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DISEASES OF THE ENDOCRINE SYSTEM

Lectures from Endocrinology

COMENIUS UNIVERSITY IN BRATISLAVA, FACULTY OF MEDICINE

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University teaching text

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Preface

This book comprises teaching texts for those students and young physicians beginning to study endocrinology. It is an overview of the most important endocrine diseases, it helps to learn the correct endocrine diagnostics and offers an effective treatment of endocrine diseases. I wish it would be a principal aid in basic medicine study for students of medicine, but also a concise endocrinology guide for physicians who exert a medical practice.

A profound thought of Doctor Francis W. Peabody from the year 1927:
"The essence of the practice of medicine is that it is an intensely personal matter…the treatment of a disease may be entirely impersonal; the care of a patient must be entirely personal. The significance of the intimate personal relationship between physician and patient cannot be too strongly emphasized, for in an extraordinarily large number of cases both diagnosis and treatment are directly dependent on it… One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient", is timely until now and should serve as additional guidance.

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Introduction

Endocrine diseases – basic terms and definitions

The endocrine system co-ordinates the body´s internal physiology, regulates its development throughout life, and helps it to adapt to nutrition and other external environmental changes. The system is based on a number of glands, which secrete hormones into internal medium to act on target tissues.
Hormones first interact with specific high-affinity receptors in the cells, or on the cells of target tissues.
Receptor activation then initiates a cascade of linked biochemical reactions within the cells, that produce the specific response.

Endocrinology concerns the synthesis, secretion and action of hormones. Hormones represent chemical messengers - diverse molecular structures (proteins, peptides, steroids) - are released from endocrine glands - coordinate the activities of many different cells.
Endocrine diseases – heterogeneous group – wide range of manifestations affecting many other organs.

Hormones – active molecules
Hormones are biologically high active drugs of the body which control the metabolic activity all different tissues and organs in the body. They play an important role in development and growth of the body, they control the reproduction mechanisms, they help how to adapt on everyday life-stress and how to survive.
Hormones can be classified according to chemical composition, solubility properties, the location of receptors, or the nature of the signal used to mediate their action within the cell.

Peptides (e.g. Insulin), polypeptides and proteins
Glycoproteins (thyroid stimulating hormone, TSH)
Steroids (adrenal cortex hormones, sex hormones – androgens, estrogens, gestagens)
Amines (e.g. Noradrenalin, Adrenalin) act on:

- specific cell surface receptors / through G-proteins & enzymes on the cytosolic side of the plasma membrane/,
- specific intracellular receptors / bind to response elements on DNA to regulate gene transcription (steroid hormones, thyroid hormones, Vitamin D).

Endocrine pathology

Pathology arising within the gland is called a primary disease (e.g. primary hypo-thyroidism in Hashimoto´s thyroiditis)
Abnormal stimulation of the gland from pituitary = secondary disease (e.g. secondary hypothyroidism (in patients with pituitary tumour and TSH deficiency).

Some endocrine diseases are common:
Thyroid gland disease (occurs in >10% population in areas with iodine deficiency)
Reproductive system diseases
B-cells of the pancreas – Diabetes mellitus (DM) Type 1
Many rare endocrine syndroms – particular – are a diagnostic challenge to primary care (i.e. phosphor metabolism abnormalities)

The sites of the principal endocrine glands

Hypothalamus & Hypothalamic hormones

In the median eminence the following releasing and inhibiting hormones are synthesized:
TRH – thyrotrophin releasing hormone,
GnRH – gonadotrophin releasing hormone,
CRH – corticotrophin releasing hormone,
GHRH – growth hormone releasing hormone,
Somatostatin (somatostatin releasing inhibiting hormone = SRIH), /peptide/,
PIF – prolactin inhibiting factor (dopamine) /biogenic amine/.

Pituitary gland & Pituitary hormones

Anterior pituitary:
TSH – thyroid stimulating hormone = thyrotrophin /glycoprotein/,
LH – luteinizing hormone,
FSH – follicle-stimulating hormone,
GH – growth hormone,
Pre-pro-opiomelanocortin [ACTH, β-lipotrophin, α-melanocyte-stimulating hormone (MSH), corticotropinlike intermediate lobe peptide - endogenous opioids – endorphins, enkephalins, (CLIP)],
ACTH – adrenocorticotropic hormone,
PRL – prolactin /proteins/.

Posterior pituitary:
oxytocin, vasopressin (ADH) = adiuretin = arginine vasopressin (AVP) /peptides/.

Thyroid gland:
T4, T3 – thyroxine and triiodothyronine /tyrosin derivatives/.

Parathyroid glands:
(four): parathyroid hormone /peptide/.

Adrenal gland: (two glands, left and right adrenal gland):

Adrenal cortex:	aldosterone,
	cortisol /steroids/,
	androgens,
	esterogens /steroids/.
Adrenal medulla:	epinephrine (adrenaline),
	norepinephrine (noradrenaline),
	opamine /catecholamines/.

Pancreas (islets of Langerhans):
insulin, glucagon, somatostatin /proteins/.

Testis (two) testes:
testosterone,
5α dihydrotestosterone /steroids/.

Ovary (two) ovaries:
oestogens,
progesteron,
androgens /steroids/.

Gastrointestinal hormones

synthesized in stomach (gastrin) /peptides/,
duodenum and jejunum (secretin, cholecystokinin) /proteins/.

Hypothalamic hormones - physiological function

* TRH: thyrotrophin-releasing hormone =thyroliberin – releases TSH and PRL
* LH FSH-RH = GnRH: gonadotrophin releasing hormone = gonadoliberin – secretion of LH, FSH
* Dopamine – Prolactin inhibiting factor: - inhibits PRL secretion – (breast lactation)
* GHRH: growth hormone releasing hormone = somatoliberin - GH - IGF-I, IGF-II – insulinlike growth factors (body growth)
* Somatostatin: inhibits GH secretion
* CRH: Corticotropin releasing hormone – ACTH cortisol secretion in adrenal cortex
* Oxytocin – uterus, breast (parturition, lactation)
* Adiuretin (ADH) distal nephron (water balance)

Pituitary hormones – physiological function

Pituitary control of the function of the peripheral glands - most endocrine glands are controlled by hormones released from the pituitary (gland).

Anterior pituitary (adenohypophysis) hormone secretion is controlled by substances produced in hypothalamus and released into portal blood circulation. Anterior pituitary hormones = trophins are controlled by hypothalamic releasing/ or inhibiting hormones.

Posterior pituitary hormones are synthesized in the hypothalamus (nucleus supraopticus, nucleus paraventricularis) – transported down nerve axons to be released from the posterior pituitary (neurohypophysis)

Anterior pituitary - The hypophysiotrophic hormones – trophins regulate the function of peripheral endocrine glands

TSH – thyroid stimulating hormone: thyroid growth, hormone secretion of thyroid: T4,T3

LH – luteinizing hormone
- female: ovulation, corpus luteum, progesterone synthesis
- male: testosterone synthesis, dihydro-testosterone synthesis

FSH – follicle stimulating hormone
- female: growth of follicles, oestrogens synthesis
- male: interstitial cells - spermatogenesis, secretion of inhibin –
  - feedback of spermiogenesis control

ACTH – adrenocorticotropic hormone (pre-pro-opiomelanocortin)
growth of adrenal cortex, cortisol synthesis

(**MSH**, also a functional part of ACTH) melanocyte stimulating hormone – controls melatonin synthesis in the skin (after UV- light exposition)

GH – growth hormone: growth stimulation through IGF-I (insulin like growth factor-I) = somatomedin C (IGF-I is synthesized in the liver)

PRL – prolactin: lactation, growth of breast in pregnancy, inhibits LH and FSH secretion

Posterior pituitary

Oxytocin: contraction of smooth muscles in uterus during labour (parturition)
In myoepithelial cells in the duct of mammary gland (lactation)

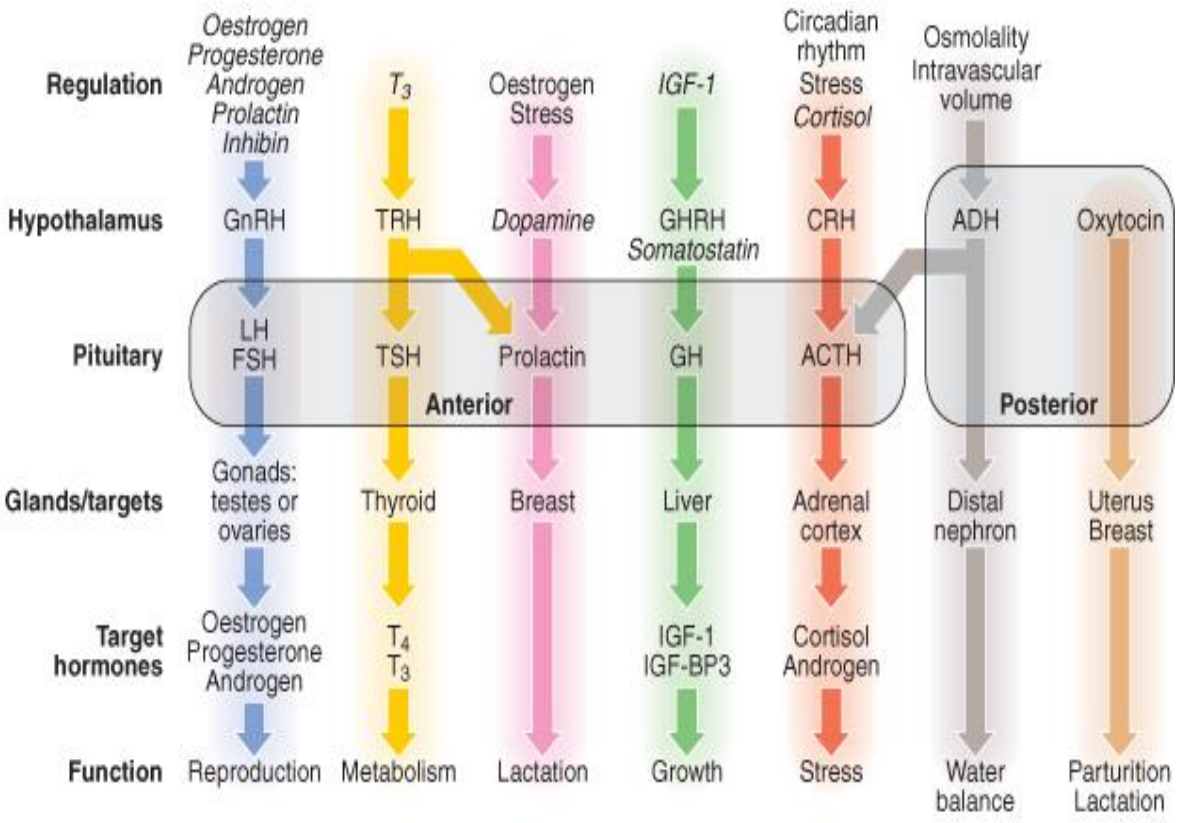
Adiuretin - (antidiuretic hormone) - also called vasopressin: water excretion in distal nephron (water balance) is a potent vasoconstrictor.
Hormone release (in the hypothalamus and pituitary) is regulated by numerous stimuli of nervous metabolic, physical hormonal origin, in particular feedback control by hormones produced by the target glands (thyroid, adrenal cortex and gonads). These integrated endocrine systems are called axes:

The principal endocrine 'axes' and glands

Axis hypothalamus – pituitary – peripheral gland

- thyroid
- adrenal cortex
- ovaries
- testes

Figure 1: Anatomical relationships and function of the pituitary and hypothalamus



Source (Figures no. 1-3): BOON, N.A., COLLEDGE, N.R., and WALKER, B.R., (eds.). Davidson's Principles and Practice of Medicine. 20th ed. Philadelphia: Churchill Livingstone/Elsevier Health Sciences Division, 2006, xvi, 1381 p. ISBN 978-0-443-10057-4. Available at: www.studentconsult.com

Figure 2

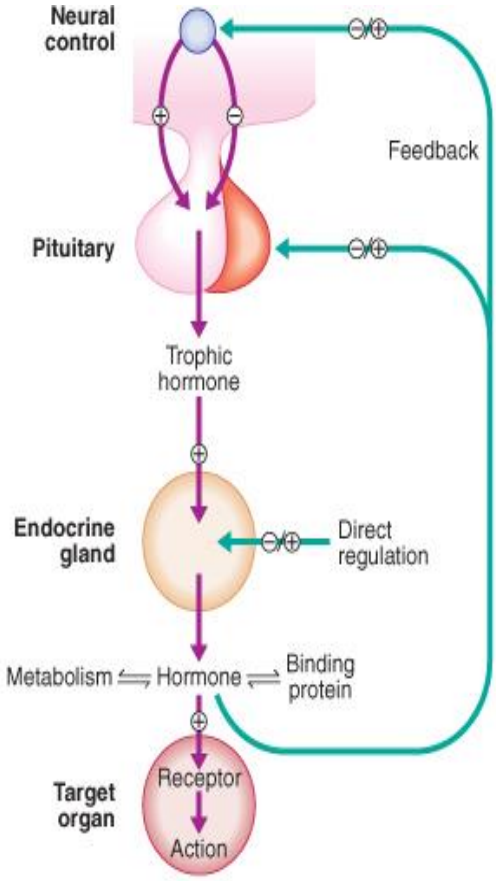
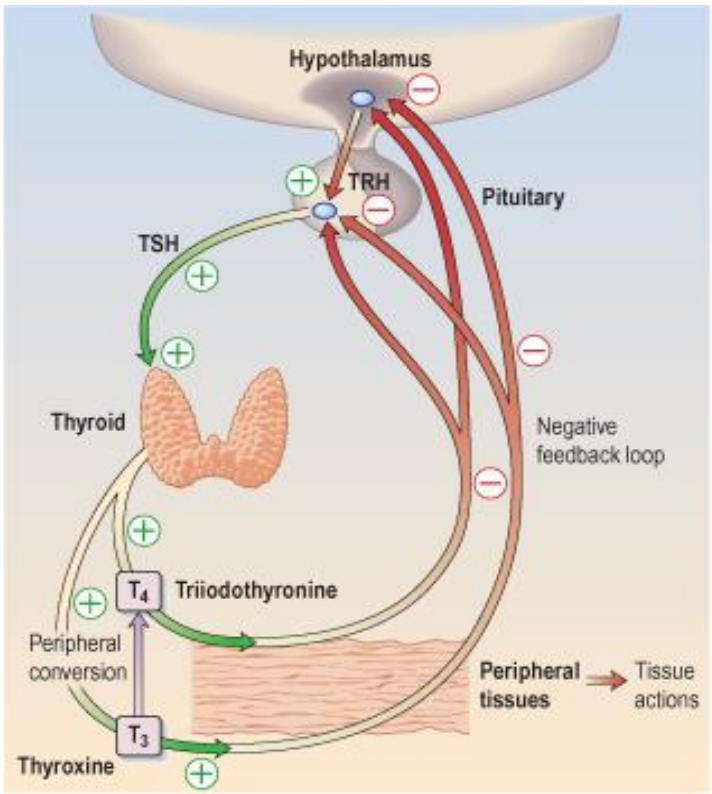


Figure 3



Hypothalamo-pituitary axis

Anterior pituitary trophins – peripheral glands

The hypothalamo-pituitary axis plays the central role in the endocrine system.

Releasing hormones of hypothalamus →
→ anterior pituitary − trophins → peripheral glands

TSH − Thyroid

hyperfunction		hypofunction	
primary	secondary	primary	secondary
Morbus Graves	tumour with ↑TSH	Morbus Hashimoto	tumour with ↓TSH

ACTH − Adrenal cortex

hyperfunction		hypofunction	
primary	secondary	primary	secondary
Cushing´s syndrome	tumour-Morbus Cushing	Morbus Addisoni	↓CRH↓ACTH = →↓Cortisol (empty sella)

LH, FSH − Ovaries

hyperfunction		hypofunction	
primary	secondary	primary	secondary
tumour-ovary	pituitary tumour	ovarial insufficiency menstrual dysturbances	infertility, Morbus Sheehan = = postpartal necrosis

LH, FSH − Testes

hyperfunction		hypofunction	
primary	secondary	primary	secondary
tumour testis	pituitary tumor	orchiis	autoimmune inflammation

impotence: impotentia generadi/ coeundi

PRL − Mammary gland

hyperfunction		hypofunction	
–	secondary	–	secondary
	prolactinoma-tumour infertilty, menstrual dysturbances		hypoPRL - inflammation

GH − Skellet

hyperfunction		hypofunction	
–	secondary	primary	secondary
	pituitary GH-tumour gigantism, acromegaly (epiphyseal fusion)	Laron dwarf, IGF1↓	hypopituitary nanism ↓GH dwarf

Hormones of hypothalamus → → posterior pituitary

Adiuretin	**Kidney**	**Distal nephron**
hyperfunction-overproduction		hypofunction
paraneoplastic (tumour) ADH secretion		↓ADH secretion − Diabetes insipidus (DI)
inappropriate ADH secretion		primary / secondary
water intoxication		Nephrogenic DI / Central DI
Oxytocin	**Uterus**	**Mammary gland**
overproduction		insufficient production
−		during parturition
		insufficient uterus contractions

Diseases of the hypothalamus – pituitary system

are rare, annual incidence of approx 1: 50 000 subjects.
Disorders of the hypothalamus and pituitary may present as endocrine or neurologic dysfunction. I. Hypersecretion (prolactinoma, acromegaly, central Cushing´s disease) /hyposecretion (hypopituitarism, adrenal insufficiency, central hypogonadism) of pituitary hormones, II. neurological manifestations (space occupying lesions, headache, visual disturbances) - due to pressure effects from tumor or cause abnormal autonomic function. Endocrine manifestations of hypothalamic and pituitary causes are similar. The pituitary plays a central role in several major endocrine axes, so that investigation and treatment involves several other glands.

A Diseases of the hypothalamus – Classification

A.1 Hypothalamus hormone excess syndrome
- A1.a Pubertas praecox
- A1.b Cushing´s disease (Morbus Cushing)

A.2 Hypothalamus deficiency syndrome – Hypopituitarism – Hypothalamic hypopituitarism
- A.2.a Kallmann´s syndrome
- A.2.b Fröhlich syndrome
- A.2.c Prader-Willi syndrome
- A.2.d Laurence-Moon-Biedl syndrome
- A.2.e Anorexia nervosa
- A.2.f Diabetes insipidus centralis

A.1 Hypothalamus hormone excess syndrome

A.1.a **Pubertas praecox** – Precocious puberty
– presenting clinical features of hypothalamic disease in children. The presence of hypothalamic tumours may initiate the early onset of normal mechanisms of pubertal maturation, with excessive skeletal growth but a reduced ultimate height. Gn-RH: stimulation

of pituitary secretion of LH, FSH and secretion of testosterone in testes, secretion of estradiol (17 β-E2) in ovaries, hCG- human chorionic gonadotrophin increases steroid synthesis in gonads.

