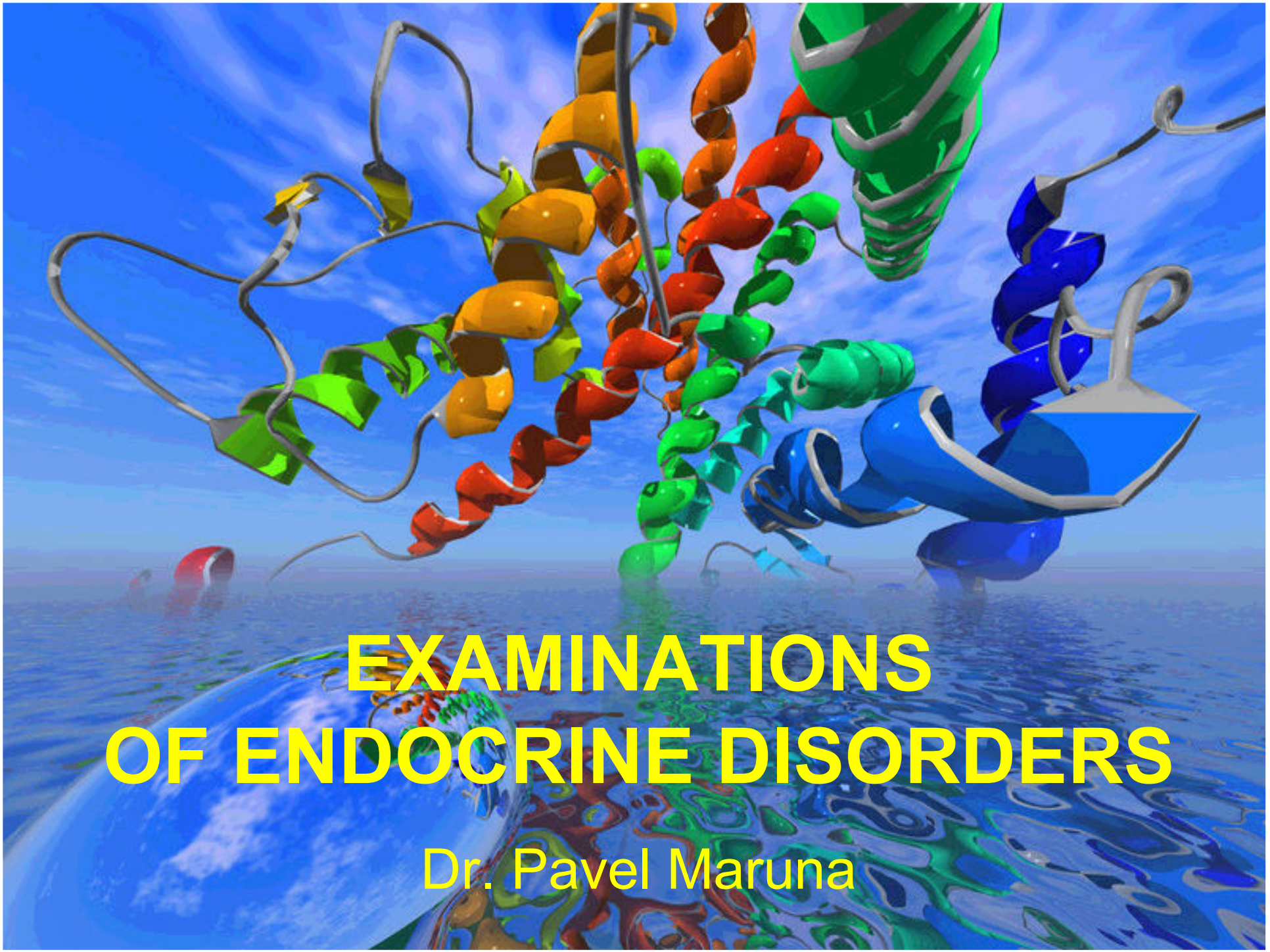
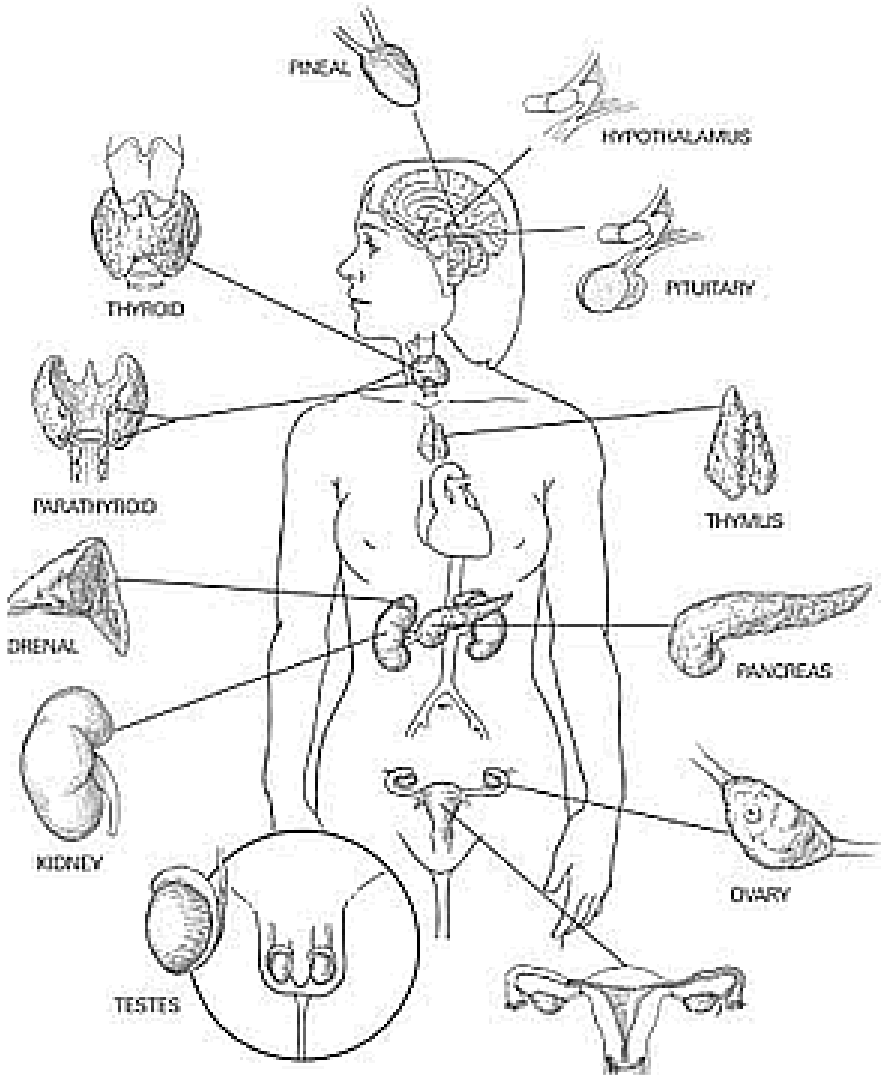


