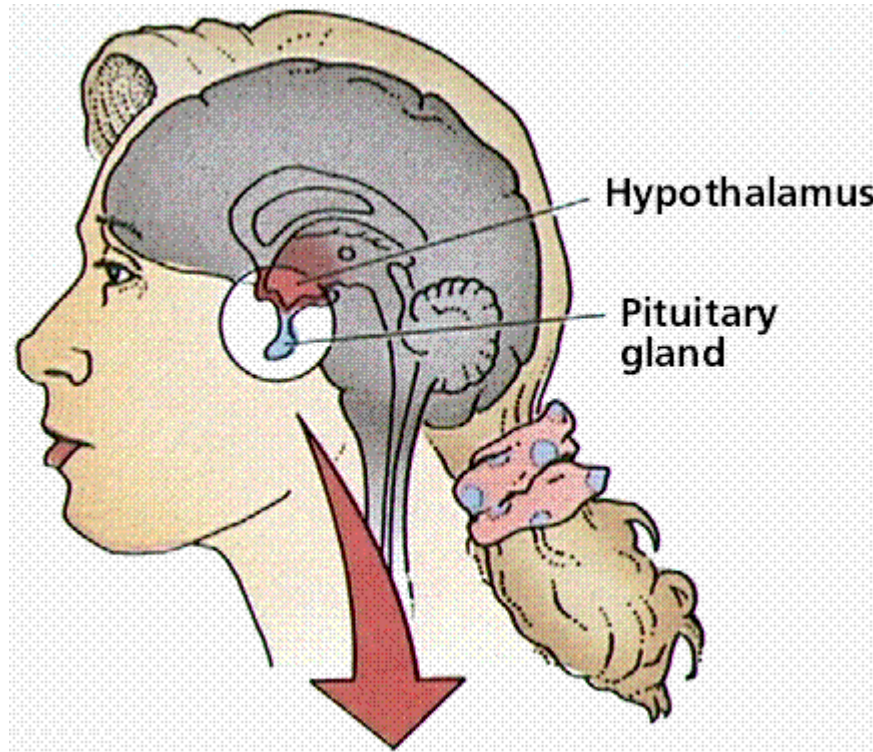
3. Steroids

- **Estrogens:**
 - estradiol
- **Progestines:**
 - progesterone
- **Androgenes:**
 - testosterone
- **Glucocorticoids:**
 - hydrocortisone
- **Mineralcorticoids :**
 - aldosterone



Testosterone
(a steroid)

HYPOTHALAMUS AND HYPOPHYSIS (PITUITARY GLAND)



Pituitary gland itself is controlled by the hypothalamus

Hypothalamic-releasing hormones influence the anterior pituitary through a portal system.

The hypothalamus is linked with the posterior pituitary through tracts.

HYPOTHALAMIC AND PITUITARY HORMONES

<i>Gland</i>	<i>Hormones</i>	
Anterior pituitary	<ul style="list-style-type: none"> ✦ Thyreotropic ✦ Adrenocorticotrophic ✦ Gonadotropic (FSH) ✦ Somatotropin (growth hormone) ✦ Prolactin 	TROPHIC HORMONES – activate other endocrine glands
Intermediate pituitary	✦ Intermedin (melanocytes stimu	influence on different body tissues – not
STORED hormones of hypothalamus released from posterior pituitary	Vasopressin (antidiuretic) Oxytocin	directly on other endocrine glands

SIDE EFFECTS OF ANTERIOR PITUITARY HORMONES

GLOSSARY

- **Lipoatrophy** is the term describing the localized loss of fat tissue within subcutaneous tissue
- **Gynecomastia** is a non-cancerous increase in the size of breast tissue in males because of the disorder of the endocrine system

DRUG	Typical SE, Other SE*	The mechanism of SE	Contraindications
Adreno-cortico-tropic hormone	Edema	The result of sodium retention	Renal unsufficiency, heart failure
	Arterial hypertension	↑ circulating blood volume	Severe AH
	Arrhythmia	Hypocalcemia contributes to arrhythmia development and sudden cardiac arrest	Heart rate disorders
	Increased CNS excitability		Psychoses
	Up to psychosis development*		
	Hyperglycemia*	Glyconeogenesis intensification	Diabetes mellitus
	GIT ulceration*	Catabolic processes prevalence	Ulcer disease
	Nausea, vomiting	Activation of the chemoreceptors of the medulla vomiting centre trigger zone	Dyspepsia
	Allergic reactions		Allergic reactions in anamnesis
	Hyperpigmentation*	Due to the melanocytes stimulation	Skin pigmentation
	Insomnia*	Result of the CNS excitation	Sleep disorders
	Hypokalemia, hypocalcemia*	Inhibition of potassium and calcium tubular reabsorption	Arrhythmia, osteoporosis
	Virilization*	↑ in secretion of adrogens by adrenal glands	Therapy with androgens
	Leucocytosis*	↑ in glucocorticoids secretion	Leucocytosis

DRUG	Typical SE, Other SE*	Contraindications
Somatotropin STG	Allergic reactions (skin rash, itching)	Allergic reactions in anamnesis, individual hypersensitivity
	Breasts hardening	Pregnancy, lactation
	Headache	Migraine
	Pain and hyperemia at the place of administration	
	Lipoatrophy the place of administration*	
	Hyperglycemia*	Diabetes mellitus
	Increase in antibodies titre*	Oncological diseases

DRUG	Typical SE, Other SE*	Contraindications
Menopausal gonadotropin (FSH+LH), Chorionic gonadotropin (LH) •	Ovarian hypertrophy	Hormonally active tumours of gonads, prostate cancer, early menopause
	Ovarian hyperstimulation syndrome (abdominal pain)	Hyperstimulation of the ovary or its threat
	Polyfetal pregnancy	
	Pain and hyperemia at the place of administration */•	
	Gynecomastia*/•	Endocrine disorders in males with the increase in breasts
	Allergic reactions	Allergic reactions in anamnesis, individual hypersensitivity
	Headache•	Migraine
	Depression•	Depressed mood
	Nausea	Dyspepsia
	Thromboembolism•	Trombophlebitis
	Increase in testicles size•	Premature pubescence
	Peripheral edema•	AH, renal insufficiency, heart failure

SIDE EFFECTS OF POSTERIOR PITUITARY HORMONES

DRUG	Typical SE, Other SE*	Contraindications
Oxytocin	<i>In mother:</i>	
	Nausea, vomiting	
	Heart rhythm disorders	Arrhythmia
	Uterine hypertone	Preterm labour, cesarean section in anamnesis
	Allergic reactions	Allergic reactions in anamnesis, individual hypersensitivity
	Fluid retention	AH, renal unsufficiency
	Preterm placental abruption	Partial placenta previa
	<i>In foetus:</i>	
	Arrhythmia (bradycardia)*	
	Asphyxia*	
	Foetal death	