A.1.b **Cushing´s disease** – Morbus Cushing - Central Cushing´s syndrome
Central hypercortisolism
CRH↑ → ACTH↑ → cortisol↑ in adreno-cortex
See Lecture: Adrenal cortex diseases and Cushing´s syndrome

A.2 <u>Hypothalamus deficiency syndromes</u> - Hypothalamic hypopituitarism

A.2.a **Kallmann´s syndrome**
Hypothalamic defect of Gn-RH deficiency causes secondary deficiency of pituitary gonadotrophins LH, FSH and consequent hypogonadism (low testosterone secretion in boys, low estrogen secretion in girls).The initial defect can be congenital, which can be associated with a reduced sense of smell – anosmia.

A.2.b **Fröhlich syndrome,** Dystrophia adiposogenitalis
Hypothalamic defect caused by a tumor, inflammation or degenerative changes in hypothalamic area. Reduced secretion of Gn-RH results in hypogonadism development. Dominant clinical signs are obesity in childhood, associated with underdeveloped infantile genitalia as a consequence of gonadotrophin deficiency. Th.: In case of tumor-neurosurgical extirpation of tumor and Gn-RH substitution therapy.
A variant is the syndrome of small genitalia in fat boys. The reduction in genital size is not real, as a penile shaft is buried in the suprapubic fat pad and is normal in size. The testes are also normal in size for a prepubertal boy = <u>Pseudo dystrophia adiposogenitalis</u>. Th.: Dietary recommendations and reduction of body fat.

A.2.c **Prader-Willi syndrome,**

A.2.d **Laurence-Moon-Biedl syndrome**
- familial disorders associated with characteristic facies, mental retardation, hypotonia, hyperphagia resulting in severe obesity, disordered diurnal rhythm. Disease manifestation in childhood. Reduced Gn-RH secretion in hypothalamus results in central hypogonadism with underdeveloped small genitalia. **Laurence-Moon-Biedl syndrome** is a central hypogonadism associated with retinitis pigmentosa, polydactylia and congenital heart defects.

A.2.e **Anorexia nervosa**
Anorexia nervosa (AN) is a disorder of unknown ethiology, (mental abnormality) seen in young women under the age of 25 years, particularly common in females adolescents. Disorder presents as anorexia, severe weight loss, amenorrhea, behavioral changes- hyperactivity and preoccupation with food. Hypothalamic-pituitary dysfunction.↓Gn-RH, decreased LH a FSH secretion, profound E2 deficiency → central hypogonadism, euthyroid sick syndrome development. If weight is regained, Gn-RH secretion returns to the adult pattern. Treatment: estrogens replacement is indicated, continued preoccupation with food and persistent dieting behaviour. Treatment of anorexia nervosa remains a major therapeutic challenge.

A.2.f **Diabetes insipidus centralis**
See lecture Diabetes insipidus in chapter Pituitary insufficiency – Hypopituitarism, ↓ADH Diabetes insipidus page 19-20.

B Diseases of the pituitary – Classification

– two different forms of diseases

B.1 Syndromes of hormone excess:
Prolactinoma, Acromegaly, Central Cushing´s syndrome

B.2 Syndrome of hormone deficiency:
Hypopituitarism, Isolated secondary hypogonadism, adrenal insufficiency
space occupying lesions: headache and/or visual disturbances

Classification of diseases of the pituitary

B.1 Pituitary hormone excess

Anterior pituitary – Hyperpituitarism

B.1.a Prolactinoma
B.1.b Acromegaly
B.1.c Central Cushing´s disease
B.1.d Rare TSH-, LH- and FSHomas

B.2 Pituitary hormone deficiency

Anterior pituitary – Hypopituitarism

Growth hormone deficiency
Gonadotrophin (LH, FSH) deficiency
Adrenocorticotrophin (ACTH) deficiency
Thyreotrophin (TSH) deficiency

Posterior pituitary – Cranial diabetes insipidus

C Hormone resistance – Growth hormone resistance (Laron dwarfism)
Diabetes insipidus

D Non functioning tumours

Pituitary adenoma
Metastatic tumours
Craniopharyngioma

B.1 Anterior pituitary hormone excess - Anterior pituitary hyperpituitarism

B.1.a **Prolactinoma**

Aetiology

Elevation of plasma PRL levels – common finding. PRL arises from a variety of causes:

Physiological

* Stress
* Pregnancy
* Lactation
* Chest wall reflex (e.g. nipple stimulation)
* Wet nursing reflex (e.g. baby crying)

Drugs
Dopamine antagonists
* Antipsychotics (phenothiazines, butyrophenones)
* Antidepressants
* Antiemetics (e.g. Metoclopramide, domperidone)
Dopamine-depleting drugs
* Reserpine
* alpha Methyldopa
* Oestrogens
* Oral contraceptive pills
Pathological
Common
* Disconnection hypeprolactinemia (e.g. non-functioning pituitary macroadenoma)
* Prolactinoma (usually microadenoma)
* Primary hypothyroidism
* Polycystic ovarian syndrome
Uncommon
* Hypothalamic disease
* Pituitary tumour secreting PRL and GH
* Renal failure
Rare
* Post herpes zoster
* Ectopic source

Clinical features
Cardinal features. In women: (microadenoma)
Galactorrhoea & hypogonadism
hypogonadism: oligomenorrhoea or amenorrhoea and menorrhagia
anovulation with infertility
In men:
decreased libido, erectile impotence, reduced shaving frequency, lethargy, galactorrhoea (macroadenoma)

Investigation:
PRL more than 500 mU/l
During pregnancy and lactation 20 000 mU/l
Stress, drugs, non-pregnant, non-lactating woman 500-1000 mU/l
Microprolactinoma, disconnection hyperprolactinemia: 1000-5 000 mU/l
Levels above 1 000 mU/l highly suggestive of prolactinoma
Macroprolactinomas 1000 000 mU/l
Examination of thyroid function: TSH fT4 - to exclude primary hypothyroidism
PRL more than 1000 is an indication for MRI, CT exam. of hypothalamus and pituitary
MRI will detect all macroadenomas and 70% of microadenomas (in 30% normal scan) – the presumptive diagnosis is small microadenoma.

Management
Dopamine agonist therapy
Bromocriptine 2.5mg in treating infertility headache, vomitus
Cabergoline 0.25 mg unsuitable for treating infertility
Quinagolide 50 ug non-ergotamine untested in pregnancy

(**Pergolide** 5.0 mg old drug bromocriptine-like vomitus, headache)
Surgical
microadenomas - removed selectively by trans-sphenoidal surgery
cure rate about 80%
External irradiation to prevent regrowth of tumour residuum

B.1.b **Acromegaly**

caused by Growth hormone (GH) secretion from a pituitary tumour, usually a macroadenoma
GH hypersecretion
- before epiphyseal fusion – gigantism
after fusion in adult life – acromegaly

Clinical features of acromegaly:
Soft tissue changes
* Skin thickening
* Increased sweating
* Headache
* Enlargement of lips, nose, tongue
* Acromegalic arthropathy
* Myopathy
* Carpal tunnel syndrome
* Visceromegaly (e.g. thyroid, heart, liver)

Acral enlargement
* Large hands (difficult to remove rings)
* Large feet (increasing shoe size)

Other bone changes
* Growth of lower jaw – prognathism
* Skull growth – prominent supraorbital ridges with large sinuses
* Kyphosis
* Osteoarthritis

Metabolic effects
* Glucose intolerance (25%)
* Diabetes mellitus (10%)
* Hypertension (25% associated with increased body sodium)

Long-term complications
* Atheromatous diseases (two-to threefold relative risk)
* Colonic cancer (two- to threefold relative risk)

Investigations
Measuring GH levels in plasma is needed
Measuring GH levels during an oral GT test.
(Interpretation)
In normal subjects
GH level is suppressed to below 2 mU/l.
In acromegaly
GH level is not supressed, in about 50% of patients
paradoxal rise of GH level
Hyperglycaemia, glucose intolerance,
IGF-1(somatomedin C)↑, PRL↑ 30% of patients - increased PRL

X-ray of skeleton and skull - sella turcica,
MRI, CT examination of the pituitary fossa should be performed
Ophthalmological examination
– Visual field: Diplopia, strabism: pressure on the 3rd, 4th or 6th cranial nerves.
– Visual field defect: bitemporal hemianopia and upper quadrantanopia– compression in optic chiasm and optic nerve
X-ray of chest: heart hypertrophy
Additional tests: screening for colonic neoplasm with colonoscopy

Management - Therapeutic modalities
Surgical
Trans-sphenoidal surgery – 1st line of treatment
Radiotherapy
External radiotherapy – second-line of treatment, if acromegaly persists after surgery (to stop tumour growth)
Medical
In patients with persisting acromegaly after surgery to lower GH levels < 5 mU/l
Somatostatin analogues (e.g. Octreotide Lanreotide i.m. every few weeks)
Dopamine agonists less potent, helpful in patients with associated hyper PRL
Bromocryptine - Parlodel
GH receptor antagonists (e.g. Pegvisomant)

B.1.c **Central Cushing´s syndrome**
(Cushing´s disease, Morbus Cushing)

CRH↑ → ACTH↑ → cortisol↑ in adreno-cortex
Central hypercortisolism
See Lecture: Adrenal cortex diseases
Cushing´s syndrome

B.1.d **Rare tumours of TSH-, LH-, and FSH-omas**
Excess of TSH secretion – central hyperthyrodims

B.2 Pituitary hormone deficiency syndromes

– Anterior pituitary hypopituitarism
describes combined deficiency of any of the anterior pituitary hormones
clinical features are highly variable and depends on the underlying lesion.

Growth hormone (GH) deficiency – Hypopituitary nanism - congenital defects of the hypothalamus – short statue. In adults GH secretion – the earliest to be lost. Lethargy, muscle weakness increased fat mass in abdomen.

Gonadotrophin (LH, FSH) deficiency
In male: loss of libido, impotence, gynaecomastia, absence of axillary and pubic hair decreased frequency of shaving
In female: oligomenorrhoea or amenorrhoea, infertility, absence of axillary and pubic hair, the finer and wrinkled skin.

Adrenocorticotrophin (ACTH) deficiency

Cortisol insufficiency – Central Morbus Addisoni = Central Addison´s disease
With lack of stimulation of melanocytes by β-lipotrophic hormone (MSH) – a fragment of the ASTH precursor peptide in the skin – white Morbus Addisoni

Clinical features

Fatigue, weakness, anorexy, hypotension, hypoglycaemia, normal plasma potassium levels (angiotensin II - dependent zona glomerulosa is not lost – normal aldosterone secretion maintains normal plasma K !!)
Adrenocortical insufficiency often precipitated by mild infection.
Untreated severe hypopituitarism results in coma.
See lecture: Diseases of adrenal cortex - Adrenal insufficiency, Addisons´s disease p. 54

Thyreotrophin (TSH) deficiency – secondary hypothyroidism

Clinical features

Apathy, cold intolerance, Absence of frank myxoedema (in contrast to primary hypothyroidism), low pulse rate, hypecholesterolemia, atherosclerosis development, coronary heart disease (CHD) development Low TSH – low thyroid hormones level in blood: ↓T4 ↓T3
See Lecture: Thyroid disease – Hypothyroidism, central and peripheral hypothyroidism p.32

Causes of hypopituitarism

Hypothalamus

Acquire	Craniopharyngioma	Sarcoidosis
	Head injury	TBC, Syphilis
	Surgery	Histiocytosis
	Radiotherapy	Encephalitis
Congenital	GnRH Kallmann´s syndrome	

Pituitary

Structural	Pituitary tumour	secondary tumour
	Surgery	post-partum necrosis
	Radiotherapy	(Sheehan´s syndrome)
	Head injury	autoimmune inflammation
	Local meningioma	haemorrhage (apoplexy)
		Haemochromatosis
Functional	Anorexia nervosa	
	Malnutrition	

Investigations

In acutely unwell patients the priority is to diagnose and treat cortisol deficiency
Plasma cortisol, free cortisol excretion in 24 hours urine.
TSH, fT4 fT3,

Specific dynamic tests

ACTH stimulation test 250 ug ACTH (Synacthen) by i.m. Injection at any time of day
Blood samples: 0 and 30 minutes for plasma cortisol
0 minutes also for ACTH (on ice)
Results: normal plasma cortisol ≥ 550 nmol/l at baseline or at 30 minutes
lower plasma cortisol - adrenocortical insufficiency

GnRH test

TRH test

CT or MRI to identify pituitary / hypothalamic tumours.

Management
The treatment of acutely ill patients in adrenocortical insufficiency:
Medical emergency
Hydrocortisone succinate 100 mg i.v.
Intravenous isotonic saline fluid and 10% dextrose, or 5% glucose
Parenteral hydrocortisone 100 mg i.m. 6-hourly, until gastrointestinal symptoms abate
oral cortisol therapy
Chronic hormone replacement therapies
Cortisol (hydrocortisone) 15 mg and 5 mg at 18,00 hrs
The precise dose adjusted for the individual patients by analysis of free cortisol excretion in 24 hrs urine

Thyroid hormone replacement
Thyroxine 0.1 – 0.15 mg once a daily p.o.
TSH assay is not helpful T4 and T3 assay
Sex hormone replacement
in premenopausal females
Cyclical oestrogen therapy on days 1-21 and progesterone on days 14-21
in post-menopausal females HRT is effective for menopausal symptoms and prevention osteoporotic fractures.
Androgen replacement therapy in men: Testosterone implant 600-800 mg subcutaneously every 3-6 months

The adult patients with hypopituitarism feel better and have objective improvements, if they are given GH replacement. GH improves quality of life.

– Posterior pituitary deficiency syndrome

Diabetes insipidus

Uncommon disease. Diabetes insipidus is characterised by a persistent excretion of excessive quantities of diluted urine and by thirst.
Diabetes insipidus (DI) is divided into:
Cranial diabetes insipidus - deficient production of ADH
Nephrogenic diabetes insipidus – distal nephrons are unresponsive to ADH (adiuretin)

Clinical features
Polyuria, polydipsia, 5-20 liters or more of urine in 24 hours, with low specific gravity and osmolality

Causes of diabetes insipidus (DI)
- Cranial
Hypothalamic or high stalk lesion
Craniopharyngioma, head injury, surgery, histiocytosis, sarcoidosis, pituitary tumour with subprasellar extension, basal meningitis, encephalitis
Idiopathic
Genetic defect
DIDMOAD syndrome DI associated with DM, optic atrophy, deafness
- Nephrogenic
Genetic defect
Metabolic abnormality: Hypokalaemia, hypercalcaemia
Drug therapy: lithium, demeclocycline
Poisoning: heavy metals

Investigations
Elevated plasma osmolality i.e. > 300 mOsm/kg
normal 285-295 mOsm/kg
ADH not measurable
Osmolality of urine < 660 mOsm/kg normal more than 800 mOsm/kg

Dynamic tests
Water deprivation test (-3% of the body weight)
Infuse of hypertonic saline (5% saline) measure ADH secretion in response to increasing plasma osmolality.

Differential Diagnosis of primary polydipsia
Plasma is diluted, plasma osmolality < 285 mOsm/kg
Nephrogenic DI – remove drug treatment (lithium), restore electrolyte balance in plasma for K and Ca

Management
Treatment of cranial DI (central DI) with dDAVP (d-deamino-arginine-vassopressine) (Adiuretin AD) Diamino-arginin vasopressin drops 2x2 into the nose. Analogue of ADH with a longer half-life. Measuring of plasma sodium concentration and plasma osmolality
Nephrogenic DI
Thiazide diuretics (bendroflumethiazide 2.5-5 mg/day, amiloride 5-10 mg/day)
Indometacine 18 mg hourly.

C **Hormone resistance** – Laron syndrome (Laron dwarfism)

Growth hormone resistance – defects in the GH receptor.

D **Non functioning tumours**

Pituitary adenoma
Metastatic tumours
Craniopharyngioma

Pituitary tumours are usually benign adenomas. Primary carcinoma of the pituitary gland is rare, but a metastatic tumour from a primary in the breast, lung, kidney may occur in the hypothalamus and reduce pituitary function. Other tumours – pinealoma, ependynoma or meningioma are associated with damage of pituitary/hypothalamus.

Craniopharyngioma

Benign tumour - develops in cell rests of Rathke´s pouch
Location: within sella turcica and in suprasellar space. Tumour is cystic and calcified
Expansion- pressure effect on adjacent structures - hypopituitarism

Investigation
Computed Tomography (CT), Magnetic Resonance Imaging (MRI)

Management
Surgery involves craniotomy – high risk for hypothalamic damage, tumours often recur – repeated surgery
Hypothalamic obesity, visual failure.
Sex hormone replacement treatment, when necessary

Thyroid disease

Thyroid disease is common in its various types, affecting some 5% of the population, predominantly females.
The thyroid secretes **thyroxine (T4)**
triiodothyronine (T3)
85% of T3 deiodination of T4 in peripheral tissues: liver, muscle, kidney.
T4 is not metabolically active until converted to T3 (T4 prohormone)
T4, T3 circulate in plasma almost entirely (more 99,9%) bound to protein: **TBG thyroxine-binding globulin**
fT3 (fT4) **free hormone** diffuses into tissues and exerts its metabolic action.

Advantage of the free hormone measurement – **not influenced by changes in the concentration of binding protein.**
In pregnancy TBG levels are increased, total T3, T4 may be increased, but thyroid hormone **levels are normal**.

Production of T3 T4 in the thyroid is stimulated by thyrotropin or TSH (thyroid-stimulating hormone)
TSH – glycoprotein released from anterior pituitary in response to the hypothalamic TRH (thyrotrophin-releasing hormone)

Negative feedback: peripheral thyroid hormones / pituitary thyrotropin and hypothalamic TRH
T3 T4 are raised, TSH secretion is suppressed

Hypothyroidism – disease of the thyroid gland
– low T4 T3 levels – combined by high circulating TSH levels.