EXAMINATIONS OF ENDOCRINE DISORDERS

Dr. Pavel Maruna

Basic theses



Endocrine system

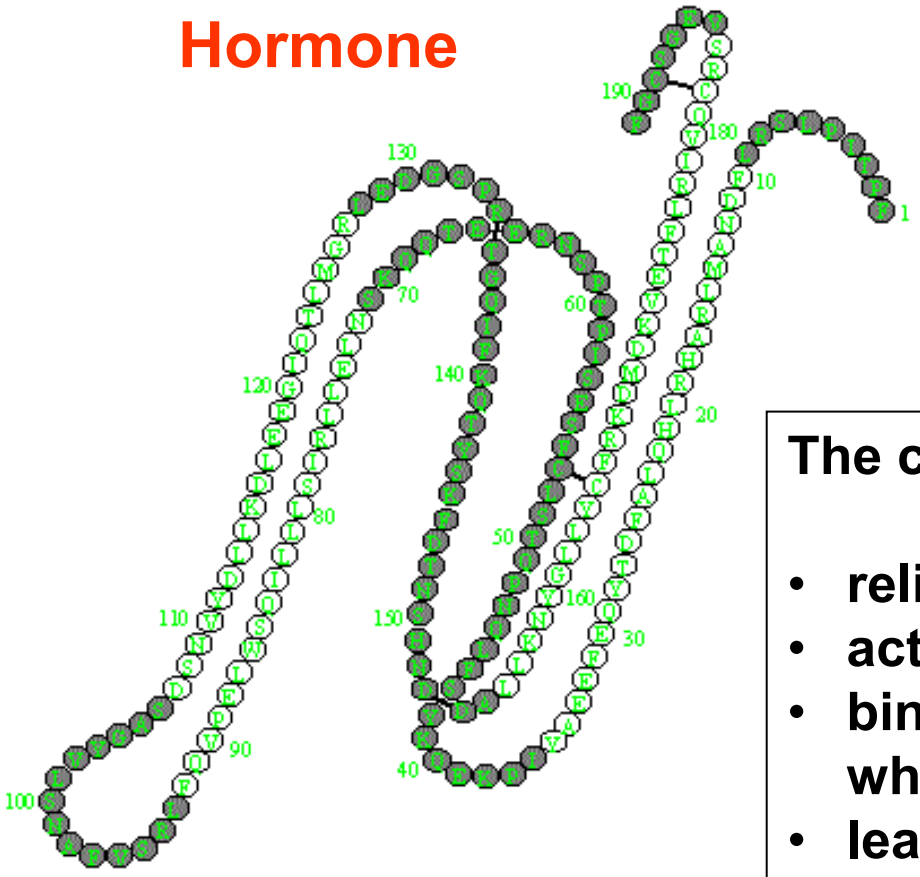
One of the body's main systems for intercellular communicating, controlling and coordinating. In coordination with nervous system, It helps maintain and control:

- **body energy levels**
- **reproduction**
- **growth and development**
- **internal balance of body systems, (homeostasis)**
- **responses to surroundings, stress, and injury**

The endocrine system accomplishes these tasks via a network of endocrine glands and organs that produce, store, and secrete hormones.

Basic theses

Hormone



The chemical messenger that is

- **relieved to the blood,**
- **acts on distant target cells,**
- **binds to receptor on target cells, which**
- **leads to some change in that physiologic state.**

Basic theses

Hormones - chemical structure

1. **Polypeptides / proteins**

   (Pituitary, hypothalamus, PTH, insulin, glucagon ...)

2. **Steroids**

   (Adrenal cortex, gonads, placenta)

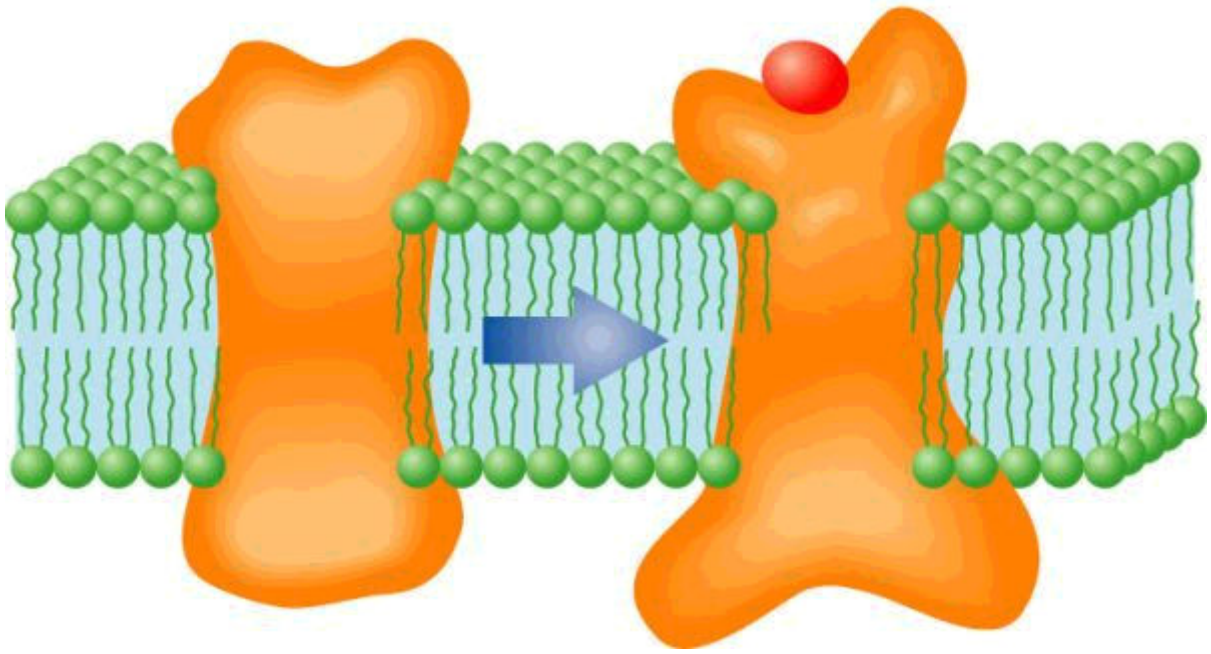
3. **Aminoacids**

   (Adrenal medulla, thyroid gland, hypothalamus, epiphysis ...)