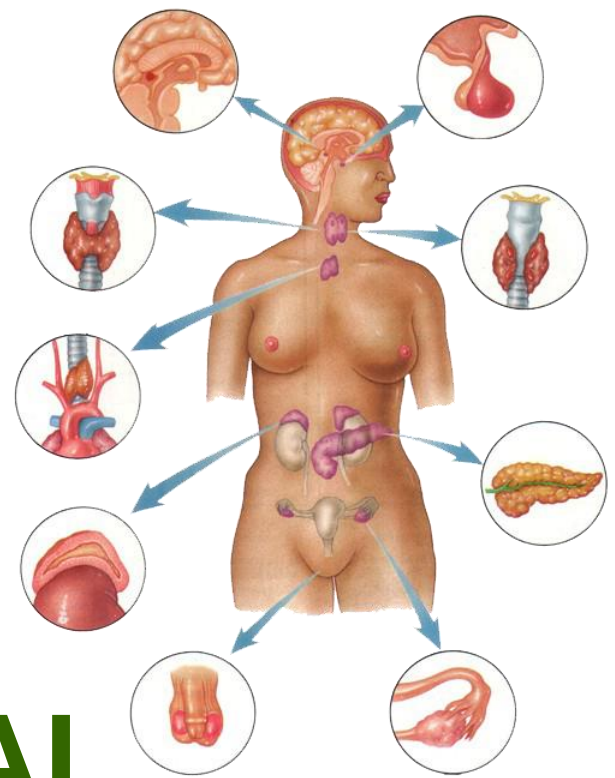
DRUG	Typical SE, Other SE*	Contraindications
Adiurecrin	Arterial hypertension	AH, stable stenocardia
	Edema	AH, renal unsufficiency, heart failure
	Allergic reactions	Allergic reactions in anamnesis, individual hypersensitivity
	Irritation of the oral mucosa	Age before 3 years, diseases of the respiratory system, paranasal sinuses and nasal cavity, oral mucosa

SE are increased

- In prolonged use of corticotropin – exhaustion of adrenal cortex
- Combination with anticoagulants is forbidden as the drug increases blood coagulability
- In combined administration of oxytocin with α -adrenomimetics there is an increase in BP
- Adiuretin at high doses leads to increase in BP

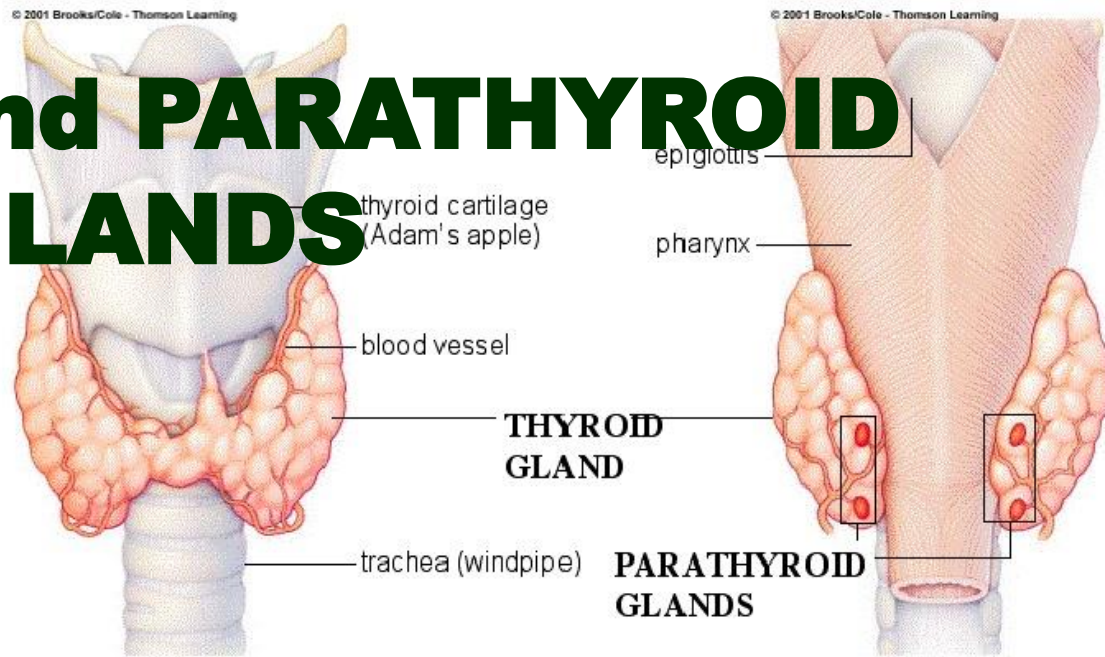
SE are alleviated

- Corticotropin is used only parenterally and should be injected in the morning when the effect is most high and there is no disturbance of the physiological rhythm of glucocorticoids secretion
- Prolonged synthetic drugs with corticotropin activity have a less risk of allergic reaction
- Menopausal gonadotropin should be used only under constant medical control
- Chorionic gonadotropin should be cancelled if the syndrome of ovarian hyperstimulation develops; in used with cautions in boys of pubertate age, as well as in patients with AH, renal insufficiency, migraine, bronchial asthma
- Oxytocin is not used in severe preeclamptic toxemia, severe disorders of the cardiovascular system; the drug is used only under the conditions of specialized clinics



PERIPHERAL ENDOCRINE GLANDS

THYROID and PARATHYROID GLANDS



<i>Hormones</i>	<i>Functions</i>
Thyroxine	Increases metabolic rate, intensify the activity of the sympathetic nervous system Required for normal metabolical growth
Triiodthironine	
Thyrocalcitonine	Decreases calcium level in blood
Parathyroid	Regulates exchange of calcium between blood and bones Increases calcium level in blood

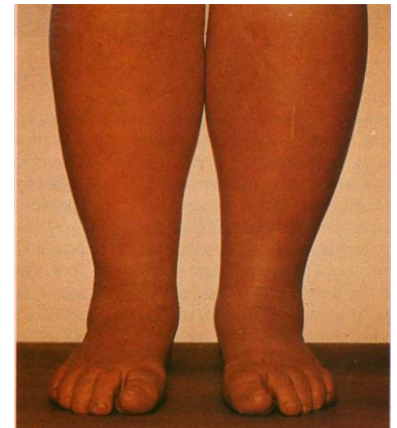
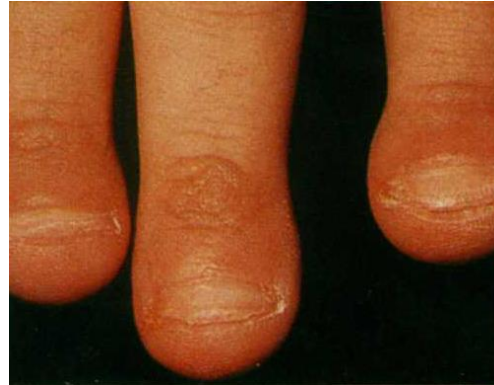
THYROID GLAND DYSFUNCTION