Hyperthyroidism – disease of the thyroid –
– high T4 T3 levels – TSH secretion is suppressed

Subclinical hyperthyroidism: Normal T4,T3, suppressed TSH

Subclinical hypothyroidism: Normal T4, T3, raised TSH

Major manifestations of thyroid disease
Hyperthyroidism
Hypothyroidism
Goitre

Patients: Middle aged female, some 5% of the population suffers from this type of disease.

Hyperthyroidism

over 90% of patients have hyperthyroidism due to

1) Toxic diffuse goitre (Graves´ disease = Basedow´s disease)
2) Toxic multinodular goitre
3) Toxic adenoma – autonomously functioning thyroid nodule
4) Excess pituitary secretion of TSH (tumour)
5) Intrinsic thyroid-stimulating activity of hCG (human chorionic gonadotropin in hydatidiform mole or in choriocarcinoma)
6) Struma ovarii - ovarian teratoma with thyroid tissue
7) Metastatic differentiated carcinoma of the thyroid are very rare
8) Drug induced hyperthyroidism:
   iodide-induced, amiodarone,
   factitious hyperthyroidism,
   iodine prophylaxis programme.

Clinical features of hyperthyroidism

Goitre
*Diffuse
*Nodular
Gastrointestinal
*Weight loss (despite normal or increased appetite)
*Diarrhoea and steatorrhoea
*(Anorexia and Vomiting)
Hepatic dysfunction
*Hyperbilirubinemia, (slightly raised)
*AST, ALT, GMT, ALP (slightly raised) (from bone and liver)
Cardiorespiratory
*Palpitations, sinus tachycardia atrial fibrillation
*Increased pulse pressure
*Ankle oedema in absence of cardiac failure
*Angina pectoris, cardiomyopathy and cardiac failure
*Dyspnoea on exertion
*Exacerbation of asthma
Neuromuscular
*Nervousness, irritability, emotional lability, psychosis
*Tremor
*Achilles tendon hyper-reflexia
*Muscle weakness, proximal myopathy, bulbar myopathy
*Periodic paralysis (predominantly Chinese)
Dermatological
*Increased sweating, moist hands,
*Palmar erythema, spider naevi
*Onycholysis
*Alopecia
*Pigmentation, vitiligo
*Digital clubbing
*Pretibial myxoedema

Reproductive

*Amennorrhoea/oligomenorrhoea
*Infertility, spontaneous abortion
*Loss of libido, impotence

Ocular

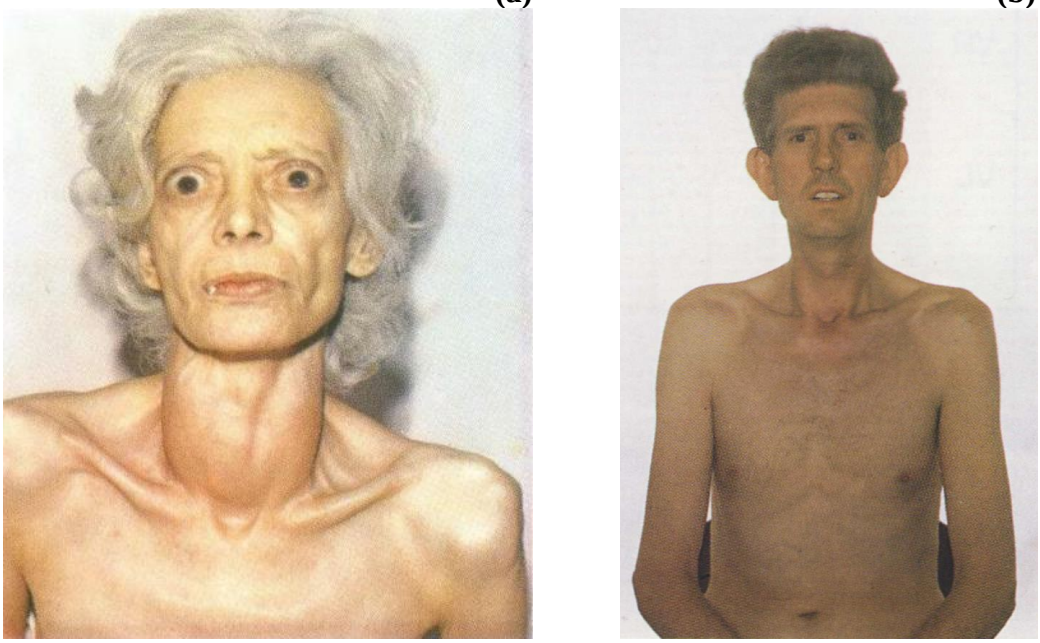
*Lid retraction, lid lag
*Grittiness, excessive lacrimation
*Chemosis
*Exophthalmos, corneal ulceration
*Ophthalmoplegia, diplopia
*papilloedema, loss of visual acuity

Other

*Heat intolerance
*Fatigue, apathy
*Gynaecomastia
*Lymphadenopathy
*Osteoporosis
*Thirst

Figures 4 (a-b)

(a) **(b)**



"Weight loss may be apparent on inspection of the face (**a**) or trunk; muscle wasting may accompany a proximal myopathy (**b**). Splenomegaly and lymphadenopathy are seen in a few patients with long-standing disease. Ankle oedema is common even in the absence of heart failure."

Source: HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Investigations

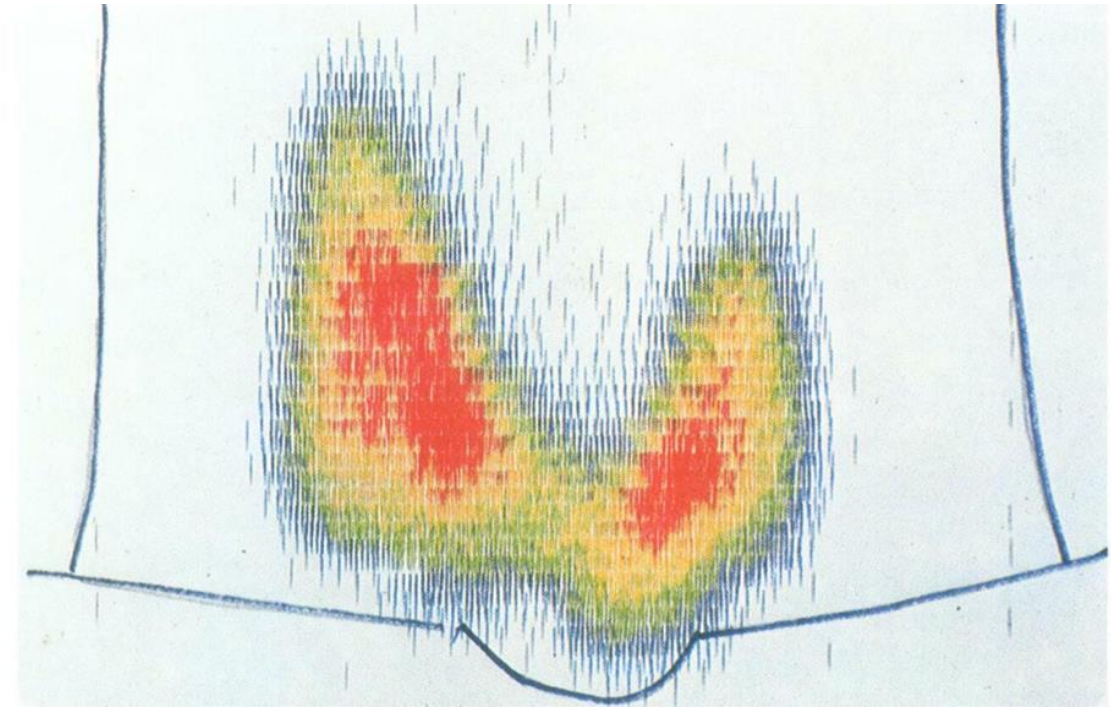
Serum T3 T4 levels are elevated, T4 is in the upper part of normal range,
when T3 is increased = T3-thyrotoxicosis
TSH less than 0,1 mU/l (Normal range: 0,35 – 4,2)

TSH receptor antibodies (TRAb, aTSH, TRAK) elevated in Graves´diease
aTPO antibodies against thyroid peroxidase ↑,
aTG antibodies against thyreoglobulin ↑
Ultrasonund (ultrasonography) of thyroid enlargement

Radioactive iodine uptake test (Accumulation test) with 131 I,
Isotope scanning of thyroid by 131 I, or 99Tc
Liver function tests
Bilirubin, AST ALT GMT, ALP, LDH, CHE (elevated)

Serum T3 T4 normal, TSH suppressed = Subclinical hyperthyroidism
Patients are at increased risk of atrial fibrillation, osteoporosis
Annual control of TSH T3 T4, antibodies, ECG,
alternative: 131 I therapy of thyroid

Figure 5: Goitre



„Enlargement oft he thyroid gland is present in at least 90 per cent of hyperthyroid patients. In men the goitre may be less apparent, often being small, firm and close to the trachea. It is typical fort he goitre tob e diffusely enlarged and vascular. The figure 5 shows a typical scan oft he diffuse goitre of Graves‘ disease.“

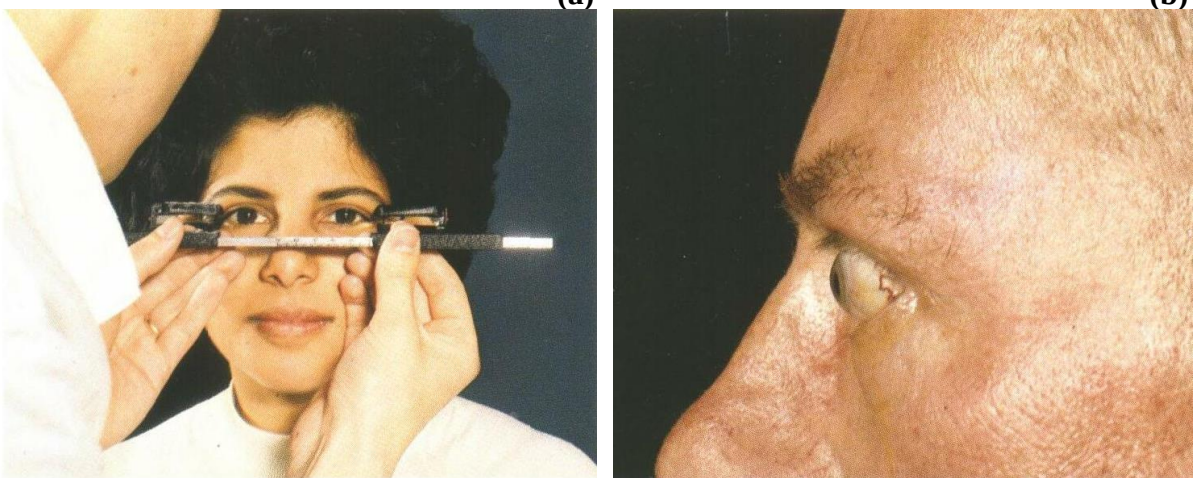
Source: HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Graves´ Basedow disease

is distinguished clinically from other forms of hyperthyroidism.
* Diffuse thyroid enlargement
* Ophthalmopathy
* Tachycardia
(rarely pretibial myxoedema)
It can occur at any age, but…. 30-50 year-old age group (most frequent)

Figures 6 (a-b)

(a) **(b)**

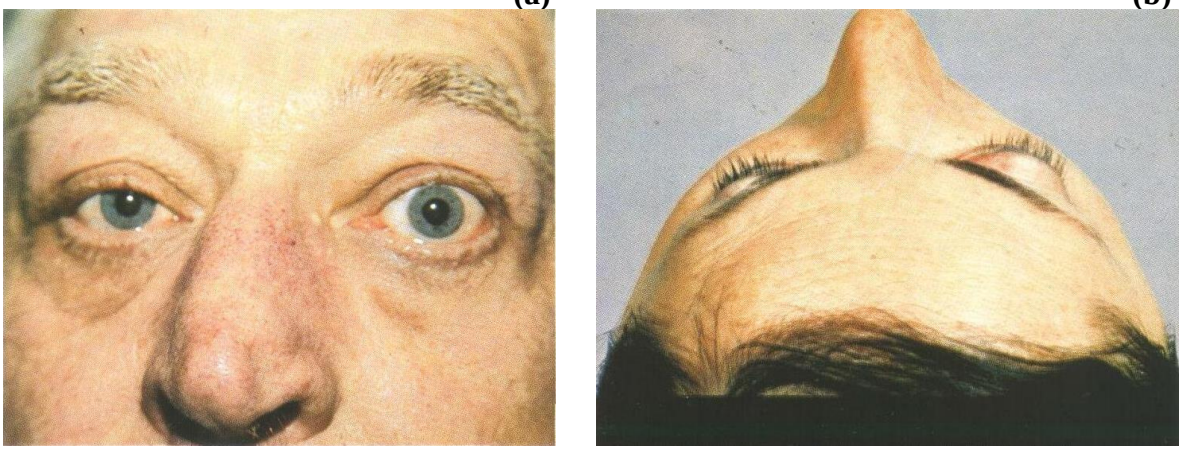


„The exophthalmos can be measured using a Hertel exophthalmometer (**a**). When the distance from the lateral orbital margin to the anterior point of the cornea exceeds 18 mm, exophthalmos is present (**b**)."

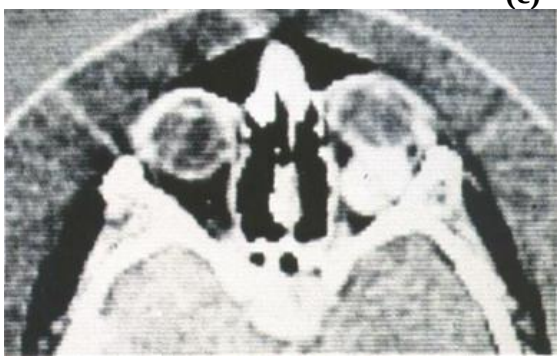
Source (Figures no. 6-10): HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Figures 7 (a-c)

(a) **(b)**



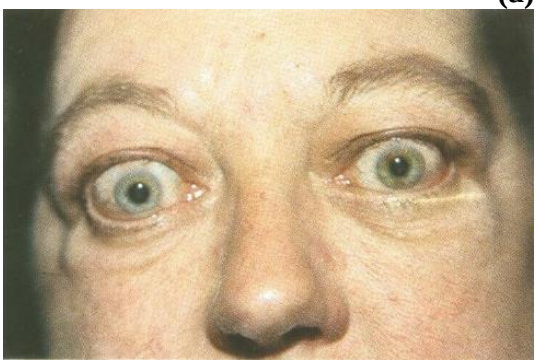
(c)

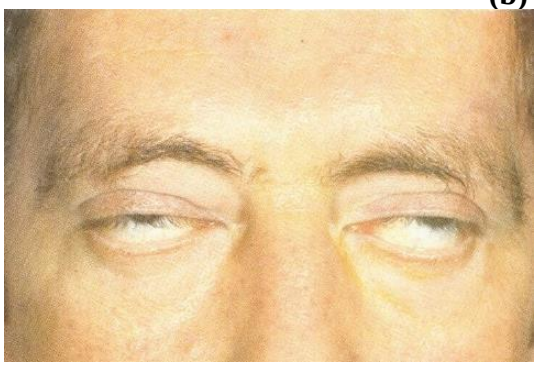


„Exophthalmos is usually bilateral in hyperthyroid Graves' disease, but is often unilateral in the ophthalmic form of Graves' disease in which the patient is not clinically hyperthyroid (**a**). The asymmetry of the exophthalmos in Graves' disease rarely exceeds 5 mm; asymmetry greater than this should raise the suspicion of an orbital tumour. The figure (**b**) shows proptosis caused by an orbital tumour and subsequent demonstration of the tumour by computerised axial tomography (CAT) (**c**).“

Figures 8 (a-b)

(a) **(b)**

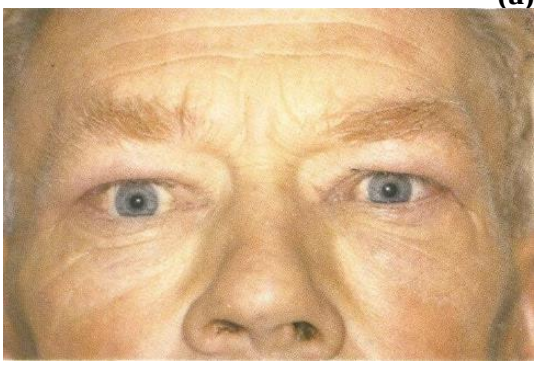


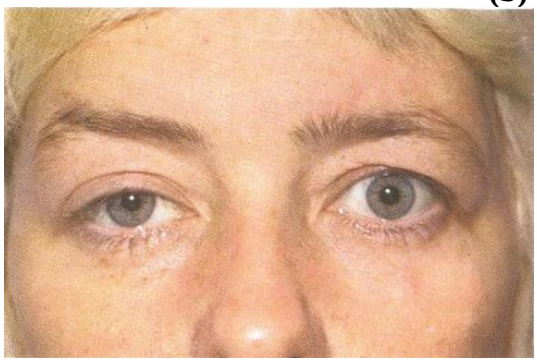


„*Lid retraction* This is a common eye sign in Graves' disease and may be identified by the appearance of sclera between the lower margin of the upper lid and the cornea in the relaxed position of forward gaze (**a**). When lid retraction is severe lid closure may be incomplete (**b**) particularly at night, and can lead to exposure keratitis.“

Figures 9 (a-b)

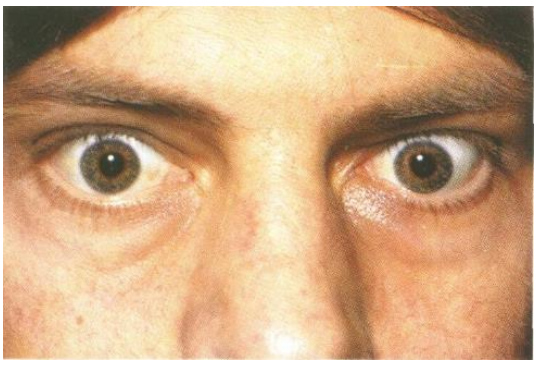
(a) **(b)**





„Swelling an overhanging of the upper lid may obscure the lid retraction (**a**). Unilateral lid retraction is common in the ophthalmic form of Graves' disease (**b**).”