Notice: Only steroid and aminoacid hormones are suitable for oral treatment.

Basic theses

Receptor

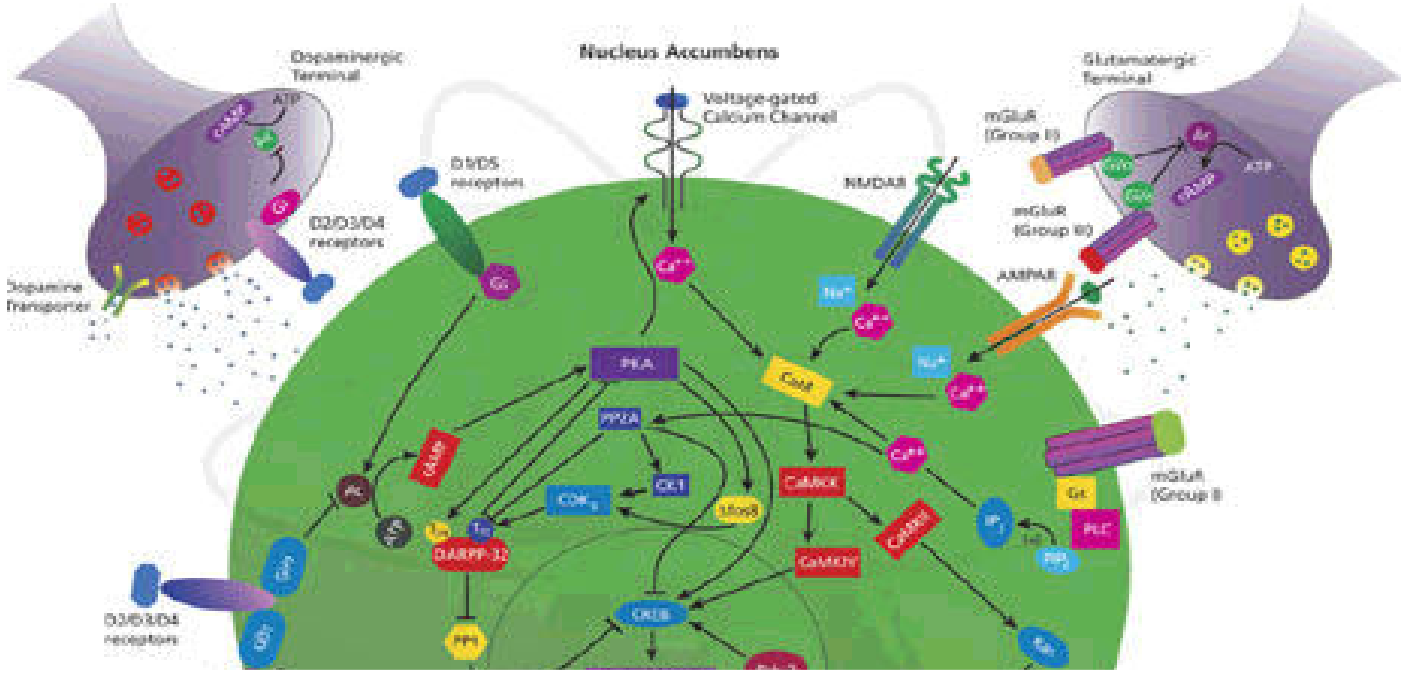


The cellular protein that binds hormones (or other mediator) with high affinity and initiates a physiologic response. Receptors for peptide mediators are located in the plasma membrane, while receptor for both steroid or aminoacide hormones are found within the cytoplasm or nucleus.

Basic theses

Second messenger

The small molecule generated inside cells in response to binding of hormone or other mediator to cell surface receptors. Examples include cyclic AMP and calcium.



Basic theses

Intercellular signaling

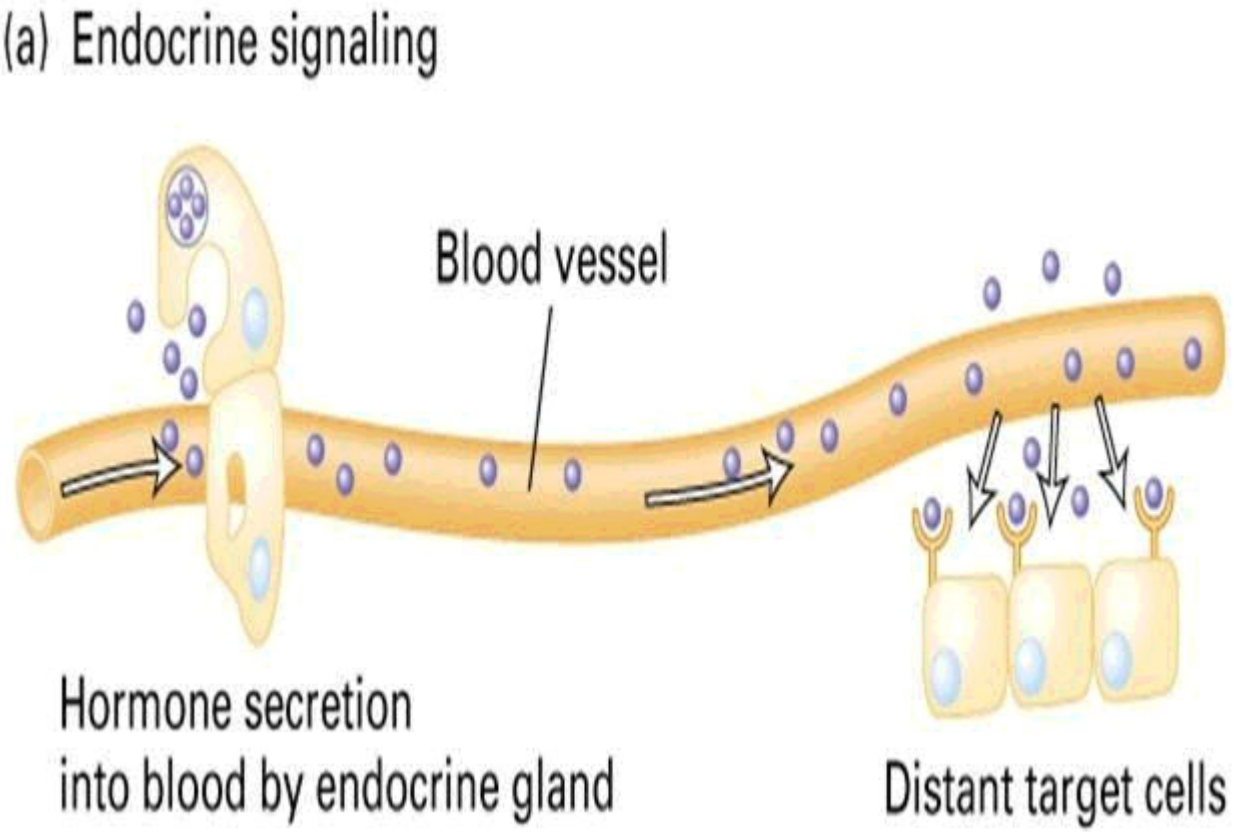
(a) Endocrine = The activity of a hormone (or cytokine or growth factor) that circulates in blood, and binds to and affect cells distant from the source of secretion.