Mixedema

hypothyroidism

Hypothyroidism

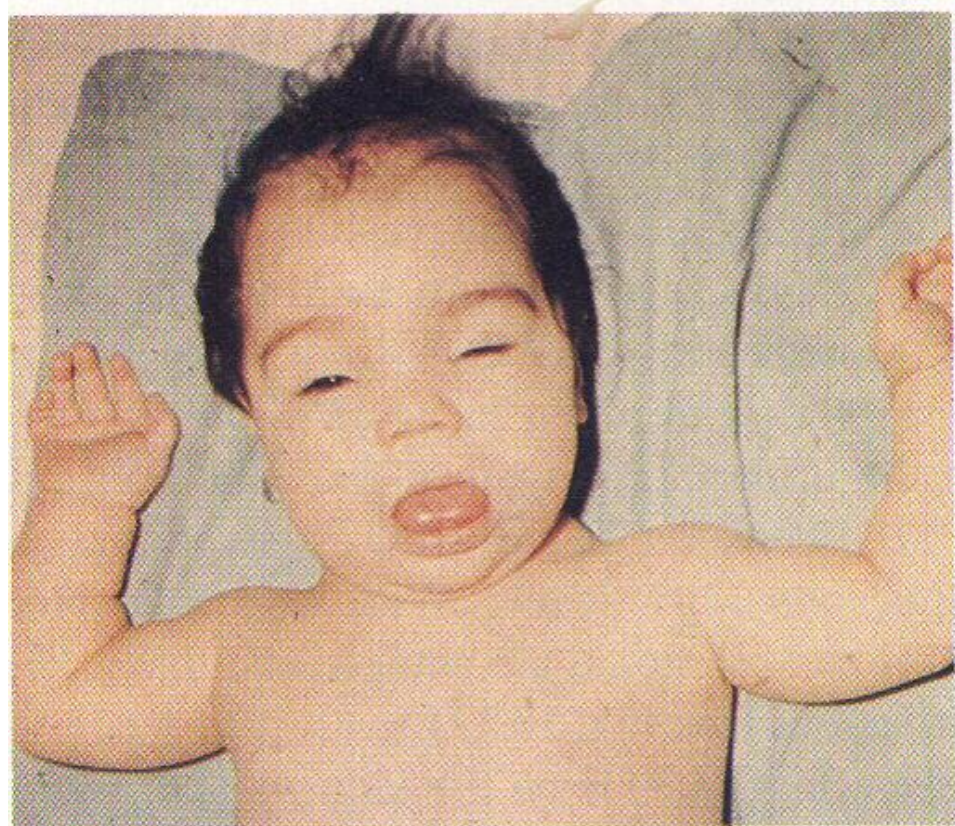
- aka myxedema
- if low thyroxin in adult
- low BMR
- lethargy
- dry brittle hair
- impaired memory
- thick tongue
- slow speech
- voice deep and coarese
- diminshished perspiration
- reddened cheeks
- megaloglossia
- increased pigment elbows/knees



THYROID GLAND DYSFUNCTION

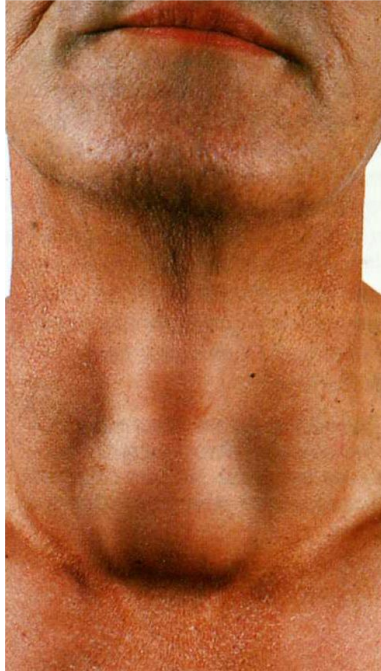
cretinism

- lack of thyroxine from birth
- or before birth
- could be from lack of thyroid gland
- or lack of iodine in mother
- severe and irreparable mental defects
- stunted growth
- reduced growth and function of many organs

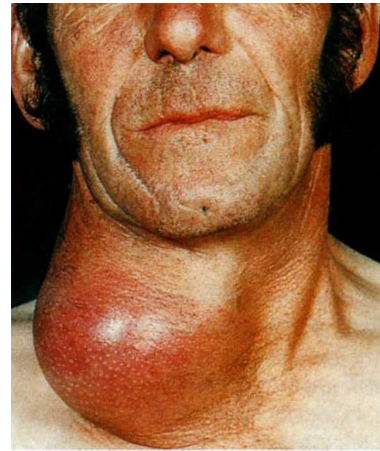


(a) Cretinism

THYROID GLAND DYSFUNCTION



***Toxic goiter
(thyreotoxicosis)***



***Endemic goiter
(hypothyroidism)***

SIDE EFFECTS OF THYROID HORMONES

Glossary

- **Arthralgia** – pain in joints
- **Hyperhidrosis** – increased perspiration

- **Myalgia** – pain in muscles
- **Cachexia** – extreme exhaustion with loss of weight, muscle atrophy, fatigue, weakness, and significant loss of appetite

DRUG	Typical SE, Other SE*	Contraindications
Levothyroxine sodium Lyothyronine Thyrocomb Thyrotom	Increased excitability, tremor	Hyperthyreoidism
	Insomnia	Sleep disorders
	Arrhythmia	Heart rhythm disorders
	Chest pain	Coronary unsufficiency, myocarditis, acute myocardial infarction
	Tachycardia	Heart rate disorders (Increase in heart rate)
	Adrenal glands unsufficiency	Addison's disease
	Diarrhea	
	Allergic reactions	Allergic reactions in anamnesis
	Decrease in body mass	Cachexia
	Hyperglycemia	Diabetes mellitus
	Hyperhidrosis *	Increased perspiration

SIDE EFFECTS OF ANTITHYROID HORMONES

DRUG	Typical SE, Other SE*	Contraindications
Thiamazole Propylthiouracil	Dyspepsia	Nausea, vomiting
	Allergic reactions	Allergic reactions in anamnesis, individual hypersensitivity
	Hepatotoxicity	Hepatic cirrhosis, hepatitis
	Leucopenia, agranulocytosis	Leucopenia, agranulocytosis
	Goitrogenic effects*	Goiter with nodes formation, hypothyroidism
	«Lupus syndrome»	Autoimmunic diseases