Figure 10



„Lid retraction must be differentiated from the elevation of the upper lids observed in the anxious patient who stares. Unilateral or bilateral lid retraction is occasionally seen in patients with vascular, neoplastic or other lesions of the upper brain stem (the figure 10 shows bilateral lid retraction in a patient with a vascular lesion of the brain stem), when other features of Graves' disease absent."

Pathogenesis

* Graves´ Basedow disease - immunologically mediated form of hyperthyroidism results from the production of IgG-antibodies directed against the TSH-receptor on the membrane of thyroid folicullar cells.
* ↑ thyroid hormone production (T4 T3), the consequence is → goitre formation
* TSH receptor antibodies (TRAb = aTSHR = TRAK) elevated in the serum of most patients with Graves´ disease, association of Graves´ disease with HLA-B8 DR3 and DR2
* The trigger for the development of hyperthyroidism in genetically susceptible individuals is an infection with viruses or bacteria.
* Yersinia enterocolitica, Escherichia coli possess cell membrane TSH-receptors.
* Production of antibodies to the microbial antigens – cross reaction with the TSH-receptor on the host thyroid follicular cell – results in the development of hyperthyroidism.
* Stress: temporal relationship between the onset of hyperthyroidism and a major live event: death of a close relative.
* Regions of iodine deficiency: Iodine supplementation – development of hyperthyroidism in persons with pre-existing subclinical Graves´disease.

Pathogenesis of ophthalmopathy and dermopathy

Both ophthalmopathy and dermopathy are immunological mediated.

* Autoantigens – local accumulation of lymphocytes within the orbit and the dermis – cytokine-mediated proliferation of fibroblasts – secretion of hydrophilic glycosaminoglycans – increased interstitial fluid content, chronic inflammatory cell infiltration – swelling of extraocular muscles – rise in retrobulbar pressure – displace of eye bulb forwards - - - proptosis and exopthalmos; severe cases – optic nerve compression.
* Ultimately comes to fibrosis of the extraocular muscles.
* Smoking – development of ophthalmopathy.

Pathogenesis of ophthalmopathy and dermopathy

Dermopathy: dermis accumulation of lymphocytes – proliferation of fibroblasts – glycosaminoglycans, fluid retention, swelling, fibrosis development in the dermis.

Clinical features of Graves´disease

* Goitre - diffusely enlarged gland 2-3 times the normal volume (young men).
* Increased blood flow manifest by a thrill or bruit
* Elderly patient: no thyroid enlargement is palpable, or the gland may be nodular.
* Ophthalmopathy - Is only present in 50% of patients, may develop after successful

treatment of hyperthyroidism of Graves´disease, or precede its development by many years (exophthalmic Grave´disease). Cigarette smokers !
* Proptosis - lid retraction - excessive lacrimation – conjunctivitis - corneal ulceration, the loss of visual acuity or visual field from corneal oedema or optic nerve compression.
* Extraocular muscles swelling and fibrosis – diplopia

* Tachycardia
Heart rate - frequency 100-120 beats/min Hyperthyroidism – toxic cardiomyopathy
* Pretibial myxedema - infiltrative dermopathy: pink-coloured plaques on the anterior parts of the leg, extending on to the dorsum of the foot (more frequent in primary hypothyroidism).

Management of hyperthyroidism of Graves´disease
A) Antithyroid drugs
First episode in patients < 40 yrs
Thionamids
Carbimazol:
(1-metyl-2-thio-3-karbetoxyimidazol)
Carbimazol Slovakofarma 5 mg tbl., Carbimazol Henning 5 mg tbl.,
Carbistad Stada Arzneimittel 5 mg tbl.,

Methimazole:
(active metabolite of carbimazole) (1-metyl-2-merkaptoimidazol)
Thiamazol Henning, 5, 20 mg tbl., amp 40 mg
Tapazol Lilly,
Favistan Biochemie, Kundl 20 mg tbl or 1 m inj. form 40 mg

Propylthiouracil: (6-n-propyl-2-thiouracil)
Propycil, Léčivá 50 mg tbl
Thyroid hormone synthesis reduction by inhibiting the iodination of tyrosine on Thyroglobulin
Carbimazole - immunosuppressive action - reduction of TRAb concentration

Disadvantage of the treatment
>50% relapse rate within 2 years of stopping drug.
Leukocytopenia under 3 000 (normal 4 – 10 000 Le)
Agranulocytosis development
! Sore throat patients, fever development within 7-28 days of starting treatment
Prevention:
On 7th 14th day WBCC after starting antithyroid drugs (Carbimazol) treatment
! White blood cell count !

B) Subtotal thyroidectomy

Recurrent hyperthyroidism after Th of antithyroid drugs, large goitres, compressive syndrome-retrosternal extension of the goitre, or
severe hyperthyroidism (T3 >9,0 nmol/l) (normal r. 3,4 – 6,5 nmol/l)

Patients must be rendered euthyroid before surgery !!!!

Antithyroid drug is stopped 2 weeks before surgery, replaced by potassium iodide 60 mg 8-hourly orally
or Lugols´solution 20 drops 8-hourly orally – inhibition of thyroid hormone release and reduction of the vascularity of the gland.

Disadvantages/complications: Transcient hypocalcaemia 10%
Hypoparathyroidism 1%
Recurrent laryngeal nerve palsy 1%
(paresis n. recurrentis)

1 year after surgery: 80% of patients euthyroid
15% permanently hypothyroid
5% remain thyrotoxic

C) Radioactive iodine
Patients >40 yrs, recurrence following surgery of hyperthyroidism, elderly patients, other serious comorbidity CHD
Destruction of functioning thyroid cells, inhibition of their ability to replicate.
185-370 MBq (5 – 10 mCi) of 131 I is given orally-
effect in 75% of patients within 4-12 weeks.
During this lag period symptoms can be controlled by beta- blockers, by carbimazole (in more severe cases) 48 hrs after radio-iodine administration.

Disadvantage: hypothyroidism approx. 40% in first year, 80% in 15 years

D) Beta-blockers (symptomatic treatment)
A non selective beta-blockers: propranolol 160 mg daily alleviates symptoms of hyperthyroidism (tachycardia) within 24-48 hrs: useful in the short time treatment

Management of ophthalmopathy
Lid retraction resolves when patient becomes euthyroid – 1 year. Symptomatic treatment of ophthalmopathy methylcellulose eye drops, artefitial tears, tinted glases, side schields protection against sunshine and wind.
* Papilloedema, or loss of visual acuity, field defects require urgent treatment
* Prednisolone 60 mg daily, if effect is not evident within 7-10 days – then
* Radiotherapy of orbital space & Prednisolone treatment, or
* Surgery treatment in Ophthalmology department: Orbital decompression

Management of dermopathy
Triamcinolone local injections, betamethasone ointment - local application

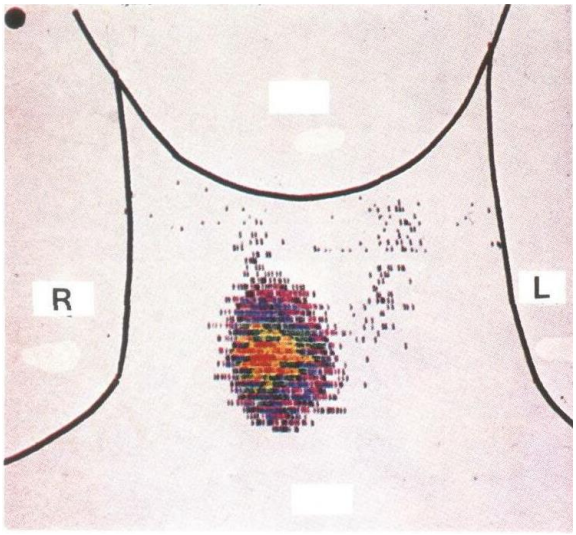
Toxic adenoma

Toxic solitary nodule is the cause of less than 5% of all cases of hyperthyroidism
Mild hyperthyroidism in predominantly female patients over 40 years of age.

Pathogenesis of toxic adenoma
Clons of active thyroid cells with higher function activity & specific growth factor & iodine deficiency.
Consequence:
Follicular adenoma which autonomously secretes excess of thyroid hormones. In this way

toxic adenoma inhibits endogenous TSH secretion with subsequently atrophy of the rest of the thyroid.

Figure 11: Toxic adenoma



„Autonomous function of one or more thyroid adenomas may cause hyperthyroidism, or the excess of thyroid hormones may only be sufficient to suppress pituitary TSH secretion and reduce the function of the rest of the thyroid without causing clinical evidence of hyperthyroidism (subclinical toxic adenoma)."

"The appearance of the thyroid scan is characteristic (11); uptake over the nodule is not suppressed by triiodothyronine administration, but uptake of the rest of the gland can be enhanced by thyroid-stimulating hormone. Such hot nodules are very rarely malignant."

Source: HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Invesitgation
Palpable nodul on thyroid
T4 increased or T4 normal accompanied with increased T3 in 50% of patients i.e.
T3-thyrotoxicosis
TSH suppressed
Diagnosis can be made in certainty only by isotope scanning of the gland
^{131} I, or ^{99}m Tc

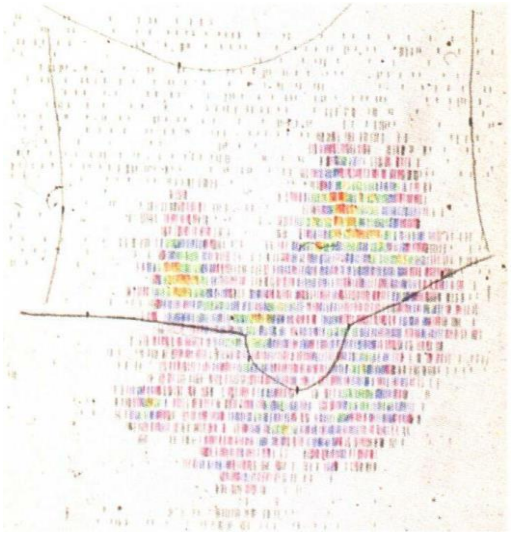
Management of toxic adenoma
A) Hemi-thyroidectomy,
B) Ablation by radio-iodine ^{131}I: (555-1110 MBq 15-30mCi)
! Permanent hypothyroidism does not occur after treatment with radioactive iodine, (the atrophic thyroid cells surrounding the nodule receive little or no irradiation).
C) Application of absolute spirit – alcohol – intranodular 1-2,5 ml every week several times

Toxic multinodular goitre

Relation to toxic solitary adenoma, manifestation in higher age
The mean age of patients is 60 years, more common in women
T4 T3 are slightly elevated TSH suppressed
Isotope scanning of the gland 131 I, or 99m Tc (99m Technetium scan)
Mild hyperthyroidism, older persons - predominance of cardiovascular features: atrial fibrillation, cardiac failure

Management of the disease
large dose of ^{131}I, 555 - 1850 Bq, 15 - 50 mCi (resistance to radiation)
retrosternal extension of the goitre – partial thyroidectomy is indicated
antithyroid drug is not appropriate

Figure 12: Toxic multinodular goitre



„Toxic multinodular goitre is commoner in areas of iodine deficiency, particularly after the introduction of ionised salt (Jod-Basedow phenomenon). The condition may represent autonomous hyperfunction of a varying number of nodules when the appearance of the thyroid scan is characteristic (12) and eye signs are absent. Alternatively, typical Graves' disease may occur in a patient with a pre-existing nodular goitre."

Source: HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Hyperthyroid crisis

A rare but life-threatening increase in the severity of the clinical features of hyperthyroidism.

Clinical features and signs:
fever, agitation, confusion, tachycardia or atrial tachyfibrillation,
older patient - cardiac failure
Medical emergency – mortality rate: 10 %, despite early recognition and treatment.
Intensive care unit!!!
Pathogenesis of hyperthyroid crisis (thyrotoxic crisis)

* Infection in a patient with unrecognised inadequately treated hyperthyroidism
* after subtotal thyroidectomy in an ill-prepared patient
* surgery of thyrotoxic patient
* after 131 I therapy - acute irradiation damage - transient rise of thyroid hormone levels in serum

Management of crisis
Intensive care unit!!!
Rehydratation,
broad spectrum antibiotic
beta-blockers (propranolol) 80 mg 6-hourly orally (p.os application)
or 1-5 mg 6-hourly intravenously
(parenteral application)

antithyroid drugs: Carbimazol 40-60 mg daily orally
(inhibition of hormone systhesis)
sodium iopodate 500 mg per day orally (restoration of T3 levels to normal in 48-72 hours)
(radiographic contrast medium – inhibits the release of thyroid hormones
- reduces the conversion of T4 to T3)

Alternative treatment
The Lugols´solution (KJ +J) 1 ml 6-hourly orally
or potassium iodide (KJ) 3 drops of conc. solution 6-hourly orally
or potassium iodide in i.v. infusion
0,5-1,0 g KJ 5% glucose + isotonic sol 0,9% NaCl
max. dosis: 500-1000 mg KJ per day
Glucocorticoids: Hydrocortisone solubile 100 mg inj. 300 mg bolus i.v.
afterwards 100 mg 8-hourly i.v.
(glucorticoids reduce the conversion of T4 to T3)

Sodium iopodate and beta-blockers can be withdrawn after 10-14 days, patient maintained on carbimazol.
White blood cell count is necessary !

Hypothyroidism

* Primary hypothyroidism
reduced synthesis and secretion of thyroid hormones in thyroid gland with following consequence:
(Increased secretion of hypothalamic TRH)
Increased production of pituitary TSH.

Increased TSH – 1st symptom of starting hypothyroidism:
subclinical hypothyroidism
characterized by normal level of peripheral thyroid hormones (T4,T3)
increased level of TSH.

Primary hypothyroidism is pathological process existing in the thyroid gland.
Manifestation of this disease increases with age:
Developed form → clinical manifestation of disease ←
terminal state of autoimmune disorder – chronic diffuse lymphoid thyroiditis

The prevalence of primary hypothyroidism	1:100
Inclusive subclinical hypothyroidism	5:100
The female / male ratio approx.	6:1

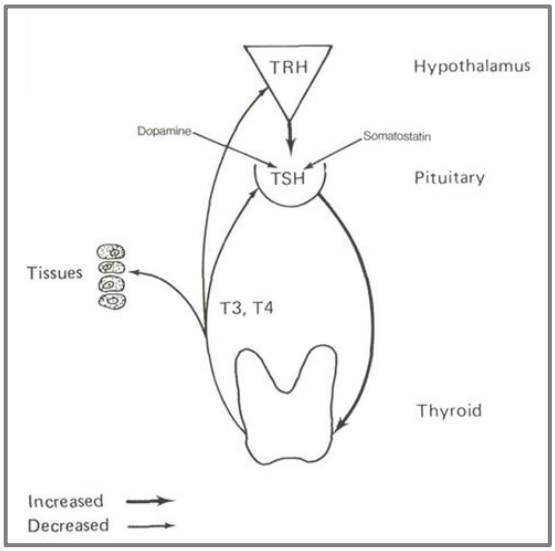
Hypothyroidism

"Hypothyroidism is the clinical condition which results from decreased circulating levels of thyroid hormones. It may be classified as primary when resulting from diseases of the thyroid, secondary when hypothalamic or pituitary disease is responsible, and peripheral when, very rarely, it results from a decreased tissue responsiveness to thyroid hormones.

Primary hypothyroidism may be caused by the following:

Athyreosis or hypoplasia,
Ectopic thyroid,
Endemic cretinism,
Endemic iodine deficiency,
Dyshormonogenesis,
Drug administration,
Autoimmune thyroid disease,
Post-destructive therapy for hyperthyroidism or carcinoma."

Figure 13: Pituitary thyroid relationships in primary hypothyroidism



"The pituitary thyroid relationships in primary hypothyroidism are shown (13). Primary hypothyroidism is characterised by lowered circulating levels of thyroid hormones and a aised level of thyroid-stimulating hormone."

Source: HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Classification of primary hypothyroidism

*** (Idiopathic) primary hypothyroidism i.e. Spontaneous atrophic hypothyroidism**
*** Post-ablative hypothyroidism (post 131 I)**
*** Hypothyroidism after thyroidectomy: 90 % of primary hypothyroidism**
*** Drug induced hypothyroidism**
*** Aplasia of thyroid and ectopic thyroid**
*** Congenital hypothyroidism and Iodine deficiency**
*** Dyshormonogenesis**

Clinical features of hypothyroidism

depend on the form, duration and severity of hypothyroidism

General
* Tiredness, somnolence
* Weight gain
* Cold intolerance
* Hoarseness (voice)
* Goitre

Cardiorespiratory
* Bradycardia, angina pectoris, cardiac failure
* Xanthelasma
* Pericardial and pleural effusion

Neuromuscular
* Muscle stiffness (aches and pains)
* Delayed relaxation of tendon reflexes
* Depression, psychosis
* Cerebellar ataxia
* Myotonia
* Carpal tunnel syndrome
* Deafness, Cretinism

Haematological
* Macrocytosis
* Anaemia
  - Iron deficiency
  - Normochromic
  - Pernicious

Dermatological
* Dry skin and hair, alopecia
* Carotenaemia
* Vitiligo
* Myxoedema

Reproductive
* Infertility
* Menstrual cycle disturbances
* Galactorrhoea (↑PRL)
* Impotence

Gastrointestinal
* Constipation
* Ileus

Investigation

T4 T3 low TSH elevated (in excess of 20 mU/l) TRH test
Antibodies: aTPO, aTG, TRAb
Ultrasound examination of thyroid:
thyroid enlargement: diffuse (benign)
nodular: multi nodular goitre (benign)
solitary thyroid nodule (1:20 chance of malignancy)
Isotope scanning of thyroid: 99m Tc (technetium scans)

Liver function test: LDH, CK increased,

Total cholesterol and triglycerides concentration increased
ECG: bradycardia with low voltage complexes ST segment and T wave abnormalities

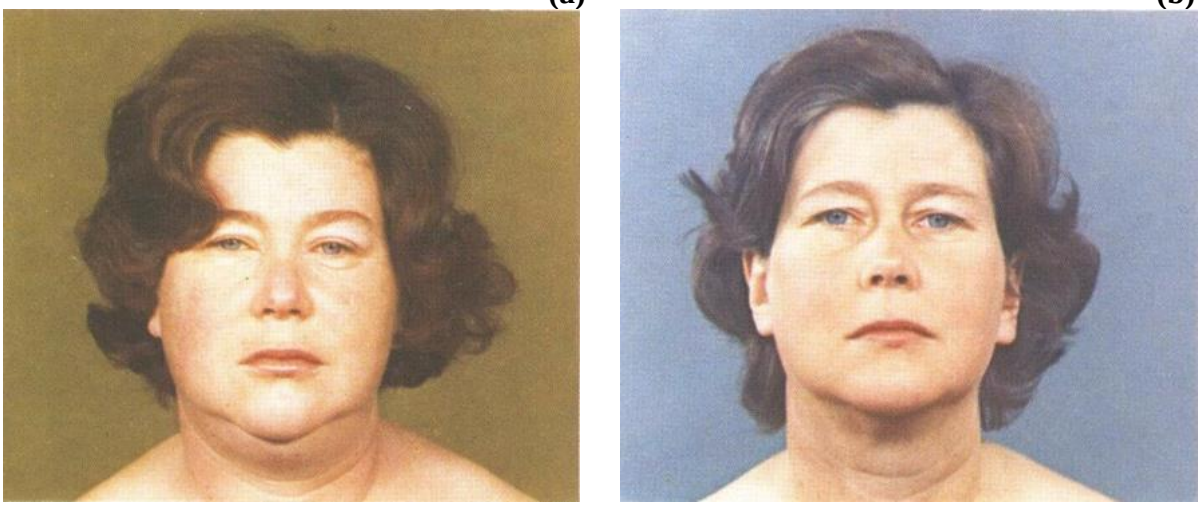
(Idiopathic) primary hypothyroidism or Spontaneous atrophic hypothyroidism
form of primary hypothyroidism
Incidence increases with age, an organ-specific autoimmune disorder.
Patients are at risk of developing other organ-specific autoimmune conditions:
Diabetes mellitus type 1,
Addison´s disease,
Pernicious anaemia in first and second-degree of relatives.