(b) Paracrine = The activity of a hormone ... that binds to and affects neighboring cells of the other type.

(c) Autocrine = The activity of a hornone ... that binds to and affect the same cell that secreted it (or the same type of neighboring cells).

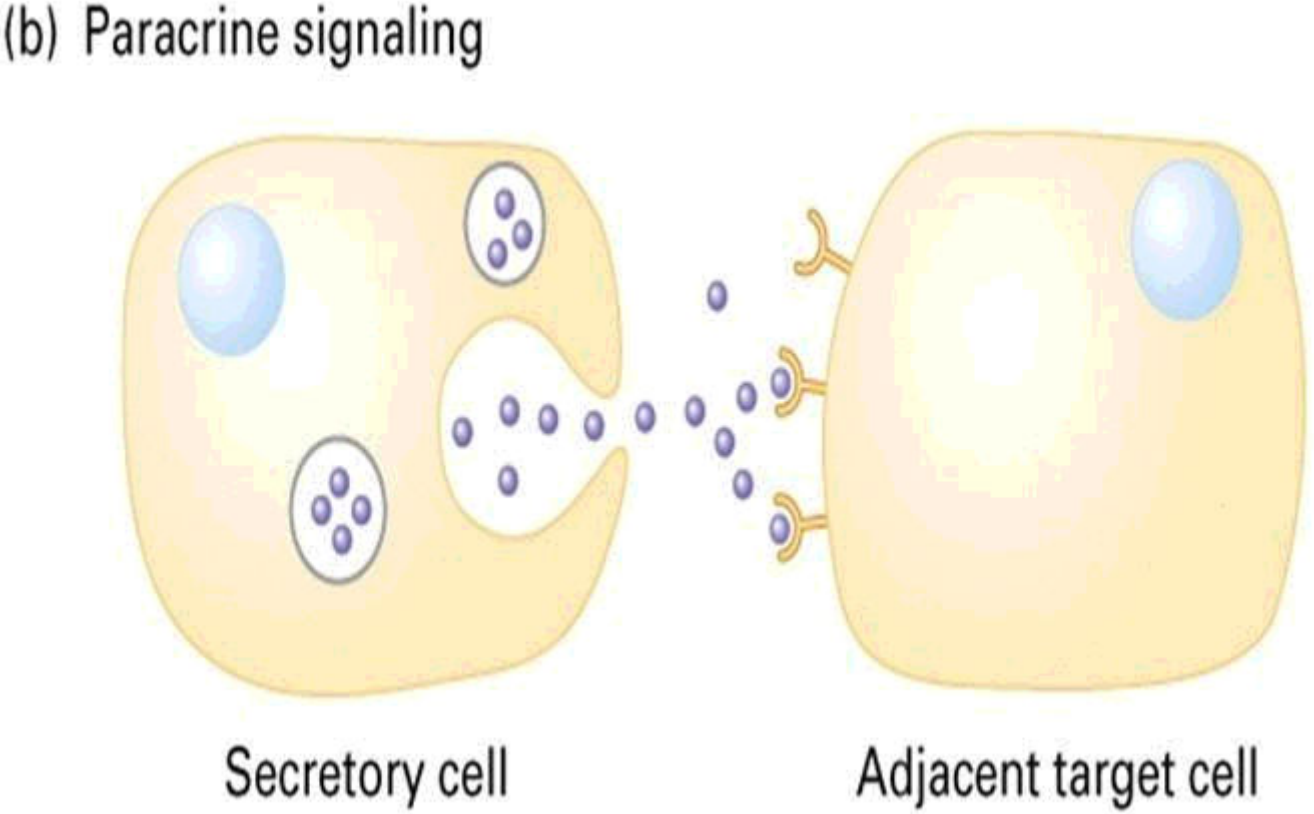
Basic theses

Intercellular signaling



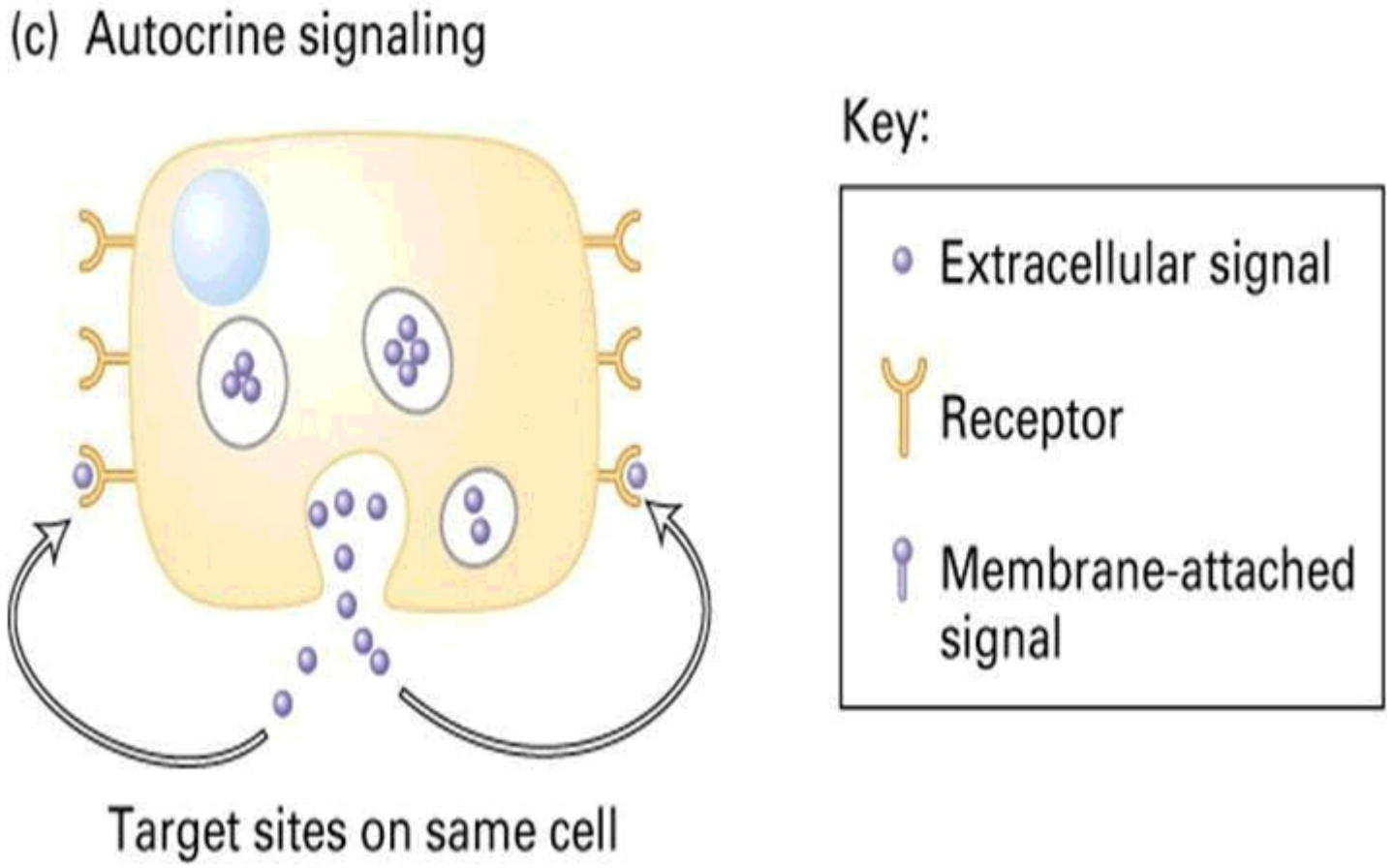
Basic theses

Intercellular signaling



Basic theses

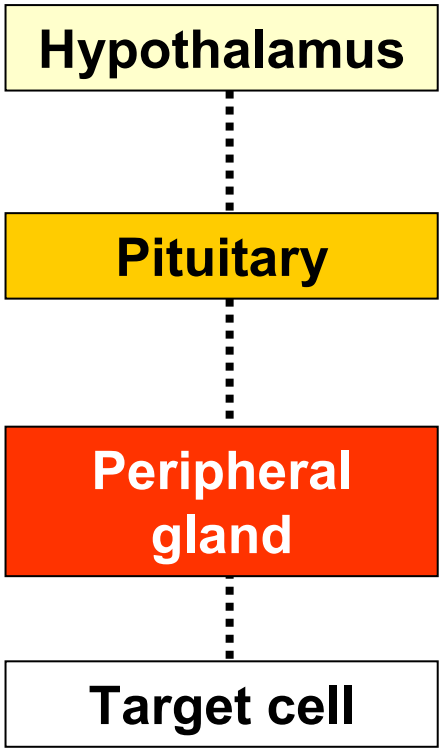
Intercellular signaling



Basic theses

Hierarchy of endocrine system