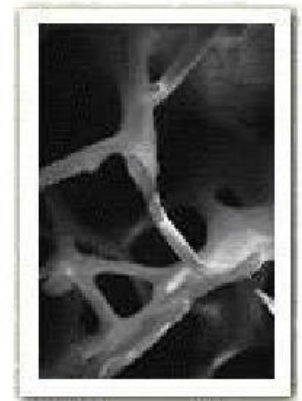
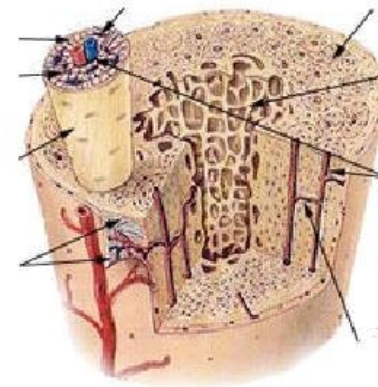
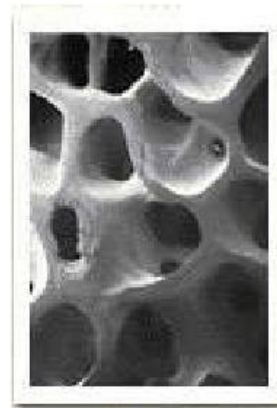
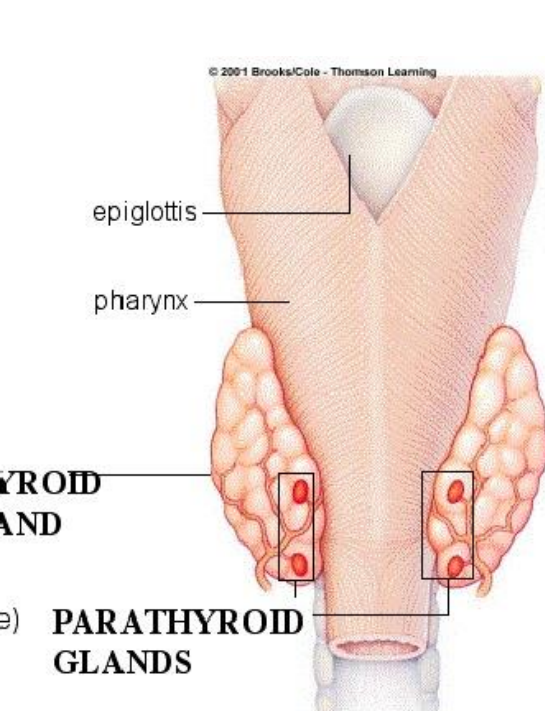
SE are increased

- When lyothyronine is combined with antidepressants, cardiac glycosides, ketamine (increase in side effects risk)
- When thyrotom is combined with indirect anticoagulants (augmentation of thyreotom action)
- When thyrotom is combined with acetylsalicylic acid (increase in thyreotom toxicity)
- When levothyroxine is taken together with salicylates, furosemid (at high doses), clofibrate, phenitoin, its effect increases as the mentioned drugs are able to displace levothyroxine at binding with plasma proteins
- When thiamazol and propylthiouracil are combined with sulfonamides (as they also suppress leucopoiesis)

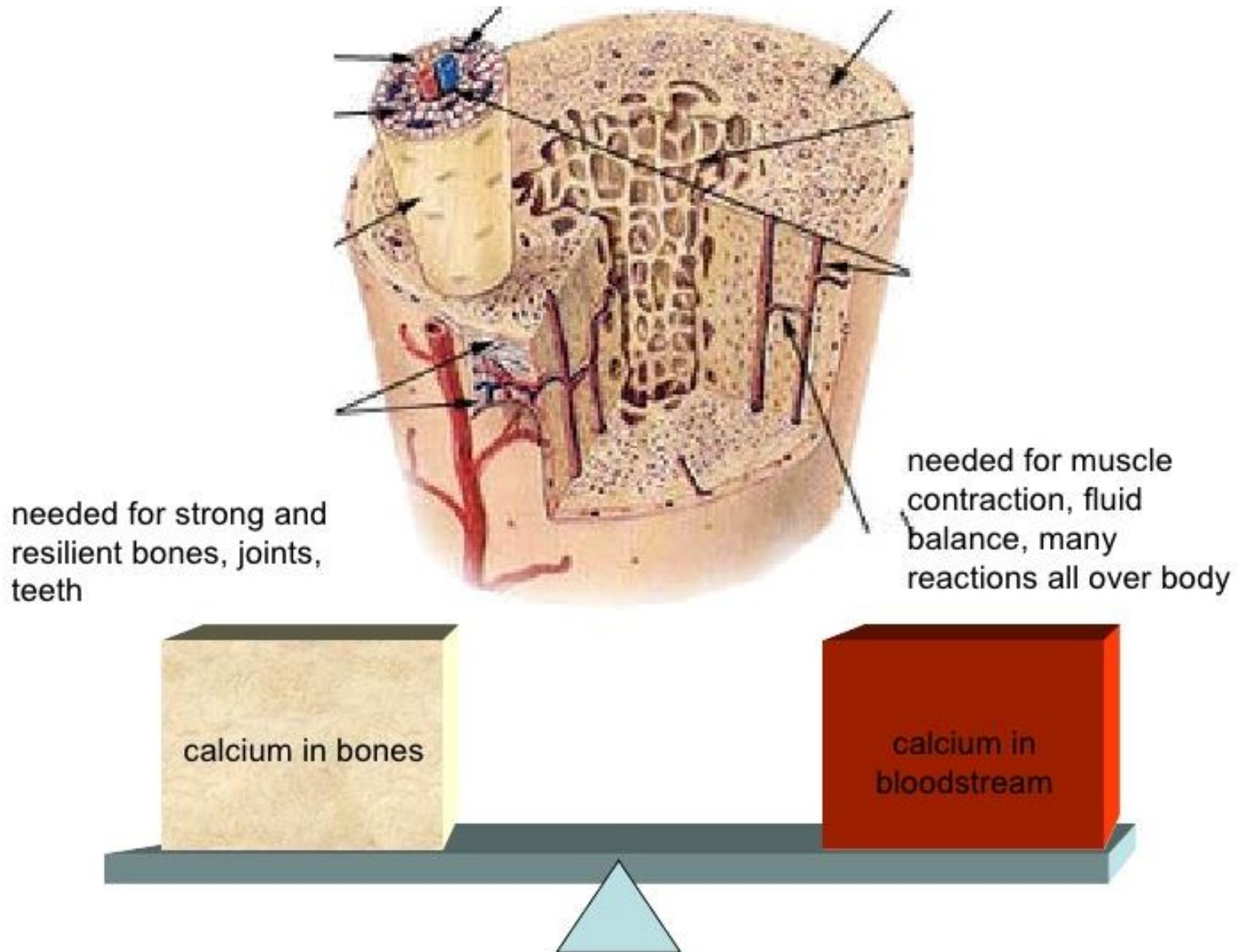
SE are alleviated

- When levothyroxine is taken together with chlorpromazine there is a decrease in hormonal activity
- Combination of thiamazol and lithium carbonate is rational