Clinical features of primary hypothyroidism
depend on the form, duration and severity of hypothyroidism
Subclinical hypothyroidism
Patient is asymptomatic or mildly hypothyroid with small diffuse goitre
Antibodies aTPO aTG are increased
T4 T3 normal TSH increased

Clinical hypothyroidism
developed form of primary hypothyroidism
Cold intolerance, bradycardia, tiredness, weight gain, hoarseness of the voice, small rubbery goitre, muscle stiffness, dry skin and hair, constipation, menstrual cycle disturbances, infertility
Haematological examination: anaemia, iron deficiency
Prolonged hypothyroidism:
infiltration of body tissues by mucopolysacharides, hyaluronic acid, chondroitin sulphate (low-pitched voice, hoarseness, poor hearing, slurred speech – large tongue)
Infiltration of the dermis:
non-pitting oedema – myxoedema of the hands, feet, eyelids, peri-orbital puffiness, facial pallor (anaemia, vasoconstriction), lemon-yellow tint of the skin (carotenaemia)

Figures 14 (a-b): The improvement in appearance resulting from therapy

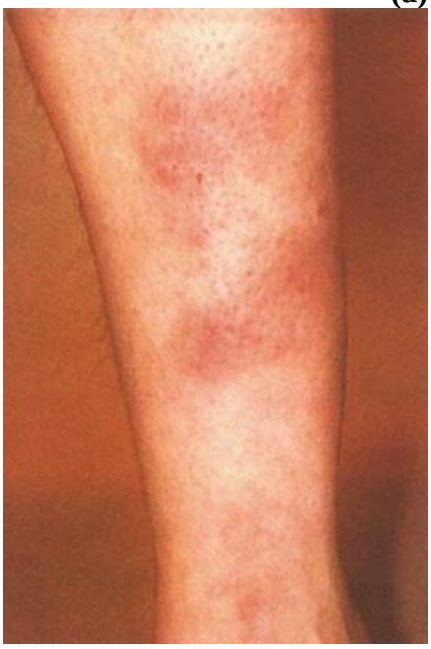
(a) **(b)**



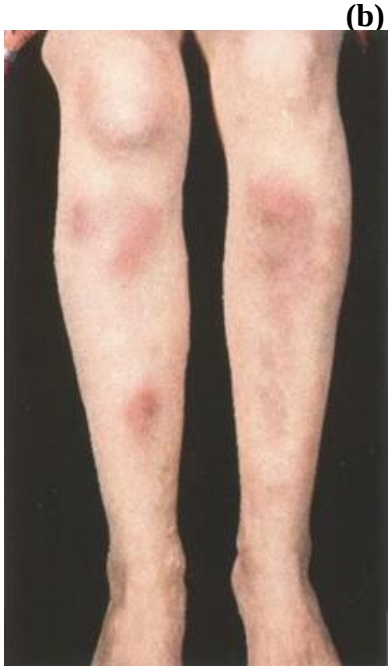
"The improvement in appearance resulting from therapy is well shown in (**a**) and (**b**)."

Figures 15 (a-e)

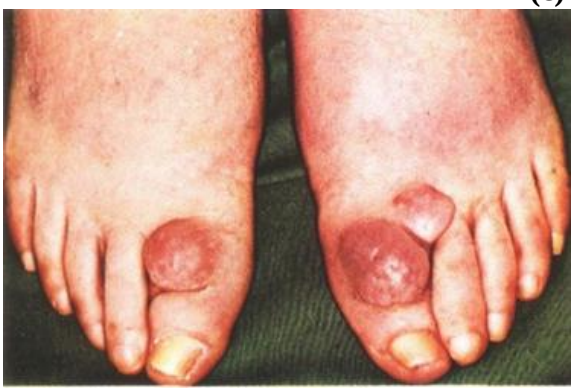
(a)



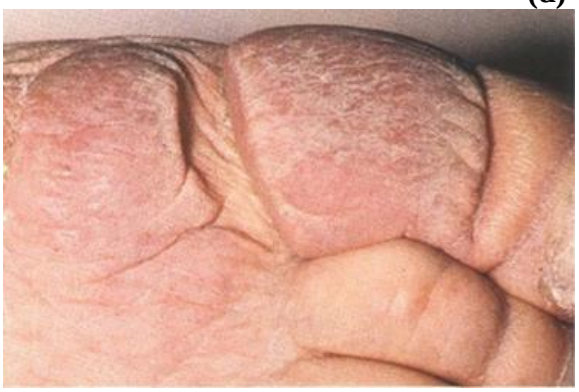
(b)



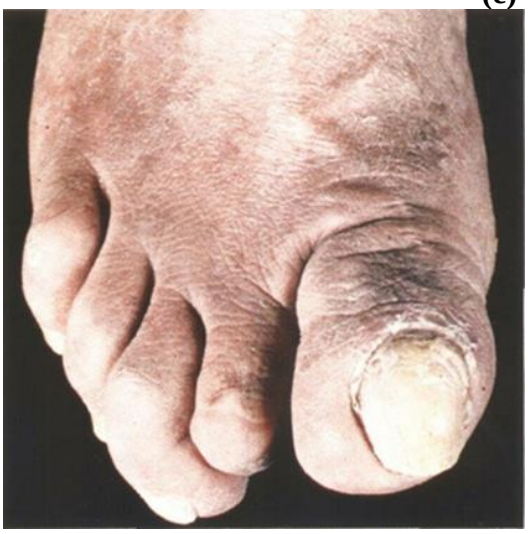
(c)



(d)



(e)



„The nodular form of localised myxoedema (**a**) has a similar appearance to erythema nodosum (**b**), but is non-tender or only slightly so. Although this variety is quite common, it is often overlooked. Spontaneous remission is the rule. Occasional horny nodules develop on the dorsum of the toes especially the big toe (**c**) and (**d**). This must be differentiated from pachyderma periostitis (**e**)."

"The oedematous form of localised myxoedema simulates venous oedema of the legs or ankles, pitting is present, the skin is little thickened yet biopsy reveals typical histological and histochemical features of localised myxoedema."

Source (Figures no. 14-15): HALL, R., EVERED, D., and GREENE, R. A Colour Atlas of Endocrinology. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Investigation
T4 T3 low
TSH elevated (in excess of 20 mU/l) TRH test
Antibodies: aTPO, aTG, TRAb
Ultrasound examination of thyroid:
thyroid enlargement: diffuse (benign)
nodular: multi nodular goitre (benign)
solitary thyroid nodule (1:20 chance of malignancy)
Isotope scanning of thyroid: 99m Tc (technetium scans)
Liver function test: LDH, CK increased,
Total cholesterol and triglyceride concentration increased
ECG: bradycardia with low voltage complexes ST segment and T wave abnormalities
Management
Supplementation with T4 50…100…150 μg daily
Monitoring therapy !
Correct dose of T4 restores serum TSH to the lower part of the reference range (0,35 – 4,2) i.e. 2,0 – 2,5 mU/l
Sense of well being
Ischemic heart disease patients: 5% patients with long-standing hypothyroidism complain of angina, approx 40% of patients with angina cannot tolerate full replacement therapy,
despite the use of beta-blockers and vasodilators.
Recommendation: coronary artery surgery and balloon angioplasty – full replacement dosage of thyroxin.

* **Secondary hypothyroidism (Central hypothyroidism)**
Failure of TRH or/and TSH secretion during a pathologial process in hypothalamus (hypothalamic hypothyroidism) and/or in hypophysis (pituitary hypothyroidism) (tumours of hypothalamus, pituitary macroadenoma, hypophysectomy, panhypo-pituitarism)
TSH low T4 T3 low TRH test low answer

Myxoedema coma

A rare presentation of developed severe hypothyroidism
Depressed level of consciousness
elderly patients myxedematous types
Body temperature as low as 25° Celsius.
Mortality rate is 50%
survival chance depends upon early recognition and treatment of hypothyroidism.
Factors contributing to the altered consciousness level drugs phenothiazine,
heart conditions: cardiac failure,
infection- pneumonia, dilution
hyponatremia,
hypoxemia and hypercapnia due to hypoventilation.
Medical emergency ! ! Intensive care unit !

Management o myxedema coma
Treatment must begin before biochemical confirmation of the diagnosis.

Hydrocortisone sodium succinate 100 mg i.m. 8-hourly
or Hydrocortisone solubile 100 mg i.v. bolus of 200 mg
Triiodothyronine intravenous bolus 20 μg followed by 20 μg 8-hourly until there is a sustained clinical improvement.
Raise in body temperature within 24 hours
After 24-72 hours oral thyroxine substitution in a dose of 50 μg per day i.v. fluids, isotonic solution & Glucose 5%
broad spectrum antibiotics (TTC), high flow-oxygen.

Simple goitre

Diffuse, or multinodular enlargement of thyroid, occurs sporadically, unknown ethiology.? Suboptimal iodine intake, minor degree of dyshormonogenesis, epidermal growth factor, immunoglobulins may play a role.
Patient female, euthyroid familial history of goitre.

– **Simple diffuse goitre**
Goitre is soft and symmetrical, thyroid is enlarged to 2 or 3 times, tight sensation in the neck when swallowing
T4, T3, TSH normal, no thyroid antibodies.
No treatment is necessary, sometimes the thyroid enlarge persists → simple multinodular goitre.

– **Simple multinodular goitre**
is nodular or lobulated on palpation, may extend retrosternally
Large goitres may cause mediastinal compression, stridor, dysphagia, obstruction of the superior vena cava.
Hoarseness due to recurrent laryngeal nerve palsy (suggestive of thyroid carcinoma)

Investigation
T4, T3, TSH normal, or T4, T3 normal, TSH undetectable (subclinical hyperthyroidism)
CT exam: Tracheal displacement & compression, retrosternal extension, intrathyroid calcification → Compressive syndrome development.

Management
Small goitre – no treatment necessary, annual review
Partial thyreoidectomy in case of mediastinal compression
cosmetical reason
T4 treatment is not indicated, suspection of hyperthyroidism

Thyroiditis

Acute thyroiditis (Bacterial thyreoiditis)

A bacterial induced inflammation of the thyroid (Staphylococcus, streptococcus, pneumococcus, E.colli, mycotic infection
Patient female : male ratio 3:1

Pathogenesis
upper respiratory tract infections (acute laryngitis, acute pharyngitis)
a rare disease complication of thyroid biopsy

Clinical features
Spontaneous pain in the region of the thyroid with radiation to the jaw, ears, painful by swallowing, coughing, movement of the neck, swelling of the gland, mildly enlarged painful at the palpation

Investigation
Red and white blood cells count, leukocytosis
T4 T3 TSH normal antibodies aTPO aTG normal
Erythrocyte sedimentation rate: mildly increased
Ultrasound of thyroid
Fine needle aspiration of thyroid: neutrophiles, microbial infiltration of the gland – material for microbiological examination

Management
Broad spectrum antibiotics (TTC), abscess - surgical intervention drainage of thyroid

Subacute thyroiditis (de Quervain´s thyroiditis)

A virus-induced inflamation of the thyroid gland (coxackie, adenovirus, mumps)
Result: release of colloid into the blood. Hyperhormonosis - hyperthyroidism
Affected patients: females aged 20-40 years.

Clinical features
Pain in the region of the thyroid with radiation to the jaw, ears,
painful by swallowing, coughing, movement of the neck
enlarged thyroid, painful at palpation

Investigation
T3 T4 levels are raised (for 4-6 weeks)
TSH endogenous secretion suppressed - Period of hyperthyroidism
Erythrocyte sedimentation rate is high 30/90
Period of hypothyroidism is asymptomatic
Full recovery of thyroid function within 4-6 months

Management of thyroiditis
in acute phasis:
salicylates, non-steroidal, anti-inflammatory drugs:
Aspirin 500-1000 mg 6-hourly
Corticoids: Prednisolon 40 mg daily for 3-4 weeks
afterwards
daily dose of Prednison must be slowly reduced
β-blockers: Propranolol 60 mg or Concor 5mg daily.
!Antithyroid drugs (Carbimazol, Propycil)
are of no benefit !
Long time T4 supplementation in hypothyroidism

Chronic lymphoid thyroiditis – Hashimoto´s thyroiditis

The most common cause of hypothyroidism, 2-4% in population
Affected patients: 20-40 year aged female
Female: male ratio 22:1

Pathogenesis of Hashimoto´s thyroiditis
Autoimmune disease
1st hypothesis:
impaired function of suppressor Ly, activation of helper lymphocytes – B Ly- thyroid antibody synthesis.
2nd hypothesis:
presumption of inpaired follicular cell function. HLA-DR anigen expression on the membranes of folicullar cells.- activacion of helper Ly – and B Ly: aTPO and aTG antibody synthesis (aTSH receptor Ab)
Clinical features
Small diffuse painless goitre, firm or rubbery in consistency, without symptoms, later discomfort in neck area at swallow.
Developed disease typical signs of hypothyroidism (cold intolerance, tiredness, weight gain, goitre, bradycardia, dry skin, hoarseness, etc.)

Thyroid status:
25% patients are hypothyroid: T4 T3 lower TSH increased
75% euthyroid, or subclinical hypothyroidism patients are at risk of developing of hypothyroidism in future years.

Investigation
aTPO antithyroid peroxidise antibodies increased
aTG antithyrogloblin antibodies increased.
Fine needle aspiration biopsy of the thyroid
Management
Replacement hormone therapy with thyroxin in the dose: 50 – 100 μg daily.

Riedel´s thyroiditis
exceptionally rare condition of unknown aetiology
Extensive infiltration of the thyroid and surrounding structures with fibrous tissue.

Clinical feature
Small slow – growing, goitre irregular, stony-hard, euthyroid condition
Tracheal compression
Esophageal stricture
Mediastinal and retrosternal fibrosis is associated with R´s thyroiditis
Recurrent laryngeal nerve palsy: surgery intervention
Differential diagnosis against thyroid malignancy (anaplastic carcinoma):
Fine needle aspiration biopsy of the thyroid.
Euthyroid status – primary hypothyroidism, hypoparathyroidism

Management of disease
Replacement T4 therapy and surgery intervention in case of esophageal and tracheal compression

Malignant tumours of thyroid

Primary thyroid malignancy is rare:
less than 1% of all carcinomas, prevalence 25 per 1 million
Thyroid cancer is more common in females. (4 f : 1m)

Classification
Differentiated carcinoma
- Papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma

Non differentiated carcinoma
- Anaplastic carcinoma

Papillary carcinoma

In most patients, presentation is with a palpable solitary nodule.
Papillary c. is the most common of the malignant tumours.

Pathogenesis
Irradiation-induced thyroid cancer in 90% cases irradiation of neck area and thyroid in childhood.
Papillary c. spreads (metastasis) to regional lymph nodes → cervical lymphadenopathy only, without enlargement of thyroid.

Follicular carcinoma

Single encapsulated lesion spreads by blood way metastases in bone, lung, brain.

Investigation
Ultrasound of thyroid, suspect solitary thyroid nodule
Isotope scanning of thyroid 99mTc - cold nodule
Fine needle aspiration biopsy of thyroid.
Histological examination

Management
Total tyreoidectomy, thereafter a large dose of 131 I (3000mBq = 80 mCi) ablation of the remaining thyroid tissue: malignant and normal.

Long term treatment with thyroxin 150-200 μg daily to suppress TSH secretion.
(differentiated thyroid carcinoma may be TSH dependent).
Follow up serum Thyroglobulin (Tg) check, Tg should be low or undetectable
Increase of serum thyroglobulin 15μg/l = suggestive of tumour recurrence, or metastases.
Whole-body scanning with 131 I, conditions:
TSH must be elevated more than 20 mU/l. Stopping thyroxin for 4-6 weeks (development of manifestation form of hypothyroidism, discomfort for patients)

New approach: Recombinant human TSH supplementation increases serum TSH to stimulate radio iodine uptake, thyroxin does not need to be discounted and therefore symptomatic hypothyroidism is avoided.

Prognosis
Very good, excellent prognosis when treated appropriately,
Patients under 50 years of age (papillary Ca) near-normal life expectancy
If the tumour (nodules) less than 2 cm in diameter, confined to the thyroid and cervical nodes, low grade malignancy confirmed histologically.
For patients with distant metastases 10-years survival is approximately 40%.