3 level signaling



---------- Liberins / statins

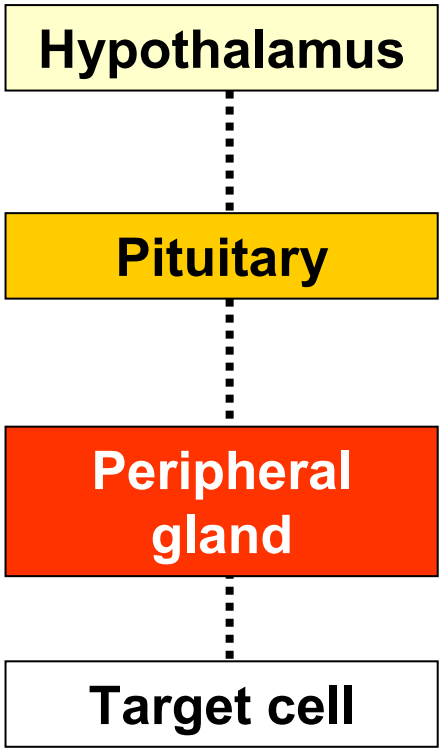
---------- Anterior pituitary hormones

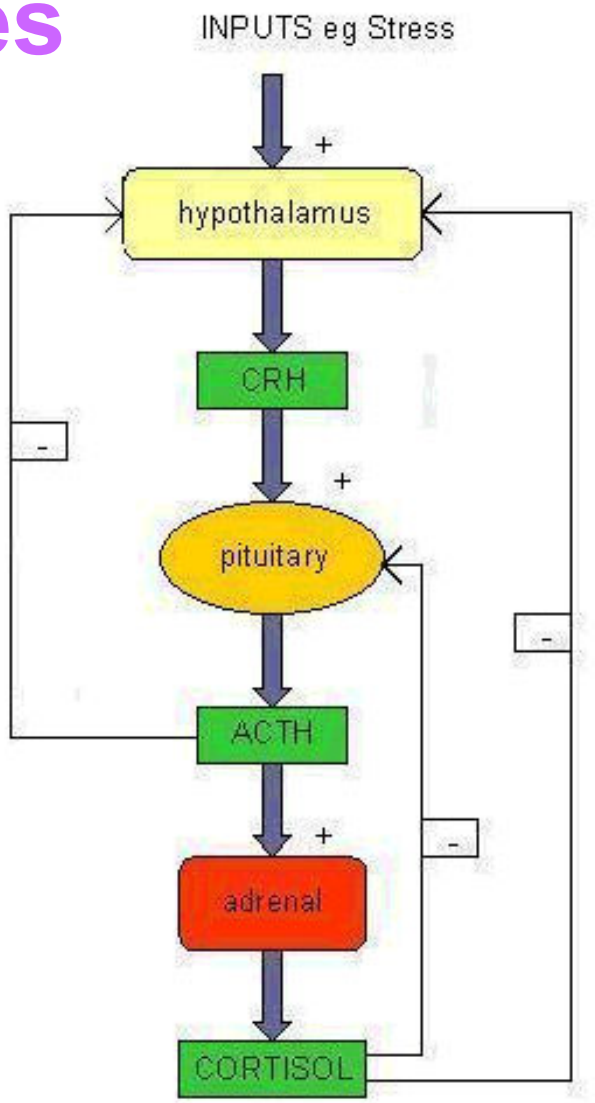
---------- Peripheral hormones

Basic theses

Negative feedback principles

- short / long feedback
- necessary for stability of system





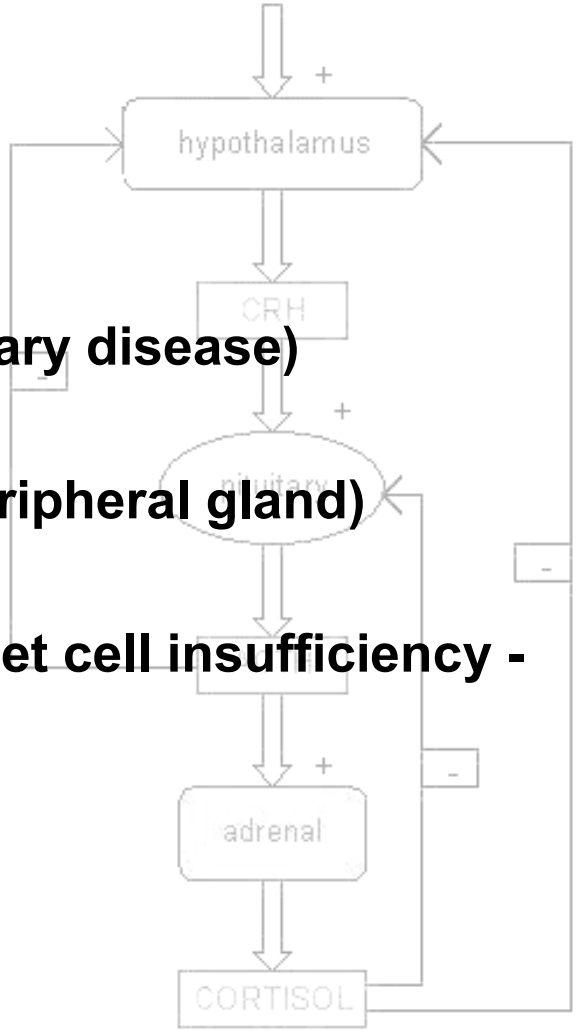
Manifestation of endocrine disorders

Endocrine disorders

(a) Central level (Hypothalamic / pituitary disease)

(b) Peripheral level (Dysfunction of peripheral gland)