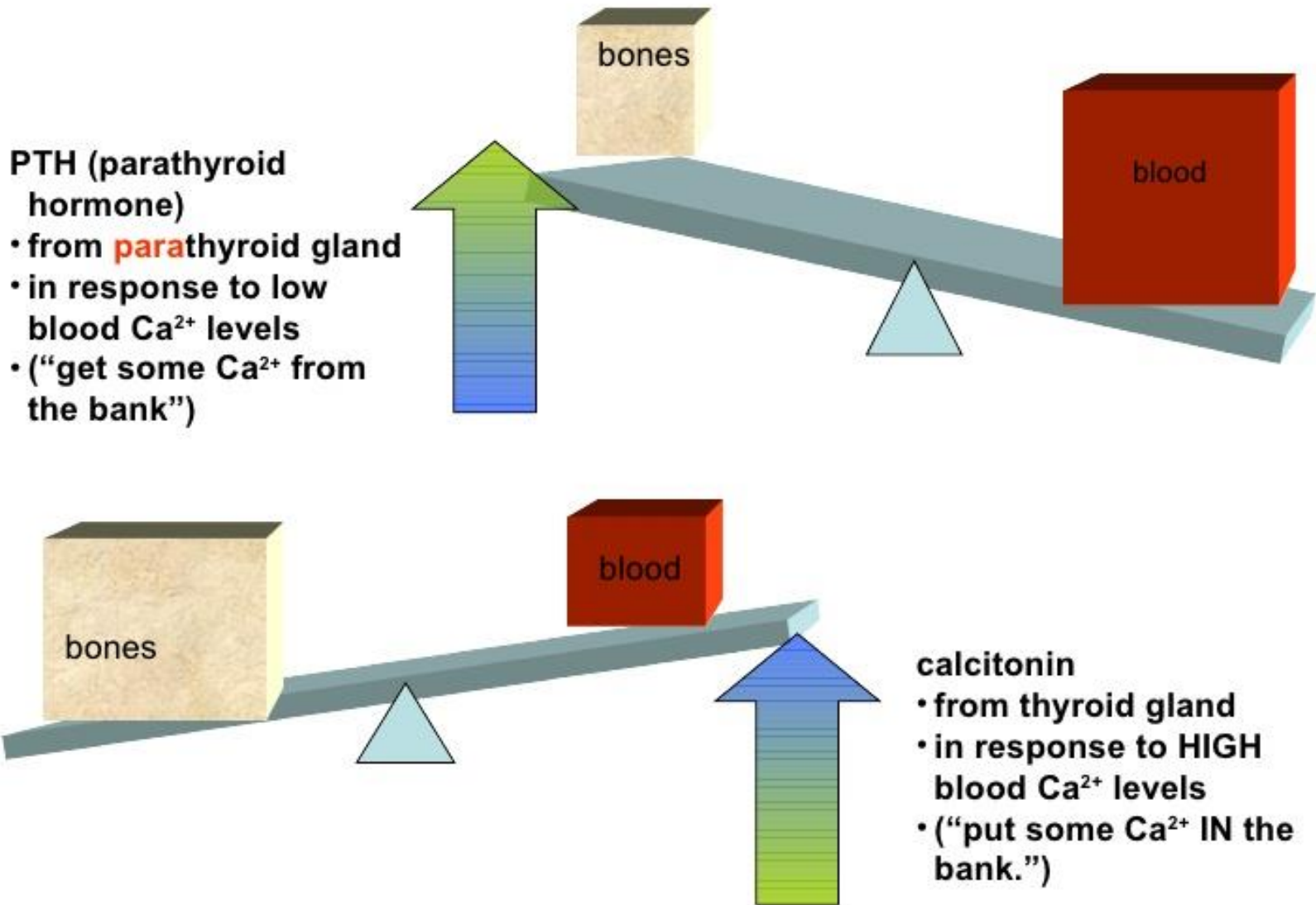
PARATHYROID GLANDS AND CALCIUM METABOLISM CONTROL



ROLE OF CALCIUM IN THE BODY



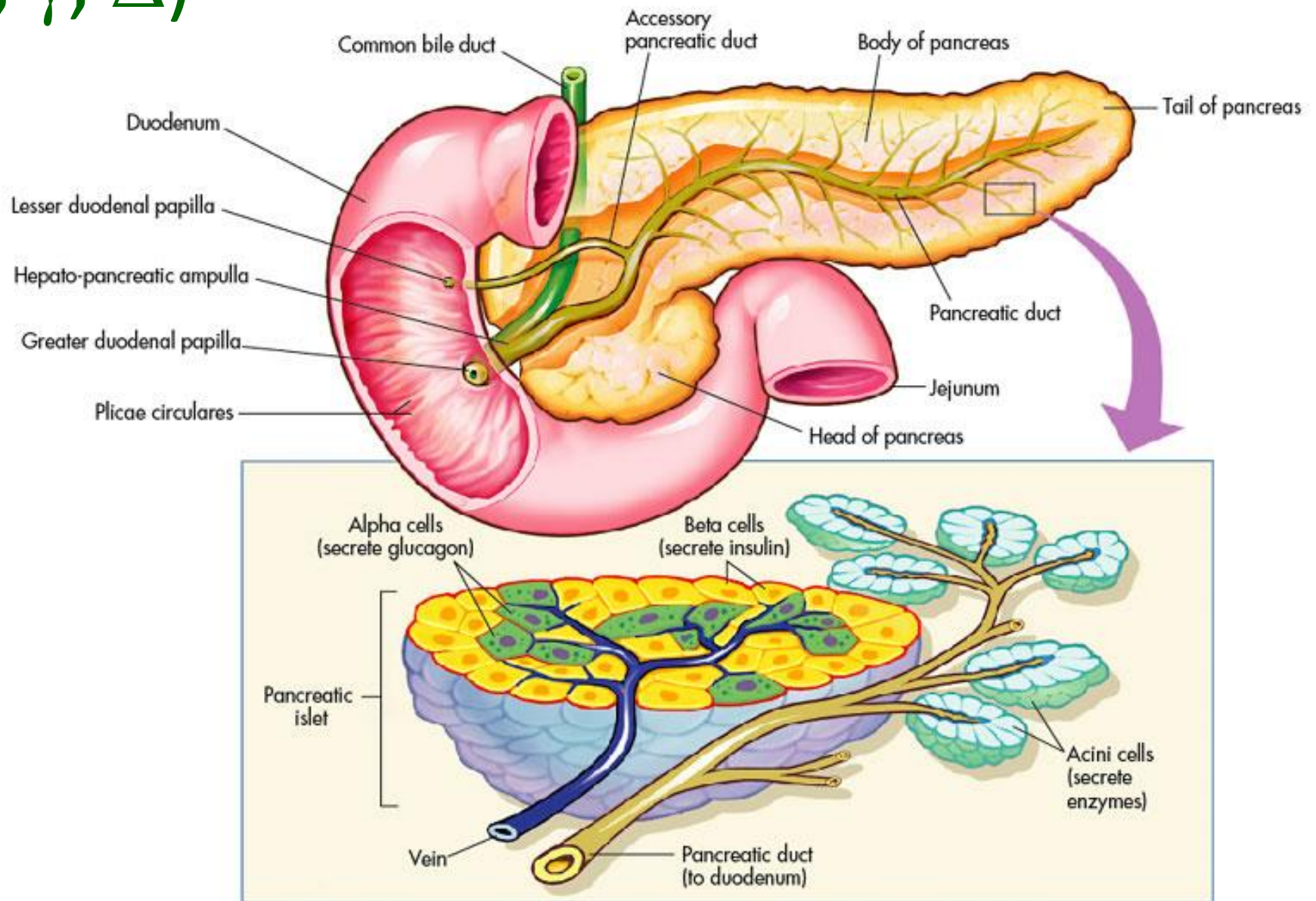
CONTROL OF CALCIUM LEVEL



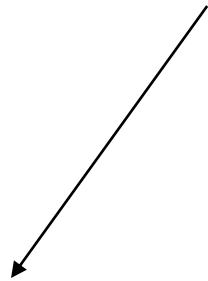
SIDE EFFECTS OF PARATHYROID HORMONES

Typical SE	Contraindications
Dyspepsia (parathyroidine, dihydrotachysterol, calcitonin, synthetic calcitonin-salmon)	Nausea, vomiting, diarrhea
Tachycardia, arrhythmia (the same drugs)	Acute miocardial infarction
Biliary diskinesia (the same drugs)	Cholecystitis
Tissue calcinosis (the same drugs)	Hypercalcemia
Disorders of kidney function (the same drugs)	Kidney unsufficiency
Allergic reactions, anaphylaxy (the same drugs)	Allergic reactions in anamnesis
Myalgia, arthralgia (dihydrotachysterol)	Inflammatory diseases of joints
Fever, leucopenia, agranulocytosis (dihydrotachysterol)	Blood system diseases, fever
Anorexia (dihydrotachysterol, synthetic calcitonin-salmon)	Cachexia
Collapse, hypotension (calcitonin, synthetic calcitonin-salmon)	Hypotension
Hypocalcemia (paresthesia, muscle fasciculation) (synthetic calcitonin-salmon)	Muscles twitching

PANCREAS – ISLETS OF LANGERHANS CELLS (α , β , γ , Δ)

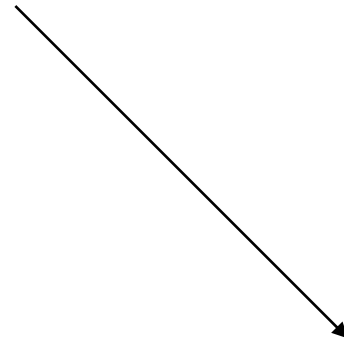


DIABETES MELLITUS



TYPE I

INSULIN-DEPENDENT

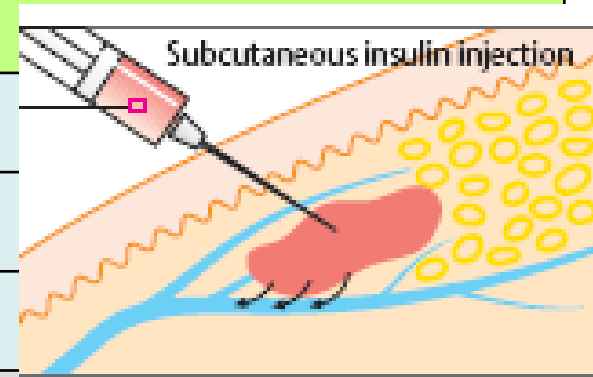


TYPE II

***INSULIN-
INDEPENDENT***

INSULIN MEDICINAL FORMS

<i>HUMAN INSULINS AND THEIR ANALOGUES*</i>		
<i>Short-acting</i>	<i>Medium-acting</i>	<i>Long-acting</i>
Insulin lispro* Human insulin Insulin aspart*	Human insulin	Human insulin Insulin glargin
<i>INSULINS OF ANIMAL ORIGIN</i>		
<i>Short-, medium- and long-acting</i>		
Porcine insulin		
<i>COMBINATION OF SHORT- AND MEDIUM-ACTING INSULINS</i>		
<i>Human</i>	<i>Animal</i>	
Human insulin	Porcine insulin	



INSULINS SIDE EFFECTS

DRUG	Typical SE	The mechanism of SE	Contraindications