Anaplastic carcinoma and lymphoma

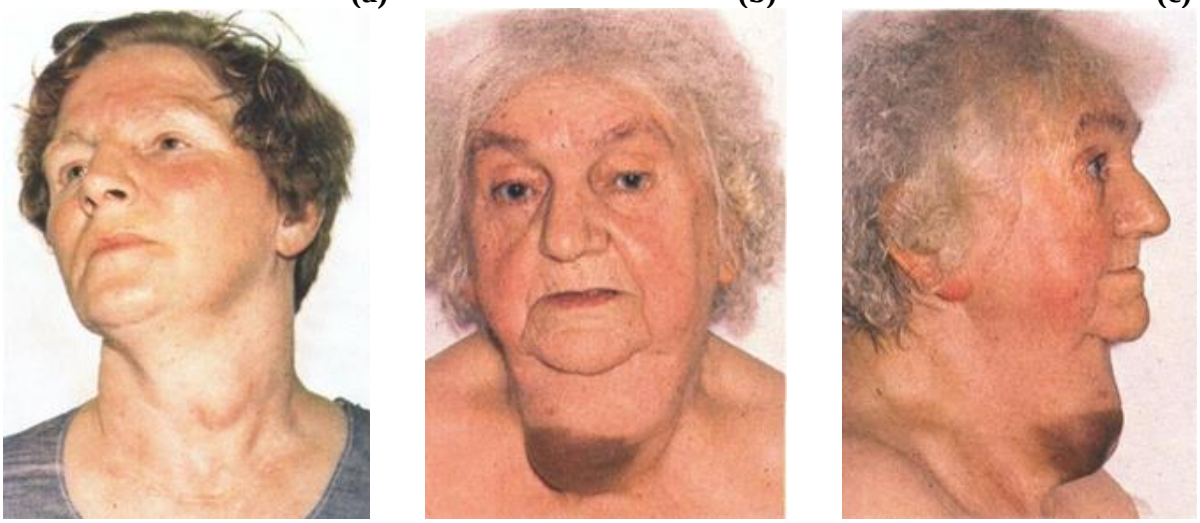
Difficult to distinguish clinically: cytological examination by needle biopsy

Clinical features
Patients: Elderly women rapid thyroid enlargement over 2-3 months, past history of head and neck irradiation
The goitre: hard and painless, asymmetrical, later tracheal compression stridor and hoarseness due to recurrent laryngeal nerve palsy.

Investigation
Euthyroidism, T4, T3, TSH normal, no thyroid antibodies are detected in serum.
Sonography of thyroid: solitary thyroid nodule or multinodular thyroid
Isotope scanning by 99mTc 131I – cold solitary thyroid nodule, cervical lymphadenopathy

Figures 16 (a-c): Thyroid nodules and neoplasm

(a) **(b)** **(c)**



"Thyroid nodules may be benign or malignant. Features which suggest that a goitre is malignant include the following:

Asymmetry,

Unusual location of the swelling (**a**),

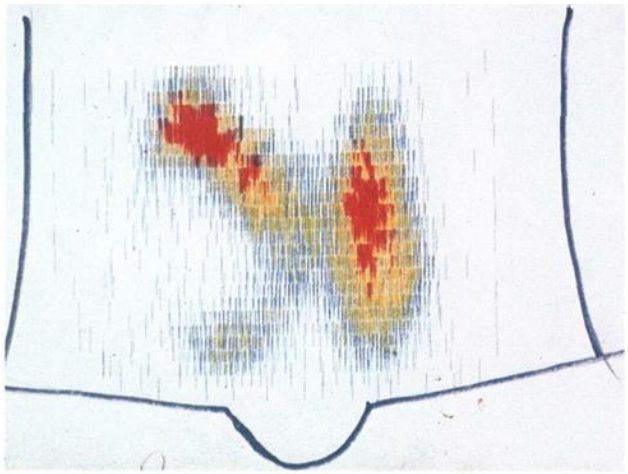
Hardness,

Rapid increase in size with pressure effects, although this can be caused by haemorrhage into the nodule, which can penetrate the thyroid capsule to give the appearance shown in (**b**) and (**c**),

Hoarseness of the voice,

Fixation to the skin and underlying tissues."

Figure 17



"A major diagnostic problem is the solitary thyroid nodule, some 10-20 per cent of which are malignant. Scanning of the nodule (preferably with ^{131}I) may be helpful; functioning thyroid nodules are rarely malignant, whereas cold nodules (the figure 17 shows a scan of a cold nodule of the thyroid) may be malignant or may represent non-functioning adenomas, cysts or areas of thyroiditis."

Source (Figures no. 16-17): HALL, R., EVERED, D., and GREENE, R. *A Colour Atlas of Endocrinology*. 1st ed. London: Wolfe Medical, 1979. 176 p. ISBN 0-7234-0411-9.

Management
There is no effectiveness treatment
Radiotherapy may afford temporary relief of mediastinal compression

Surgery decompression & radiation:
palliative intervention with temporary only effect
External radiation combined with chemotherapy by lymphoma (arises from pre-existing Hashimoto´s thyroiditis)– better prognosis – goitre shrinkage
– result in survival for 5 years or more.

Medullary carcinoma

Tumour arises from the parafollicular C cells of the thyroid
Secretion of calcitonin, (5 OH-tryptamin - carcinoid syndrome), ACTH, peptides of the tachykinin family, prostaglandins), association with Cushing syndrome, carcinoid syndrome, Feochromocytoma

Clinical features
goitre discrete enlarged firm thyroid mass (in middle age), cervical lymphadenopathy, later distant metastases

Investigation
Calcitonin ↑, rare hypocalcaemia, euthyroidism: TSH fT4 fT3 normal
Management of illness
Total thyreoidectomy, exstirpation of affected cervical nodes.
Treatment with 131I without effect. C-cells
Prognosis < 1 – 20 years or more
Medularry carcinoma of the thyroid may be part of the Multiple endeocrine neoplasia type II syndrome

Multiple endocrine neoplasia (MEN) syndromes

MEN I (Werner´s syndrome)	Primary hyperparathyroidism Pituitary tumours (prolactinoma) Pancreatic tumours (e.g. insulinoma, gastrinoma - Zollinger Ellison syndrome)
MEN II (Sipple´s syndrome)	Primary hyperparathyroidism Medullary carcinoma of thyroid Phaeochromocytoma

MEN - multiple endocrine neoplasia
rare autosomal dominant syndrome
Hyperplasia, adenomas → malignant tumours in multiple glands
MEN I: plasma calcium, PTH, prolactin, gastrin
MEN II: plasma calcium, PTH, calcitonin, urinary metanephrines
calcium pentagastrin test with calcitonin measurement
Investigation of relatives
Unaffected relatives will not pass condition to their children.

Parathyroid gland diseases

Introduction
Parathyroid hormone (PTH) is a key controller of calcium metabolism which interacts with vitamin D in kidney and bone.
Altered vitamin D in gut and renal disesaes:
Malabsorption, renal insufficiency (Secondary hyperparathyroidism)
The most common is hyperparathyreoidism resulting in hypercalcaemia, which can be mimicked by release of PTH-like peptides, e.g. in malignancies.
The four parathyroid glands behind the lobes of the thyroid
Parathyroids respond directly to changes in ionised calcium concentrations.
↓ concentration of ionised Ca is a stimulus for PTH release.

PTH directly promotes the reabsorption of Ca from renal tubules and bone.
PTH indirectly effects Ca level by increasing conversion of 25-OH-cholecalciferol to 1,25 diOH cholecalciferol – result -
- increased calcium absorption from food
- enhanced mobilisation of Ca from bone.

PTH stimulates osteolysis -
↑osteoclastic activity – returning Ca from bone to the extracellular fluid.
Investigation of Ca metabolism total Ca in serum
About 50% of Ca is bound to phosphate, citrate, proteins
Total Ca measurements need to be corrected, if the serum albumin is low.
Ca values must be upwards by 0.1 mmol/l for each 6 g/l reduction of albumin.

Diff.diagnosis of disorders of Ca metabolism requires measurement of P, ALP, PTH

Calcitonin (from parafollicular C cells of thyroid) also regulates Ca metabolism but with lower clinical relevance to calcium homeostasis in human

Major manifestations of diseases of the parathyroid glands

Hypercalcaemia and Hypocalcaemia

Causes of Hypercalcaemia
With normal or elevated (i.e. inappropriated) PTH levels
* primary or tertiary hyperparathyroidism
* lithium induced hyperparathyroidism
* familial hypocalciuric hypercalcaemia
With low (i.e. supressed) PTH levels
* malignancy (e.g. lung, breast, renal, ovarian, colonic, thyroid carcinoma
* multiple myeloma
* elevated 1,25 diOH vitamin D3 (e.g. Intoxication, sarcoidosis)
* thyrotoxicosis
* Paget´s disease with immobilisation
* Milk-alkali syndrome
* Thiazide diuretics
* Addison´s disease

Clinical features of hypercalcaemia
Polyuria and polydypsia

Renal colic
Lethargy
Anorexia nausea
Dyspepsia and peptic ulceration
Constipation
Depression
Drowsiness
Impaired cognition
In malignant hypercalcaemia – rapid onset of symptoms and clinical features

Hyperparathyroidism

Type	serum calcium	PTH
Primary Single adenoma (90%) mm-cm Multiple adenomata (4%) Noduar hyperplasia (5%) Carcinoma (1%)	raised	not suppressed
Secondary Chronic renal failure Malabsorption Osteomalacia and rickets	low	raised
Tertiary	raised	not suppressed

Primary hyperparathyroidism

Symptoms: bones, stones, abdominal groans
50% are asymptomatic
5% renal calculi, 15% of recurrent stone formers
Impaired renal, function, acute dehydratation, hypercalcaemia, hypertension
Parathyroid tumours are almost never palpable
A familial history of renal tract stones/neck surgery – MEN
Investigations – dif dg:
Low plasma P, ↑ALP, (or malignancy) PTH →↑, ↑Ca/24 h urine: PHy
High plasma P, ↑ALP, ↑kreatinin, inpairement of renal functions
→ tertiary hyperparathyreoidism
PTH low/normal, low P, high ALP, hyperCa-uria, ↑Ca - malignancy
Chest radiograph, isotope bone scan,
myeloma screen, protein elpho, ESR (erytrocyte sedimentation ratio), Bence Jones protein, β2-microglobulin
↑ACE angiotensin-converting enzyme (sarcoidosis)

Secondary Hyperparatyroidism

Increased PTH secretion to compensate prolonged hypo Ca-emia → Hyperplasia of all parathyroid tissue
Effect – to restore serum Ca at the expense of the stores of Ca in bone
Secondary HyPara – continous stimulation of the parathyroid glands – adenoma transformation and autonomous PTH secretion → **Tertiary hyperparathyroidism.**

Adrenal diseases

The adrenal glands: several separate endocrine glands within one anatomical structure.

Adrenal cortex –

cortisol & *adrenal androgens* (a part of hypothalamic-pituitary-adrenal axis)
aldosterone (under the control of the renin-angiotensin-aldosterone system)

Histologically
Cortex = three zones but these function as two units
zona glomerulosa (aldosterone)
zonae fasciculata/reticularis (cortisol, adrenal androgens)

Subtle alterations in adrenal function may be important in common diseases
Hypertension,
Obesity,
Metabolic syndrome,
Diabetes mellitus Type 2

Glucocorticoids
Cortisol: major glucocorticoid in humans
diurnality in secretion
In the circulation 95% of cortisol is bound to protein Cortisol Binding Protein (CBP)
free fraction is biologically active: glucocorticoid receptors.

Cortisol biological effects

Carbohydrates: ↑ glycogenesis in liver
↑ gluconeogenesis → hyperglycaemia→ steroid diabetes mellitus
Deficiency of glucocorticoids → hypoglycaemia
Lipids: ↑ lipolysis → ↑ free fatty acids,
↓ glycerol synthesis

Proteins: ↑ proteolysis
weakness of proximal thigh muscle

Dermis: Suppressed function of fibroblasts,
poor wound healing, ↑collagen degradation –
striae cruentae, decreased skin thickness

Immune system: reduction of inflammatory response,
immunosuppression
Reduced synthesis of prostaglandins and leukotriens
Reduced effect of histamine, bradykinin,
Lymfocytopenia: T lymphocyte depletion, ↓B lymphocyte, ↓monocytes, eosinophiles, ↑granulocytes

Bone and calcium metabolism:
reduced calcium level (Th hyperparathyroidism)

Reduced calcium absorption from guts →↓ Ca
↑ kidney excretion of calcium and P→ ↓Ca & ↓P
↑ osteoclasts activity → ↑ ostheoporosis
↑ os teolysis

Circulation (heart) and kidney function:
Positive inotropic effect on heart contractility,
multiplication of katecholamines blood pressure effect…↑BP

↑ Na (sodium) reapsorption in kidney, (mineralocorticoid effect)
↓K (hypokalaemia) oedemas develpment
Metabolic alkalosis
Glucocorticoids deficiency: ↓ volume/min – shock, ↓Na
↑K, hyperkalaemic acidosis

CNS:
cortisol can pass through the blood-encephalic barrier
Psychosis, depression: depends on cortisol levels, ↑appetite, euphoria
↓Sex appetite - libido (↓ gonadotrophins secretion = ↓ LH ↓FSH)
Psychotic patients autonomous hyperproduction of cortisol =
Pseudo Cushing´s syndrome
Growth:
inhibition of the body growth, reduced maturation of the skeleton

Endocrine system: reduced TSH secretion
Reduced T4→T3 conversion (↑rT3)
(Treatment of thyrotoxic crisis)
Reduced gonadotrophins secretion
(LH FSH)
↓TBG (thyroxin binding globulin)

<u>Mineralocorticoids:</u>
Aldosterone: the most important sodium-retaining hormone via mineralocorticoid receptors in distal nephron.
Na (sodium) is retained at the expense of increased excretion of K (potassium)

Stimulus for secretion of aldosterone: angiotensin II.
Activation of renin-angiotensin system
Low perfusion pressure in the afferent arteriole of kidney: Renin secretion from the juxtaglomerular apparatus (kidney).
Renin: Conversion of angiotensinogen to angiotensin I angiotensin I →(ACE)→ angiotensin II → cortex:
(zona glomerulosa) – aldosterone release

<u>Adrenal androgens</u>:
Secreted in respose to ACTH:
initiation of puberty,
in adult females: may be important in female libido.

Adrenal medulla – an extension of the sympathetic nervous system: secretes katecholamines.

Katecholamines:
Noradrenaline (NA), adrenaline (A), dopamine
Small amount of Noradrenaline is derived from adrenal medulla (more from nerve endings)
Noradrenaline → (Noradrenaline methyltransferase) → Adrenaline
conversion of Noradrenaline to Adrealine is induced by glucocorticoids.
Glucocorticoids stimulate the activity of enzyme noradrenaline methyltransferase

Diseases of adrenal cortex: – excess secretion of cortisol
– low secretion of cortisol and aldosterone

Cushing´s syndrome
Hypercortisolism: excess secretion of cortisol from adrenal cortex: Zonae fasciculata & reticularis

Classification of Cushing´s syndrome

ACTH dependent
Pituitary-dependent bilateral adrenal hyperplasia
(central form of Cushing´s syndrome, i.e. Cushing´s disease)
* ACTH tumour of pituitary or CRH hypersecretion in hypothalamus) 80% of cases
* Ectopic ACTH syndrome, e.g. small-cell lung carcinoma, pancreatic carcinoma, bronchial carcinoid, (paraneoplastic Cushing´s syndrome)

Non-ACTH-dependent
* Iatrogenic (chronic glucocorticoid therapy e.g. for asthma bronchiale)
* Adrenal adenoma (peripheral form of Cushing´s syndrome)
* Adrenal carcinoma (peripheral form of Cushing´s syndrome)

Differential Diagnosis*:*
Pseudo-Cushing´s syndrome, i.e. cortisol excess as a part of another ilness
Alcohol excess (biochemical and clinical features)
Major depressive illness (biochemical features only, some clinical overlap)
Primary obesity (mild biochemical features, some clinical overlap)
Stress, estrogen treatment, pregnancy,
Drugs: barbiturates, hydantoin (→ increased cortisol)

Cushing´s syndrome - hypercorticism

Clinical features
The best predictive value in favour of Cushing´s syndrome in an obese patient
bruising,
myopathy and
arterial hypertension.
Centripetal obesity
Striae cruente (hypogastrium)
Decreased skin thickness
Weakness of proximal thigh muscle
Moon face

Plethora, acne, hirsutism,
Hair thinning
Menstrual disturbances
Osteoporosis, compression fracture
Hyperglycaemia
Tendency to infections with poor wound healing and
little inflammatory response
Psychosis
Cataracts

Investigation
Tests for Cushing´s syndrome:
Day time - plasma cortisol level…. low predictive value
Urine free cortisol (24-hr timed collection)…high predictive value

1) Increased secretion of free cortisol in 24 hr urine which
2) fails to suppress with low doses (2mg) of dexamethasone
3) Loss of diurnal variation with elevated evening plasma cortisol: 8h, (12), 16, 20, 24 and 8h (in the next morning)

Overnight dexamethasone suppression test:
2 mg Dexamethason at 11,00 p.m.
Morning plasma cortisol >50 nmol/l confirms Cushing´s syndrome
Repetition with Standard dexamethasone test
Computed tomography (CT), magnetic resonance imaging (MRI) examination: adrenal and pituitary

Cushing´s disease

Pituitary tumours:↑ACTH, or ↑CRH hypothalamus and ↑ plasma cortisol level
CT and MRI of adrenal glands: bilateral adrenal hyperplasia
CT and MRI of pituitary: pituitary microadenoma confirmes Cushing´s disease:
(Pituitary macroadenoma: hypopituitarism, visual failure, hyperprolactinemia (rare))

Investigation:
Standard dexamethasone tests
1) *low dose dexamethasone suppression test*
2 mg (0,5 mg 6-hourly for 48 hrs)
24 hr urine cortisol sampling during second day
09,00 hr plasma cortisol after 48 hrs
non suppressed excretion - over production of cortisol

2) *high-dose dexamethasone suppression test*
8 mg (2,0 mg 6-hourly for 48 hrs)
24 hr urine cortisol at baseline and during second day
Urine cortisol suppressed <50% of basal secretion
Pituitary tumours have residual negative feedback sensitivity to cortisol – central Cushing syndrome: ↑ACTH

Management:
Surgical: Trans-sphenoidal surgery (treatment of choice): selective removal of the adenoma
Unsuccessful operation: then alternative bilateral adrenalectomy.