(c) Receptor / postreceptor level (Target cell insufficiency - low sensitivity to hormone action)

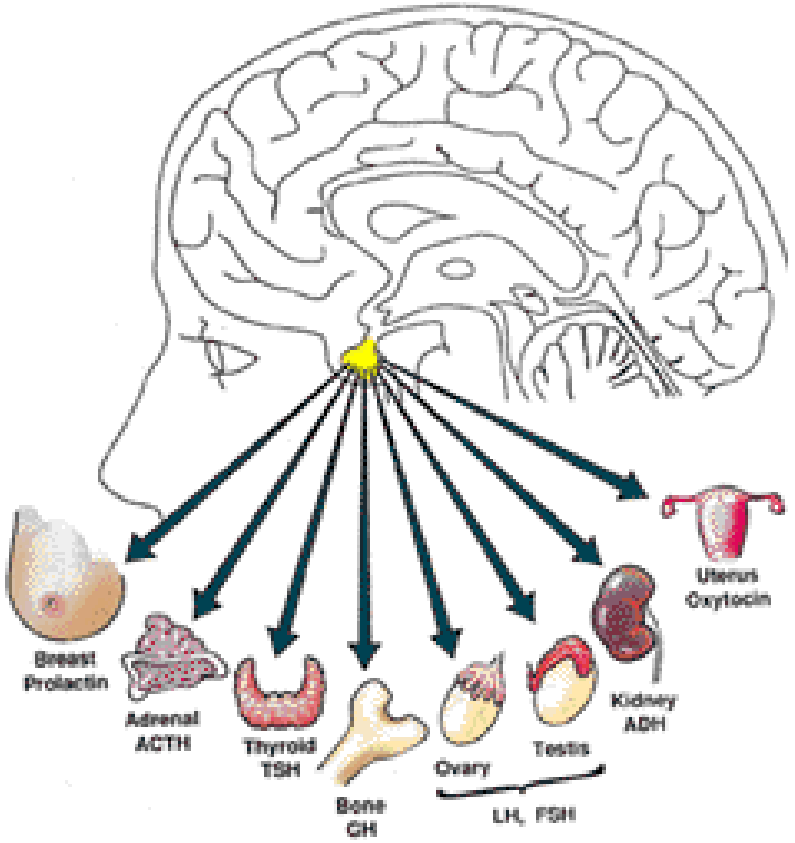


Manifestation of endocrine disorders

Central (pituitary, hypothalamic) disturbances project to peripheral syndromes

The endocrine manifestation of
central / peripheral hypothyreoidism
central / peripheral Cushing´s sy
central / peripheral hypogonadism
etc.
have the same features.

The adjustment is based on
- laboratory differences
- eventually local signs of tumour (visus, headache ...).