Short, medium- and long-acting insulins	Hypoglycemia (hunger, increased perspiration, weakness, tachycardia, syncope) Hypoglycemic coma (hunger, increased perspiration, weakness, tachycardia, syncope, loss of consciousness, convulsions)	Excessive doses, absence or late meal, intensive physical work, concomitant diseases with vomiting or diarrhea	Decreased blood glucose Precoma
	Allergic reactions (skin rash Quincke's edema, anaphylactic shock that is more typical for insulins of animal origin)	Insulins have antigenic properties	Individual hypersensitivity

Glossary

INSULINS SIDE EFFECTS

- **Lipodistrophy** is the term describing the disorder of subcutaneous fat tissue (disappearance or growth) at the place of drug administration

Short, medium- and long-acting insulins	Lipodistrophy (lipoatrophy, lipohypertrophy)	Result of lipogenesis stimulation and lipolysis suppression by insulin, through the increase in fructose-2,6-diphosphatase level leading to glucose metabolism and synthesis of lipids from glucose	
	«Insulin edema» (brain edema, lungs edema, subcutaneous tissue and internal organs edema)	Consequence of a rapid decrease in extracellular glucose level if the intracellular glucose level is still maintained	Hepatic cirrhosis, nephritis, decompensated valvular anomaly of heart
	Infiltration and necrosis at the place of administration		Coma and precoma

SE are increased

- Hypoglycemic effect of insulin is increased in combination with MAO inhibitors, α -adrenoblockers, non-selective β -adrenoblockers, sulphonamides, tetracyclines, salicylates etc.
- Patients treated with insulin should not use alcohol (ethanol) as this combination leads to a quick decrease of glycemia

SE are alleviated

- The choice of insulin, dose adjustment, change between different drugs and medicinal forms is done only by doctor
- Insulin doses should be corrected in such cases: intensive physical work, infectious diseases, surgery, thyroid gland disorders, pregnancy, age over 65 years
- If allergic reaction is manifested, insulin of other batch or of other manufacturer should be used. Sometimes insulins are combined with glucocorticosteroids to decrease allergic reactions