Ectopic ACTH syndrome (Paraneoplastic Cushing´s syndrome)

small-cell lung carcinoma, pancreatic carcinoma, bronchial carcinoid
↑ ACTH and ↑cortisol levels, higher than with other causes,

Clinical features
Pigmentation (MSH) (β-lipotrophic hormone) hypokaliemic alkalosis, myopathy, hyperglycaemia
the onset is rapid and associated with cachexia.
The best predictive value in favour of Cushing´s syndrome in an obese patient
bruising, myopathy and arterial hypertension.
Centripetal obesity
Arterial hypertension
Striae cruente (hypogastrium), decreased skin thickness (bruising)
Weakness of proximal thigh muscle (myopathy)
Moon face
Plethora, acne, hirsutism, hair thinning
Menstrual disturbances
Osteoporosis, compression fracture
Hyperglycaemia
Tendency to infections with poor wound healing and little inflammatory response
psychosis
cataracts

Investigation
Chest radiograph, CT chest, MRI chest and abdomen

1) *low dose dexamethasone suppression test (2 mg Dexamethasone test)*
non suppressed excretion – over production of cortisol

2) *high-dose dexamethasone suppression test (8 mg Dexamethasone test)*
8 mg (2,0 mg 6-hourly for 48 hrs)
24 hr urine cortisol at baseline and during second day
Urine cortisol no suppressed, >50% of basal secretion
Ectopic ACTH syndrome have no residual negative feedback sensitivity to cortisol and ↑ACTH

Management
Benign tumours: bronchial carcinoid – surgical intervention

Treatment of malignancy
palliation, reduction of severity of Cushing´s syndrome

Medical therapy
inhibitors of corticosteroid biosynthesis
Metyrapone, aminogluthetimide, ketoconazole.

The dose of these drugs must be titrated individually against 24-hour urine free cortisol.

Adrenal adenoma
(peripheral form of Cushing´s syndrome)

Or adrenal carcinoma - neopasia of cortex: 20% of cases
Autonomous excess secretion of cortisol:
↑cortisol (adrenal cortex) → ↓ ACTH (pituitary)
Hypercortisolism inhibits endogenous ACTH secretion ↓ACTH with subsequently atrophy of the rest of the adrenals.

Clinical features
The best predictive value in favour of Cushing´s syndrome in an obese patient
bruising, myopathy and hypertension

Malignancy: the onset of symptoms is rapid and associated with cachexia.
Centripetal obesity
Striae cruetne (hypogastrium)
Decreased skin thickness
Weakness of proximal thigh muscle
Moon face
Plethora, acne, hirsutism,
Hair thinning
Menstrual disturbances
Osteoporosis, compression fracture
Hyperglycaemia
Tendency to infections with poor wound healing and
little inflammatory response
psychosis

Investigation
Cortisol, ACTH, diurnal rhythm of plasma cortisol
(Loss of diurnality: evening level >75% of morning level: is Cushins´s syndrome)

Differential diagnosis of carcinoma:
↑DHEA-S, 11-OH deoxycortisol, 11-deoxycortiko-sterone, aldosterone, estrogen
Chest and abdomen radiograph lungs-, liver- metastases
CT or MRI adrenals,
Radio-cholesterol scan

Standard dexamethasone test
1) *low dose dexamethasone suppression test*
2 mg (0,5 mg 6-hourly for 48 hrs)
24 hr urine cortisol sampling during second day
09,00 hr plasma cortisol after 48 hrs
non suppressed excretion - over production of cortisol

2) *high-dose dexamethasone suppression test*
8 mg (2,0 mg 6-hourly for 48 hrs)
24 hr urine cortisol at baseline and during second day
Urine cortisol no suppressed, >50% of basic secretion

Peripheral Cushing´s syndrome have no residual negative feedback sensitivity to cortisol
↓ACTH

Management
Adrenal tumours removed via laparoscopy, or loin incision
Adrenal carcinomas resected if possible,
Irradiation of tumour
Adrenolytic drug o´p´-DDD (Mitotane) 8-10 mg/d.

Adrenal insufficiency

Inadequate – reduced secretion of cortisol and/or aldosterone

Causes of adrenocortical insufficiency
Secondary (↓ACTH) adrenal insufficiency
hypothalamic or pituitary disease
withdrawal of suppressive glucocorticoid therapy

Primary (↑ACTH) adrenal insufficiency
Addison´s disease

Addison´s disease

Common causes
Autoimmune
Tuberculosis
HIV/AIDS
Metastatic carcinomas
Bilateral adrenalectomy
Rare causes
Lymphoma
Intra – adrenal haemorrhage (Waterhouse-Friderichsen syndrome
following meningococcal septicaemia)
Amyloidosis
Haemochromatosis

Corticosteroid biosynthetic enzyme defects
congenital andrenal hyperplasia
drugs (aminoglutethimide, metyrapone, ketokonazole, etomidate)

Clinical features
- glucocorticoid insufficiency
fatigue
weight loss
malaise
weakness
anorexia
nausea, vomiting
gastrointestinal diarrhoea or constipation
shock
hypoglycaemia
hyponatraemia
hypercalcaemia

Mineralocorticoid insufficiency
Arterial hypotension
shock
hyponatremia
hyperkalaemia
ACTH excess
Pigmentation in sun exposed areas, pressure areas, palmar creases, mucous membranes, Conjunctivae, recent scars

Adrenal androgen insufficiency
Decreased body hair
Loss of libido especially in female

Differetial diagnosis:
pigmentation: malabsorption, hemochromatosis, porphyria, interstitial polyposis, colitis ulcerosa, ileitis regionalis, Ci hepatis, arsen- and bismuth- poisoning. Nelson´s syndrome

Investigation
↓Cortisol <200 nmol/l, ↑ACTH, electrolytes ↓Na, ↑K
Short ACTH stimulation test
basic concentration of ACTH in plasma
(Synacthen test) 250 µg ACTH i.v. and in 0, 30, min. plasma cortisol collection
normal plasma cortisol 200 nmol/l - baseline levels
at 30 minutes after Synacthen stimulation 550 nmol/l physiolohgical answer – normal

Diagnosis is confirmed:
insufficient answer of cortisol (low increment) and
basic ↑ACTH in plasma
Differential diagnosis:
↓cortisol and ↓ACTH (central hypocorticism /in panhypopituitarism?)
when: normal answer of cortisol in short ACTH test
: primary hypocorticism is excluded
secondary hypocorticism can not be excluded

Tests for ACTH secretion reserve of pituitary
→Metopiron test
→Insulin (hypoglycaemic) tolerance test
→CRH test
Normal answer in increment of cortisol: central hypocorticism is excluded
Low increment in cortisol: central hypocorticism is confirmed

Investigation
Autoimmune adrenal failure –
antibodies against steroid secreting cells, thyroid antigens, thyroid function tests, full blood count, glucose, calcium,
Familial examination, hereditary features: autosomal dominant transfer of this disease.
Tbc- calcification: plain abdominal radiograph, chest radiograph, HIV tests, CT or MRI of the adrenals.

Secondary (central hypocorticism)
Impaired production of
ACTH (pituitary)
CRH (hypothalamic lesion), tumour
Suppressed secretion of ACTH and CRH
Glucocorticoid treatment and abrupt withdrawal of glucocorticoids
Tumour of adrenocortex producing cortisol

Clinical features, Investigation
see primary hypocorticism, Addison´s disease

Management
Glucocorticoide replacement
Hydrocortisone the drug of the choice 20 – 10 - 5 mg, free urine cortisol analysis

Adrenal crisis

Developed form of adrenal insufficiency – medical emergency – intensive care unit

Aethiology
intercurrent disease, surgery infection in latent hypocorticism

Clinical featues
fatigue, muscle weakness, anorexis, circulatory shock, hypotension, muscle cramps, nausea, vomiting, diarrhoea, unexplained fever

Investigation
↓Na (125 mmol/l) (ref.r. 132-144 mmol/l), ↑K 3,1 mmol/l (3,3 – 4,7 mmol/l), ↓glucose, ↑Ca, ↓cortisol, ↓aldosterone

Short ACTH test
Synacthen 0,25 mg ACTH i.v.
Blood samples: 0, 30 minutes for plasma cortisol
Results:
normal subjects plasma cortisol >550 nmol/l either at baseline or at 30 minutes

Management
Hydrocortisone succinate 100 mg i.v., intravenous fluid:
! Rapid replacement of sodium deficiency: Isotonic solution (NaCl) replacement and 5% glucose, or 10% dextrose 500 ml several time per day
Hydrocortisone succinate 100 mg i.m. 6-hourly
Mineralocorticoid: Fludrocortisone (9alfa-fluoro-hydrocortisone) 0,05-0,1 mg daily
Free cortisol in 24 h urine sample.

Primary hyperaldosteronism and mineralocorticoid excess – Conn´s syndrome

Mineralocorticoid excess of ↑aldosterone production, ↓renin activity, arterial hypertension
↑BP

Causes of mineralocorticoid excesses

Primary hyperaldosteronism (with low renin activity)

* adrenal adenoma secreting aldosterone (Conn´s sy.)
* idiopathic bilateral adrenal hyperplasia
* glucocorticoid suppressible hyperaldosteronism (rare)

Secondary hyperaldosteronism (with high renin activity) e.g. diuretic therapy, cardiac failure, nephrotic syndrome, renal artery stenosis

Definition

Arterial hypertension characterized by excessive secretion of ↑aldosterone and negative feedback suppression of plasma ↓renin activity.
Adrenal autonomous excessive secretion of aldosterone: Conn´s syndrome
Adenoma, adenocarcinoma, bilateral adrenal hyperplasia

Prevalence of primary hyperaldosteronism:

adenoma plus bilateral adrenal hyperplasia = 5% patient with arterial hypertension
Patient group: 30-50 years old persons.
Female: male ratio 2:1

Pathogenesis

Autonomous excess secretion of aldosterone by adrenal adenoma, hyperplasia with suppression of the renin secretion.

Clinical features

Arterial hypertension, hypokalaemia - muscle weakness, young age, sodium retention – oedema,
Polyuria, tetany - metabolic alkalosis and low ionised calcium.

Investigation

Plasma electrolytes Na, K, elevated bicarbonates
Key measurements: plasma renin activity and aldosterone
Stop of antihypertensive drugs for at least 6 weeks (beta blockers thiazide diuretics, ACE-I, sartans)
bethanidine, debrisoquine therapy (minimal effect on renin-angiotensin system).

Primary hyperaldosteonism:

Adrenal adenoma secreting aldosterone

low renin, high aldosterone,
Ortostasis test: aldosterone does not rise on standing
CT MRI examination: confirmation of adrenal tumour

Idiopathic bilateral adrenal hyperplasia

Low renin, high aldosterone
Ortostasis test: aldosterone does not rise on standing
CT MRI exam - confirmation of bilateral adrenal hyperplasia

Glucocorticoid suppressible hyperaldosteronism

Low renin, high aldosterone
Ortostasis test: aldosterone does not rise on standing
CT MRI exam confirmation of bilateral adrenal hyperplasia
Aldosterone suppression after Dexamethasone treatment 2mg for 4 days

Investigation
Biochemistry investigation – aldosterone analysis Localisation - Abdominal CT
After biochemistry investigation – localisation - supports the diagnosis of tumour then abdominal CT
(20% of patients with hypertension have non-functioning adrenal adenomata)
vein catethrisation – aldosterone measurement
75Se-cholesterol scan of adrenals

35-year old male
Mild polyuria
Blood pressure 188/104 mmHg Na 144 mmol/l (132-144)
K 3,1 mmol/l (3,3-4,7)
lying at 9.00 hrs
renin activity < 0,5 (0,4-1,5)
aldosterone 850 pmol/l (30-440)
standing at 12.00 hrs
rennin activity < 0,5 (1,0-2,5)
aldosterone 750 pmol/l (110-860)

Management
Spironolactone (mineralocorticoid receptor antagonist) up to 400 mg/day
Normalization of hypokalaemia and hypertension
(all forms of mineralocorticoid excess)
Conn´s syndrome - pre treatment with Spironolactone (3-6 weeks) then

1) Unilateral adrenalcetomy in adrenal adenoma (hypertension remains in 75% - irreversible damage of microcirculation)

2) Unilateral or subtotal adrenalectomy in idiopathic bilateral adrenal hyperplasia

3) Dexamethasone treatment in Glucocorticoid suppressible hyperaldosteronism.
(Dexamethasone 2 mg daily)
Monitoring of potassium, sodium, blood pressure

Diseases of adrenal medulla - excess of catecholamines secretion

Phaeochromocytoma

Tumour of chromaffin tissue - catecholamine excess secretion 0,1% of arterial hypertension
Adrenal medulla 90%, extra adrenal 10%, familial 10%, malignant 10%

Clinical features
Arterial hypertension (paroxysmal),
attacks with pallor,
palpitations,
sweating,
headache,
anxiety,
abdominal pain, vomiting,
constipation,

weight loss,
glucose intolerance.
Hypertension accelerated phase of hypertension, stroke, myocardial infarction, left ventriculaf failure, hypertensive retinopathy.

At the MEN multiple endocrine neoplasia type II, i.e.
Sipple´s syndrome: Phaeochromocytoma combined with Hyperparathyreoidism and Medullary carcinoma of thyroid.
Plasma calcium, urinary metanephrines, calcium pentagastrin test with calcitonin measurements.

Investigation
Excessive secretion of catecholamines (adrenaline, noradrenaline, dopamine) in plasma
Catecholamine metabolites in urine (vanylil-mandelic acid (VMA), conjugated metanephrine, normetanephrine).

Catecholmine excretion is paroxysmal – paroxysm – 24 hour urinary catecholamine excretion analysis – if normal level of catecholamines - phaeo can be excluded.

Differential diagnosis:
Incresed urinary catecholamine excretion:
stressed patients after myocard infarction, major surgery,
Drugs: beta blockers, antidepressants: ↑catecholamines

Supression test:
Normal adrenomedullary secretion is suppresed by clonidin, pentolinium → ↓plasma catecholamines
Phaeochromocytoma: these drugs do not suppress plasma catecholamines.

Localisation
Abdominal CT - extra adrenal tumours localisation – difficult
scintigraphy: meta-iodobenzyl guanidine (MIBG) examination
MIBG labeled with ^{131}I - both benign and malignant phaeochromocytoma are detected
Selective venous sampling with measurement of plasma Noradrenlin.

Management
Medical therapy to prepare patients for surgery: Adrenalectomy, 6 weeks
Alfa blocker phenoxybenzamine (10-20mg orally 6-8-hourly), if alfa blockade produces tachycardia, then beta blockers (propranolol) or
Combined alfa- and beta- antagonist e.g. labetalol

During surgery (unilateral adrenalectomy), sodium nitroprusside and
short-acting alfa-antagonist phentolamine- controlling hypertensive episodes (anaesthetic induction, tumour mobilisation).

Post operative hypotension: fluid infusion, volume expansion, or noradrenaline infusion.

Acute situations in endocrinology

Acute situations – emergency, alarm - situations in endocrinological practice are not common but life-threatening complications which require an urgent and complex therapeutical aproach to the patients.
Dispite of intensive care and early recognition / diagnosis the mortality rate is relatively high 10 - 50%. The aim of medical care is to exert a sufficient prevention, perfect diagnostics and an effective therapy for saving the life of patient.

Hyperthyroid crisis

A rare but life-threatening increase in the severity of the clinical features of hyperthyroidism.

Clinical features and signs:
agitation, confusion, fever, tachycardia or atrial tachyfibrillation,
older patient - cardiac failure
Medical emergency – mortality rate was 50%, recenly 10 %, despite early recognition and treatment.
Intensive care unit!!!

Pathogenesis of hyperthyroid crisis (thyrotoxic crisis)

* Infection in a patient with unrecognised inadequately treated hyperthyroidism after subtotal thyroidectomy in an ill-prepared patient
* Surgery of thyrotoxic patient
* After 131 I therapy - acute irradiation damage - transient rise of thyroid hormone levels in serum

Management of crisis
Intensive care unit!!!
Rehydratation,
broad spectrum antibiotic
beta-blockers (propranolol)
80 mg 6-hourly orally (p.o. application)
or 1-5 mg 6-hourly intravenously (i.v.
(parenteral application)
antithyroid drugs: Carbimazol 40-60 mg daily orally
(inhibition of hormone systhesis)
sodium iopodate 500 mg per day orally (restoration of T3 levels to normal in 48-72 hours)
(radiographic contrast medium – inhibits the release of thyroid hormones - reduces the conversion of T4 to T3)

Alternative treatment
the Lugols´solution (KJ +J) 1 ml 6-hourly orally
or potassium iodide (KJ) 3 drops of conc. solution 6-hourly orally
or potassium iodide in i.v. infusion
0,5-1,0 g KJ 5% glucose + isotonic sol 0,9% NaCl
max. dosis: 500-1000 mg KJ per day

Glucocorticoids: Hydrocortisone solubile 100 mg inj.
300 mg bolus i.v.
afterwards 100 mg 8-hourly i.v.
(Glucorticoids reduce the conversion of T4 to T3)
Sodium iopodate and beta-blockers can be withdrawn after 10-14 days, patient are maintained on carbimazol.
White blood cell count is necessary.

Myxoedema coma

A rare presentation of developed severe hypothyroidism
Depressed level of consciousness elderly patients with myxedematous types
Body temperature as low as 25° Celsius.
Mortality rate is 50%
survival chance depends upon early recognition and treatment of hypothyroidism.

Factors contributing to the altered consciousness level
Drugs: phenothiazine,
heart conditions: cardiac failure,
infection- pneumonia, dilution
hyponatremia,
hypoxemia and hypercapnia due to hypoventilation.
Medical emergency ! ! Intensive care unit !

Management o myxedema coma
Treatment must begin before biochemical confirmation of the diagnosis.
Hydrocortisone sodium succinate 100 mg i.m. 8-hourly
or Hydrocortisone solubile 100 mg i.v. bolus of 200 mg
Triiodothyronine intravenous bolus 20 µg followed by 20 µg 8-hourly until there is a sustained clinical improvement. Raise in body temperature within 24 hours.
After 24 - 72 hours oral thyroxine substitution in a dose of 50 µg per dayi.v. fluids, isotonic solution & Glucose 5% 2 x 500 ml
broad spectrum antibiotics (TTC), high flow-oxygen.