Manifestation of endocrine disorders

Endocrine disorders

(1) Primary ... dysfunction of peripheral gland
(2) Secondary ... usually pituitary dysfunction projected to peripheral gland
(3) Tertially ... rarely used term for hypothalamic dysfunction

Note: Not all peripheral glands are regulated from pituitary gland:
- Secondary hyperaldosteronism ... = response of adrenal cortex to rennin hyperactivity.
- Secondary hyperparathyroidism ... = response of PTH to low plasma Ca^{2+}.

Manifestation of endocrine disorders

3 levels of endocrine disorders - the example of different types of hypothyroidism and plasma levels of hormones

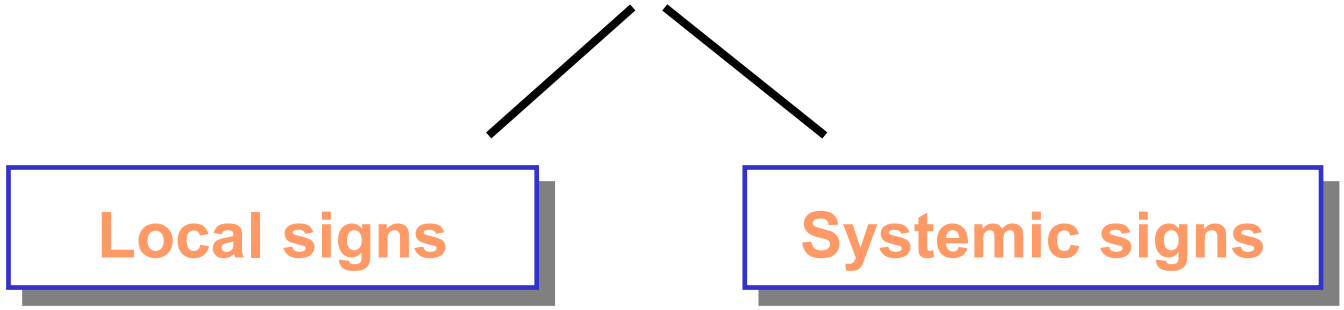
Hypothyroidism	fT4, fT3	TSH
Central (pituitary)	↓	↓
Peripheral (tryroid gland)	↓	↑
Peripheral resistance	↑	↑

Manifestation of endocrine disorders

Example: Hormonal concentrations of both central and peripheral Cushing´s syndrome

Cushing´s sy	P-cortisol	ACTH
Central (pituitary tumor)	↑	↑
Peripheral (adrenal cortex tumor / hyperplasia)	↑	↓

Manifestation of endocrine disorders



Depend on local damage or growth (tumour, nflammation...)
Non-specific symptoms

E.g.: goiter; signs of pituitary expansion - headache, visus alteration, ...

Depend on hormonal activity
Specific for concrete hyper / hypofunction

E.g.: hypertension, obesity, water loss, flush, hyperglycemia, ...

Manifestation of endocrine disorders

Paraneoplastic syndromes

= Clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease.

In a broad sense, these syndromes are collections of symptoms that result from substances (hormones, cytokines, growth factors) produced by the tumour, and they occur remotely from the tumour itself.

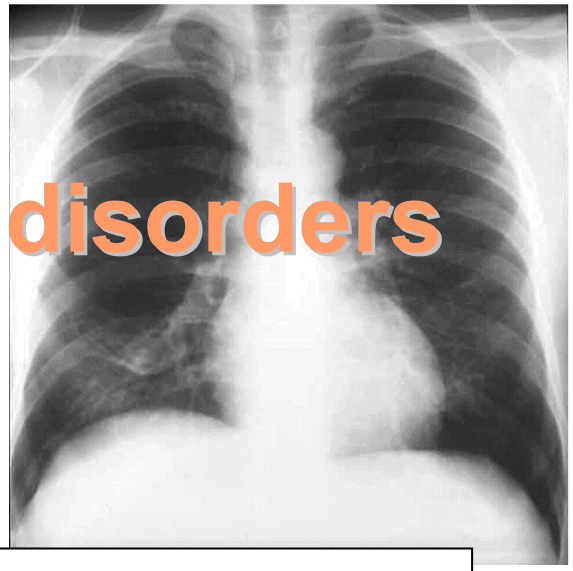
The symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, hematologic, gastrointestinal, renal, or miscellaneous in nature.

Manifestation of endocrine disorders

Paraneoplastic syndromes

Syndrome	Mediator
Cushing syndrome	ACTH, ACTH-like molekules
Hyponatremia	ADH
Hypercalcemia	PTHrP (PTH related peptide)
Hypoglycemia	IGF-1 (insulin-like growth factor)
Senzory neuropathy	many factors
Osteoporosis	IL-6, TNF (e.g. myeloma)

Manifestation of endocrine disorders



Paraneoplastic syndromes

Paraneoplastic Cushing syndrome

- The frequent type of paraneoplastic manifestation
- The ectopic production of ACTH or ACTH-like molecules from different tumours (often from small cell cancer of the lung)
- Very quick development (without typical “systemic” features of syndrome as obesity, moon face)
- Domination of metabolic disturbances - hypokalemia, hypertension
- The distinguish of pituitary and paraneoplastic Cushing syndrome is a crucial problem of diagnosis (tumour may be very small with the difficult localization)