TWO PARTS OF THE ADRENAL GLAND

Glucocorticoids
(e.g., cortisol)
Mineralocorticoids
(e.g., aldosterone)
Sex steroids
(e.g., testosterone)
Epinephrine
Norepinephrine

Cortex

Medulla

Adrenal
gland

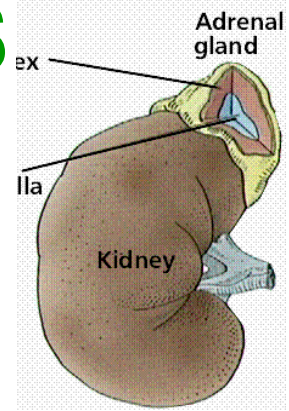
Kidney

two very different parts of the adrenal gland

adrenal cortex (outside)
secretes cortisol, aldosterone, other hormones

adrenal medulla (inside)
connected directly to nerve fibers from the hypothalamus
secretes adrenalin and noradrenalin

ADRENAL CORTICAL HORMONES



1. **Glucocorticoids** are produced by cells of the **zona fasciculata**

- a. *corticosterone*
- b. *cortisol (hydrocortisone)*
- c. *cortisone*

elevate blood glucose levels by acceleration of glycogenolysis and gluconeogenesis and cause conversion of proteins into carbohydrates in tissues]

promote protein catabolism and fat catabolism

maintain normal blood pressure through vasoconstriction

cause stress resistance

exert anti-inflammatory and immunosuppressive action

2. **Mineralocorticoids** are produced by the cells of the **zona glomerulosa**

Aldosterone

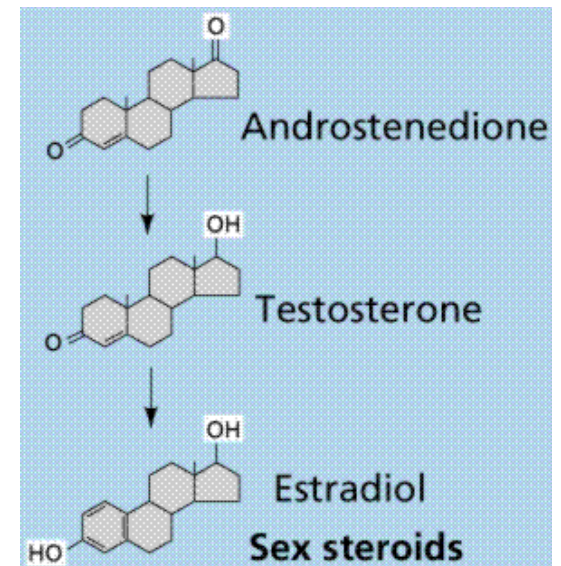
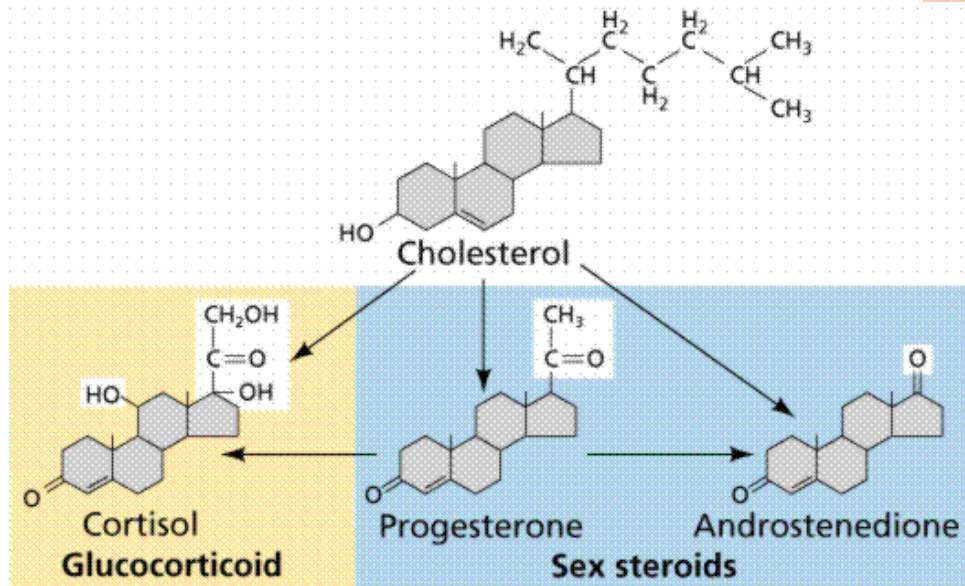
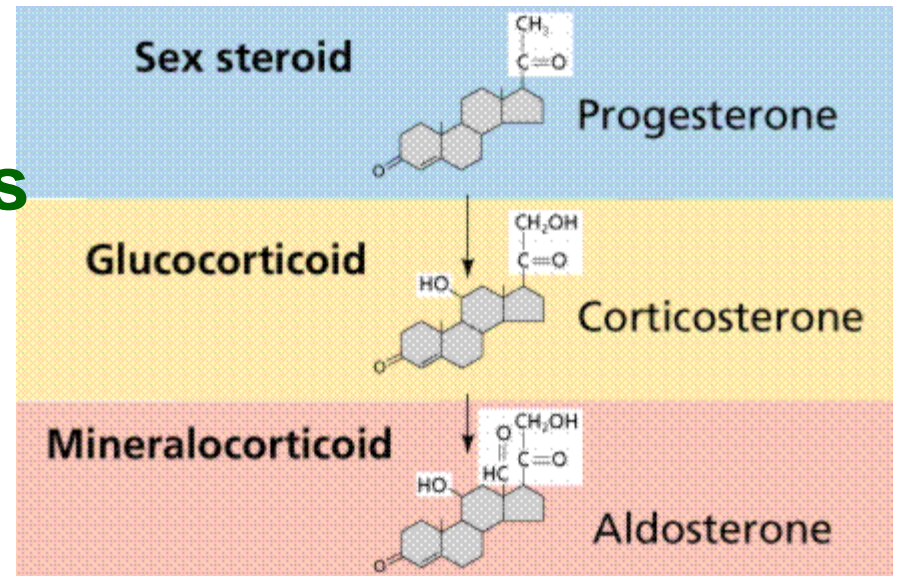
causes Na^+ retention and K^+ excretion

causes water retention and increase in blood pressure

3. **Gonadocorticoids** are produced by cells of the **zona reticularis**

these are the sex hormones that are produced by the adrenal cortex in small amounts in both males and females

**adrenal cortical hormones
are secreted
by the adrenal cortex
from cholesterol**



SIDE EFFECTS OF DRUGS WITH ADRENAL CORTICAL HORMONES ACTIVITY

- Side effects are manifested in 50% of the patients treated with glucocorticosteroids (in ½ of cases they are significant)
- Severe complications developed in 23.7% of haematological patients treated with glucocorticosteroids, lethality equaled 2.7%
- In the treatment of severe viral hepatitis by glucocorticosteroids side effects appeared in 67.7% of patients
- Up to 94% of all side effects of glucocorticosteroids are caused by prednisolone administration

ADRENAL GLANDS HYPERFUNCTION

*Itsenko-Cushing disease
is a hyperproduction of endogenous cortisol in
adrenal hyperplasia*

- Obesity
- Diabetes
- Hypertension
- Amenorrhea in women
- Osteoporosis etc.