Adrenal crisis in Addison´s disease (Addisonian crisis)

Developed form of adrenal insufficiency
Medical emergency, Intensive care unit
Aethiology:
intercurrent disease, surgery, infection in latent hypocorticism

Clinical featues
fatigue, muscle weakness, anorexis, circulatory shock, hypotension, muscle cramps, nausea, vomiting, diarrhoea, unexplained fever

Investigation
↓Na (125 mmol/l) (ref. range 132 - 144 mmol/l),
↑K 5,1 mmol/l (3,3-4,7 mmol/l), ↓glucose, ↑Ca, ↓cortisol, ↓aldosterone

Short ACTH test
Synacthen 0,25 mg ACTH i.v.
Blood samples: 0, 30 minutes for plasma cortisol
Results:
normal subjects plasma cortisol >550 nmol/l either at baseline or at 30 minutes
Insufficiency does not come to the increase of cortisol

Management
Hydrocortisone succinate 100 mg i.v.,
intravenous fluid:
! Rapid replacement of sodium deficiency: Isotonic solution (NaCl) replacement and 5% glucose, or 10% dextrose 500 ml several time per day
Hydrocortisone succinate 100 mg i.m. 6-hourly
Mineralocorticoid: Fludrocortisone (9alfa-fluoro-hydrocortisone) 0,05-0,1 mg daily
Control. Free cortisol in 24 h urine sample.

Hypercalcaemia and Hypercalcaemic crisis

Hypercalcaemia – one of the most common biochemical abnormalities.
Hypercalcaemia can present with chronic symptoms –
* polyuria and polydypsia,
* renal colic,
* dyspepsia and peptic ulceration,
* constipation

Acute emergencies with severe hypercalcaemia and dehydration → hypercalcaemic crisis: polyuria and polydypsia, anorexia, nausea, lethargy, depression drowsiness, impaired cognition

Clinical features of hypercalcaemia
Polyuria and polydypsia
Renal colic
Lethargy
Anorexia nausea
Dyspepsia and peptic ulceration
Constipation
Depression
Drowsiness
Impaired cognition
In malignant hypercalcaemia – rapid onset of symptoms and clinical features

Hypercalcaemia
Causes of Hypercalcaemia

With normal or elevated (i.e. inappropriated) PTH levels
* primary or tertiary hyperparathyroidism
* lithium induced hyperparathyroidism
* familial hypocalciuric hypercalcaemia

With low (i.e. supressed) PTH levels
* malignancy (e.g. lung, breast, renal, ovarian, colonic, thyroid Ca)
* multiple myeloma
* elevated 1,25 diOH vitamin D3 (e.g. Intoxication, sarcoidosis)
* thyrotoxicosis
* Paget´s disease with immobilisation
* Milk-alkali syndrome
* Thiazide diuretics
* Addison´s disease

Treatment of malignant hypercalcaemia
Rehydrataion with normal saline
To replace as much as 3-4 l deficit
May need monitoring with central venous pressure in old age or renal impairment
Forced diuresis with saline and furosemide
Glucocorticoids, e.g. Hydrocortisone 2 - 4 x 100 mg i.v./day or Prednisolone 40 mg daily
Calcitonin treatment
Haemodialysis
Bisphosphonates, e.g. Pamidronate 90 mg i.v. over 4 hr causes a fall in calcium which is max at 2 - 3 days and lasts a few weeks
Unless the cause is removed, follow up with an oral bisphosphonate

Hypocalcaemia

Much less common than hypercalcaemia,
Conditions:
low serum albumin
Alkalosis
Vitamin D deficiency
Chronic renal failure
Acute pancreatinis
damage of the parathyroid glands during thyroid surgery (1% compliction),
transient hypocalcaemia in 10% patients 12 - 36 hr after subtotal STE (strumectomy) for Graves´ disease.
idiopathic hypocalcaemia
Clinical symptoms
– carpopedal spasms, stridor, convulsions- tetany, Chvostek sign and Trouseau examination are positive

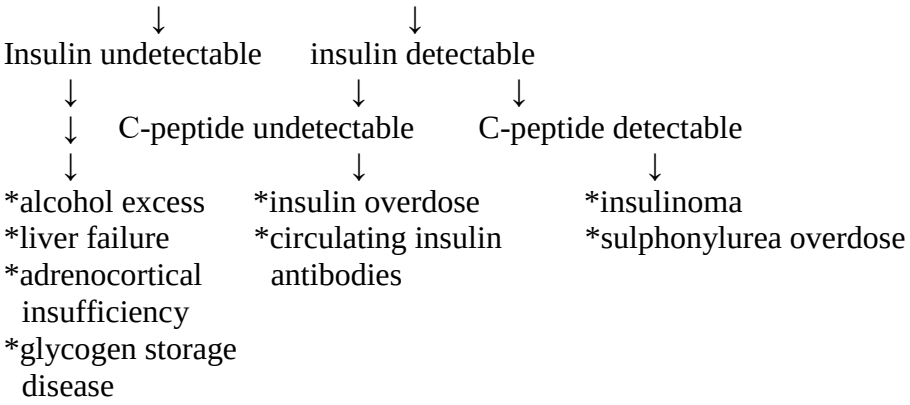
Laboratory examination
total serum calcium < 2.0 mmol/l
Magnesium depletion – contributing factor, diuretic treatment, alcohol excess, alcalosis
Management:
Respiratory Alcalosis – reversed rebrathing expired air in a paper bag or administering 5% CO_2 in oxigen.
Injection 20 - 40 ml of a 10% solution of Ca gluconate i.v.
Vitamin D_3 – calcitriol 1,25 $(OH)_2$ D_3 (1,25 dihydroxy cholecalciferol) (Rocaltrol Roche) supplementation

Hypoglycaemia

Hypoglycaemia is most common side-effect of treatment with insulin or sulphonylurea drugs in patients with diabetes mellitus (DM).
In diabetic patients < 3.5 mmol/l
In non-diabetic patients hypoglycaemia defined as a plasma glucose < 2.5 mmol/l
Hypoglycaemia can occur in people without diabetes – known as spontaneous hypoglycaemia

Causes of spontaneous hypoglycaemia:
Alcohol excess
Liver failure
Adreno-cortical insufficiency
Glycogen storage disease
Insulin and/or sulphonylurea overdose
Circulating insulin antibodies
insulinoma

Hypoglycaemia is aggravated by fasting
Provoke an attack by prolonged fast
Plasma glucose during attack < 2.2 mmol/l



Common symptoms of hypoglycaemia
Autonomic
Sweating, trembling, pounding heart, hunger, anxiety
Neuroglycopenic
Confusion, drowsiness, speech difficulty, incoordination inability to concentate
Non-specific
Nausea, tiredness, headache
Notice: Age-specific differences in symptoms occur.
Children: behavioral changes
Elderly people: more prominent neurological features.

Notice: Hypoglycaemia in the absence of insulin - impaired gluconeogenesis and impaired availability of glucose from glycogen in the liver, i.e. glycogenolysis is impaired as alcohol inhibits gluconeogenic enzymes.

Investigation
Glycaemia < 2.2 mmol; 2.2-2.5 mmol/l – pathological
CT, MRI, endoscopic laparoscopic ultrasound - tumour

Management
30-50 ml of 50% dextrose i.v. then carbohydrate p.o.
Infusion 5% glucose in sulphonylurea poisoning
Insulinoma – surgery, inhibitors of insulin secretion, treatment with Diazoxide, thiazide diuretics, somatostatin analogues

Hyperglycaemia

A common biochemical abnormality, frequently detected on routine biochemical analysis of asyptomatic persons.
Hyperglycaemia: sign of impaired glucose metabolism in DM,
in impaired glucose tolerance (IGT)
Hyperglycaemia: a sign of impaired glucose metanbolism accompanying other endocrine and non-endocrine diseases (so called secondary diabetes)

Classification:
- Destruction of pancreas – acute pancreatitis
- After surgery removal of pancreas
- Hemochromatosis

Hyperglycaemia in other endocrine diseases:
Hypersomatotropismus-acromegaly – insulin resistance
Cushing syndrome – DM and impaired GT increased gluconeogenesis and increased insulin resistanec caused by hypercortisolism.
Primary hyperaldosteronism – K deficiency in B cells
Pheochromocytoma – increased gluconeogenesis inhibition of insulin secretion, insulin resistance
Thyrotoxicosis – increased inpaired GT contra - insulin eff.
Glucagonom – (malignant) tumour of pancreas A-cells
Somatostatinom – D cells of pancreas – mild, also severe hyperglycaemia

Hyperglycaemia - diabetes mellitus (DM) induced by drugs:
Thiazide diuretics, adrenergic beta-bloctor
Calcium chanel blocator
Glucocorticoids
Ovulation blocker – DM 2.typ.
Pentamidin – destruction cytotoxic effect on B-cells
Streptozotocin, Diazoxide, Rodencid Vacor- intoxication
Thiazide diuretics – impaired glucose tolerance
Insulin receptors defects
Hyperinsulinemia in pregnancy
Renal insufficiency and Liver insufficiency
– Mild hyperglycaemia only

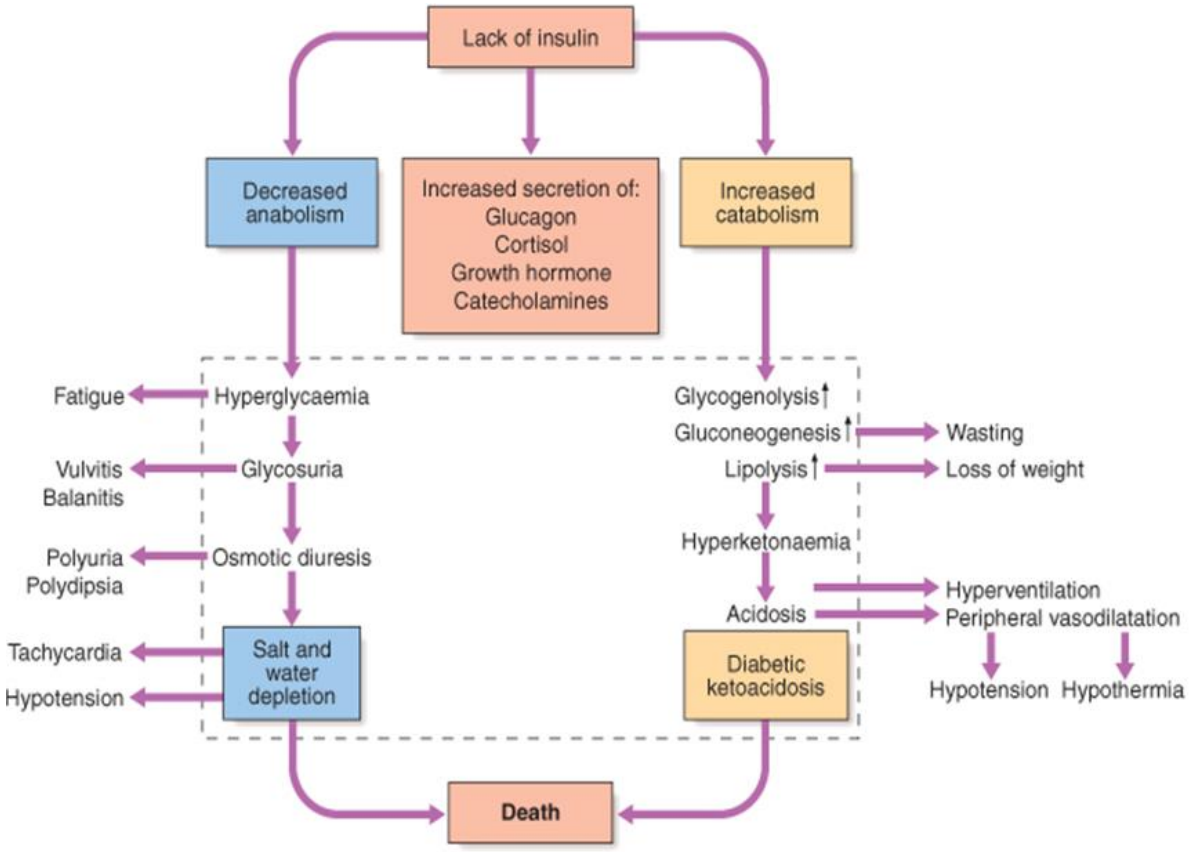
Emergency situations:

Diabetic ketoacidosis in diagnosis of diabetes

Major medical emergency, remains a serious cause of morbidity, principally in people with type 1 diabetes mellitus.
Average mortality in Developed countries 5-10%, higher in elderly.
Ketoacidosis is caused by insulin deficiency,
increase in catabolic hormones – hepatic overproduction of glucose and ketone bodies.

Cardinal biochemical features of diabetic ketoacidosis:
Hyperglycaemia
Hyperketonaemia
Metabolic acidosis

Figure 18: Metabolic disturbances in type 1 diabetes
(Pathophysiological basis of the symptoms and signs of uncontrolled diabetes mellitus)



Source: BOON, N.A., COLLEDGE, N.R., and WALKER, B.R., (eds.). Davidson's Principles and Practice of Medicine. 20th ed. Philadelphia: Churchill Livingstone/Elsevier Health Sciences Division, 2006, xvi, 1381 p. ISBN 978-0-443-10057-4. Available at: www.studentconsult.com

Hyperglycaemia → profound osmotic diuresis → dehydratation with electrolyte loss of Na, K
The metabolic acidosis forces hydrogen ions into cells → displacing potassium ions – lost in urine / through vomiting

The average loss of fluid and electrolytes in moderately severe diabetic ketoacidosis in adult
Water: 6 liters
Sodium 500 mmol
Potassium: 350 mmol
Chloride: 400 mmol

In established diabetas a common couse of events:
Develop an intercurrent infection
Lose the appetite
Stop or drastically reduce the dose of insulin (in the mistaken belief that under these circumstances less insulin is required)
Stress – produced by infection – precipitates ketoacidosis
Severe medical conditions: myocardial infarction,
septicaemia
Delays in diagnosis, management errors – even – deaths from ketoacidosis
Other precipitating cause can be found in many cases

Clinical features of diabetic ketoacidosis
Symptoms
* Polyuria, thirst
* Weight loss
* Weakness
* Nausea, vomiting
* Leg cramps
* Blurred vision
* Abdominal pain

Signs
* Dehydratation
* Hypotesion
* Tachycardia
* Air hunger (Kussmaul breathing)
* Smell of acetone
* Hypothermia
* Confusion, drowsiness
* Coma (10%)

Investigations
Urea and electrolytes Na, K, Cl, blood glucose
Arterial blood gases (to asses the severity of acidosis)
Urinalysis for ketones
Full blood count
Infection screen: blood and urine culture, chest radiograph

Management
Diabetic ketoacidosis is a medical emergency which should be treated in hospital preferably in a high-dependency area.
The principal components of treatment.
The administration of short-acting (soluble) insulin
Fluid replacement,
Potassium replacement
The administration of antibiotics, if infection is present

Table 1: Management of Diabetic Ketoacidosis

Fluid replacement

- 0.9% saline (NaCl) i.v.
  - 1 litre over 30 minutes
  - 1 litre over 1 hr
  - 1 litre over 2 hrs
  - 1 litre over next 2-4 hrs
- When blood glucose < 15 mmol/l (270 mg/dl)
  - Switch to 5% dextrose, 1 litre 8-hourly
  - If still dehydrated, continue 0.9% saline and add 5% dextrose 1 litre per 12 hrs
- Typical requirement is 6 litres in first 24 hrs but avoid fluid overload in elderly patients
- Subsequent fluid requirement should be based on clinical response including urine output

Insulin

- 50 units soluble insulin in 50 ml 0.9% saline i.v. via infusion pump
  - 6 units/hr initially
  - 3 units/hr when blood glucose < 15 mmol/l (270 mg/dl)
  - 2 units/hr if blood glucose declines < 10 mmol/l (180 mg/dl)
- Check blood glucose hourly initially-if no reduction in first hour, rate of insulin infusion should be increased
- Aim for fall in blood glucose of 3-6 mmol/l (~55-110 mg/dl) per hour

Potassium

- None in first litre of i.v fluid unless < 3.0 mmol/l
- If plasma potassium < 3.5 mmol/l, give 40 mmol added potassium
  - Give in 1 litre of fluid
  - Avoid infusion rate of > 20 mmol/hr
- If plasma potassium is 3.5-5.0 mmol/l, give 20 mmol added potassium
- If plasma potassium is > 5.0 mmol/l, or patient is anuric, give no added potassium

Additional Procedures in the Management of Diabetic Ketoacidosis

- Catheterisation if no urine passed after 3 hrs
- Nasogastric tube to keep stomach empty in unconscious or semiconscious patients, or if vomiting is protracted
- Central venous line if cardiovascular system compromised, to allow fluid replacement to be adjusted accurately
- Plasma expander if systolic BP is < 90 mmHg or does not rise with i.v. saline
- Antibiotic if infection demonstrated or suspected
- ECG monitoring in severe cases

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Other issues

Complications of diabetic ketoacidosis

Cerebral oedema

may be caused by rapid reduction of blood glucose,
use of hypotonic fluids and/or bicatbonate,
high mortality,
treat with mannitol, oxygen,

Acute respiratory distress syndrome,

Thromboembolism,

Disseminated intravascular coagulation, DIC (rare),

Acute circulatory failure.

Non-ketotic hyperosmolar diabetic coma

Characterised by severe hyperglycaemia (> 50mmol/l)
without significant hyperketonemia or acidosis
Severe dehydratation pre-renal uraemia
Elderly patients with previously undiagnosed diabetes
Mortality is over 40%

Treatment differs from that of ketoacidosis
1) Usually relative sensitivity to insulin – (half of the dosis of Insulin recommended for the treatment of ketoacidosis)
2) Plasma osmolality can be calculated using the formula
Plasma osmolality=2(Na)+ 2(K) + (glucose) + (urea)
Normal value 280-300 mmol/kg
Analysed plasma osmolality level more 340 mmol/kg
Patient should be given 0.45% saline until the osmolality approaches normal, later be substituted with 0.9 % saline
Na, K control freq. Thromboembilic complictions - heparin

Lactic acidosis

medical emergency
History:
Diabetic (comatous) patient taking metformin for type 2 diabetes, ill, overbreathing, not so profoundly dehydrated as in ketoacidosis
The patient´s breath does not smell of acetone,
ketonuria is mild, or absent
Plasma bicarbonate, pH markedly reduced, pH < 7.2
The diagnosis confirmed:
> 5.0 mmol/l plasma conc.of lactic acid (normal 3 mmol/l)

Treatment: in Intensive Care Unit
Sodium bicarbonate pH > 7.3 along with Insulin & glucose
Sodium dichloroacetate for lowering the blood lactate
Despite of energic treatment the mortality > 50%

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