GLUCOCORTICOIDS SIDE EFFECTS

Typical SE	The mechanism of SE	Contraindications
Endocrine glands		
Itsenko-Cushing syndrome	«Moonlike face» is the result of gluconeogenesis intensification and conversion of carbohydrates to lipids. The decrease in STH function leads to the decrease in lipid oxidation in the liver and accumulation of lipids in tissue depots	Itsenko-Cushing syndrome, obesity of III-IV stages
Pituitary-adrenal insufficiency	Depression of hypothalamic-pituitary-adrenocortical system, decrease in corticotropin production	Unsufficiency of adrenal cortex
Hirsutism		Increased hairiness, treatment with androgens, use of peroral contraceptives
CNS		
Psychical disorders (increased excitability, euphoria, insomnia, steroidal psychosis)	Psychostimulative effect of glucocorticosteroids	Increased CNS excitability, insomnia, severe psychoneuroses
Convulsions	Result of hypocalcemia	Proconvulsive states

Cardiovascular system		
Arterial hypertension	Increase in renin-angiotensin-aldosterone system activity; Increase in vasoconstrictory reactions caused by catecholamines	Severe AH
Arrhythmia	Result of hypokalemia	Arrhythmia
Water-salt homeostasis		
Edema	Due to mineralocorticoid activity of drugs, their ability to increase aldosterone effects and cause sodium and water retention	Kidney unsufficiency
Hypernatremia	Increase in tubular reabsorption of sodium	Kidney unsufficiency, heart failure, sodium balance disturbance
Hypokalemia	Decrease in tubular reabsorption of potassium	Potassium balance disturbance
Hypocalcemia	Decrease in tubular reabsorption of calcium	Calcium balance disturbance

Blood system		
Thrombosis, thromboembolism	Increase in platelets quantity and their aggregation	Increased blood coagulation, risk of thrombosis
Bones and muscles		
Osteoporosis	Depression of protein basis of bone as a result of the catabolic effect; increase bone resorption and removal of Ca^{2+} and phosphates from the bone	Osteoporosis, bone fractures with problematic recovery
Growth retardation in children	Decrease in STH secretion and peripheral tissues sensitivity to STH	Early age (not used in children)
Steroidal myopathy	Muscular atrophy and fibrosis as a result of protein catabolism	
Metabolism		
Hyperglycemia	Decrease in hexokinase activity (enzyme that limits a number of intracellular metabolic processes, such as glycolysis or glycogen synthesis), retardation of glucose tissue metabolism	Diabetes mellitus
Steroidal diabetes	Increase in gluconeogenesis and glucose conversion into lipids, hyperglycemia	Diabetes mellitus
Catabolic effect	Increase in RNA and protein synthesis of the enzymes that provide protein catabolism	Stomach and duodenal ulcer disease

Vision		
Increase in IOP	Augmentation in permeability of crystalline lens covering; disturbance in liquid outflow and excessive accumulation of mucopolysacharides	Glaucoma
GIT		
Pancreatitis	Inhibition of mitochondria function that leads to the release of pancreatic enzymes	Diseases of pancreas
Steroidal ulcer	Decrease in mucin production by gastric mucous membrane	Ulcerative colitis, stomach and duodenal ulcer disease
Skin		
Hypertrichosis (hirsutism)		Treatment of androgens
Retardation in wound healing	Increase in protein catabolism, suppression of protein synthesis from aminoacids	Skin tuberculosis, tropical ulcers
Skin reactions (skin atrophy, steroidal acne, ruptures of subcutaneous fat tissue, scars formation)		Acne vulgaris

Immunity

Immunosuppressive action	Suppression of immunogenesis: suppression of activity of T- and B- lymphocytes inhibiting antibodies production; suppression of secretion of cytokines (gamma-interferone, interleukines etc) by lymphocytes and macrophages	Immunodeficiency
Chronial infections exacerbation	Suppression of leucocytes migration, phagocytes maturation and mobility that leads to bacterial growth and chronial infections exacerbation	Tuberculosis, systemic mycoses, viral infections (chickenpox, herpes), candidosis

Others

Withdrawal syndrom	The result of decrease in adenal cortex function or its atrophy	Adrenal cortex hypofunction
Teratogenic action (fluorine-containing glucocorticoids)	Penetrate through placental barrier	Pregnancy

MINERALOCORTICOIDS SIDE EFFECTS

Typical SE	The mechanism of SE	Contraindications
Edema	Due to mineralocorticoid activity of drugs, their ability to increase aldosterone effects and cause sodium and water retention	Kidney unsufficiency
Arterial hypertension	Increase in renin-angiotensin-aldosterone system activity	AH
Increase IOP	disturbance of aqueous humour outflow	Глаукома
Hypokalemia	Due to the decreased tubular potassium reabsorption	Hypokalemia, heart failure with edema
Arrhythmia	The result of hypokalemia	Arrhythmia, IHD, atherosclerosis
Constipation	The result of hypokalemia	Atonia of intestine
Depression	↓ Catecholamines level	Depressed mood

SE are increased

- Combination of glucocorticoids with acetylsalicylic acid, triamcinolone with NSAIDs promotes ulcer formation in the stomach
- Combination of glucocorticoids with anticoagulants increases the risk of gastrointestinal bleeding
- Combination of glucocorticoids with androgens, estrogens, peroral contraceptives, anabolic steroids promotes formation of acne and hirsutism
- Glucocorticoids should not be used at a time of vaccination and other immunisation methods – risk of neurological complications
- Combination of triamcinolone with isoprenaline causes ventricular fibrillation

SE are alleviated

- Caution should be taken in patients with severe AH, heart failure
- In prolonged treatment with glucocorticoids ophthalmological examination should be done each 3 months
- After beclomethasone inhalation mouth rinsing and throat gargling should be done for candidosis prophylaxis
- In the period of treatment with hydrocortisone there is a need in dietary regimen with sodium restriction and potassium supplementation
- The dose of glucocorticoids should be decreased gradually for withdrawal syndrom prophylaxis
- After therapeutic effect of glucocorticoids has been reached their dose should be decreased for the prevention of severe intercurrent infections



Thank you!