Examination methods

Laboratory tests

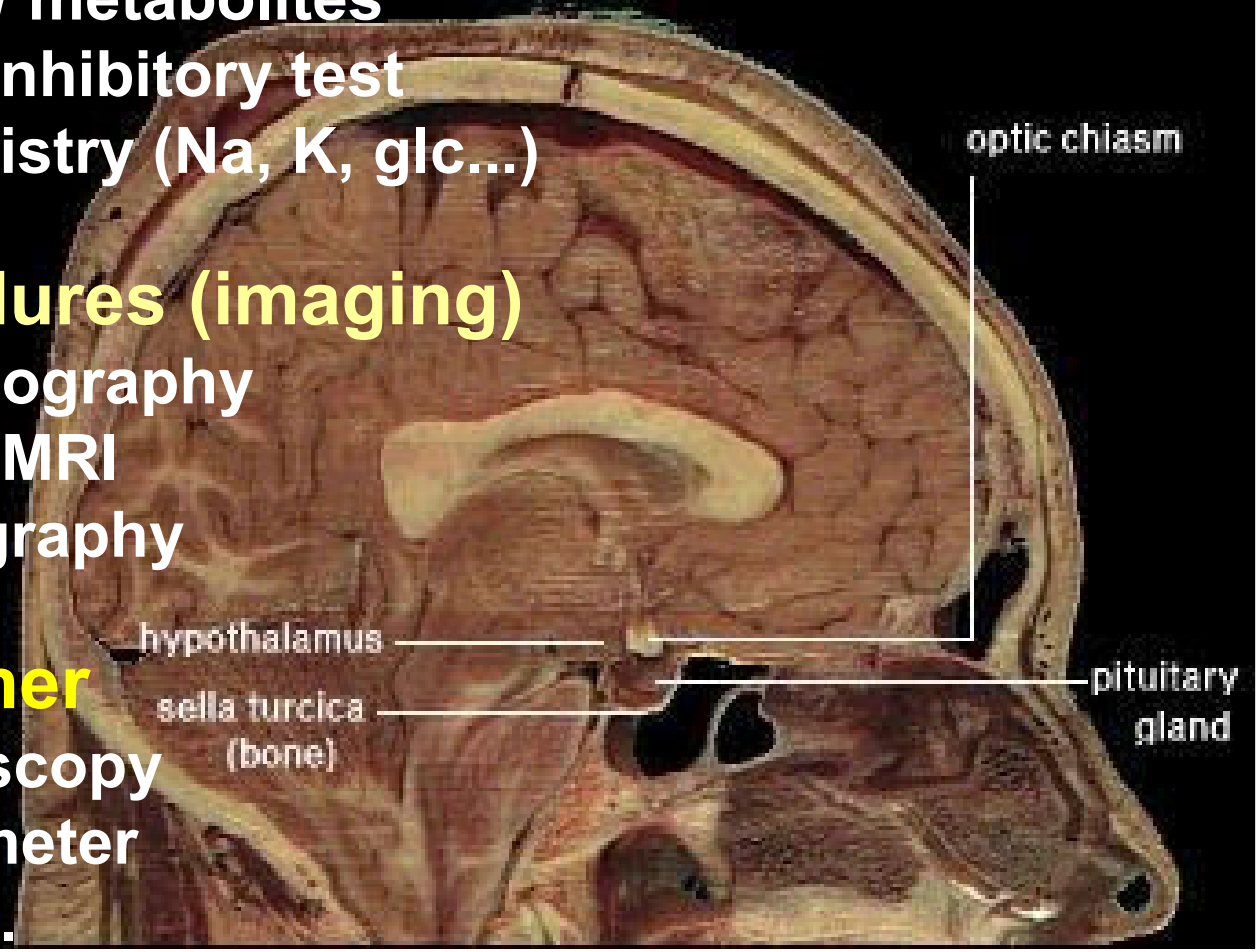
Plasma hormone levels
Hormone diurnal rhythm
U-hormones / metabolites
Stimulatory / inhibitory test
Standard biochemistry (Na, K, glc...)

Graphic procedures (imaging)

Ultrasonography
CT / MRI
Scintigraphy

Other

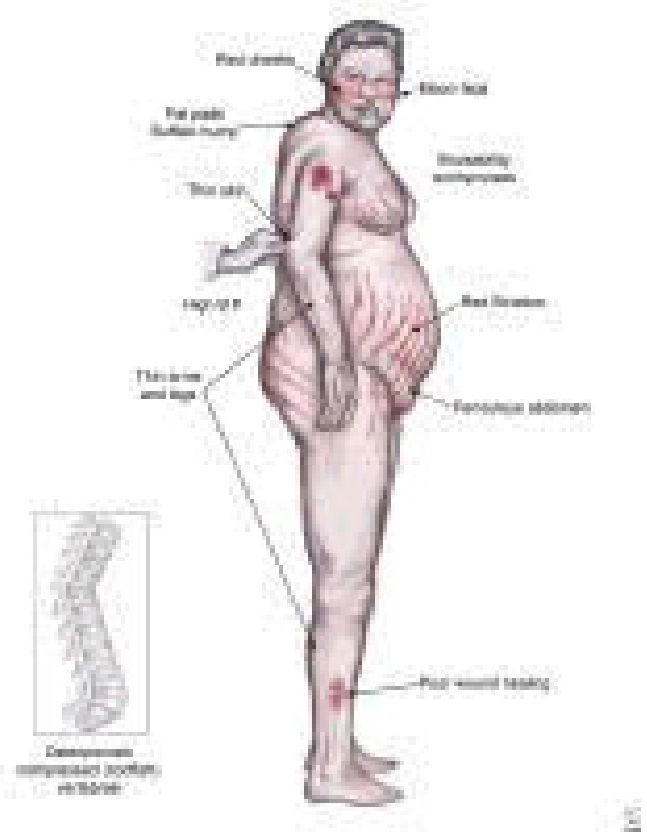
Endoscopy
Perimeter
...



Typical clinical features

Cushing´s syndrome

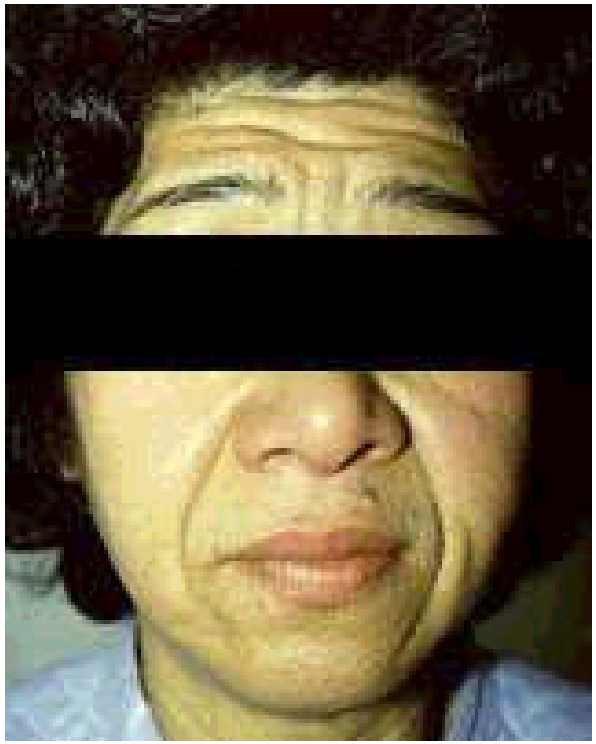
Moon face

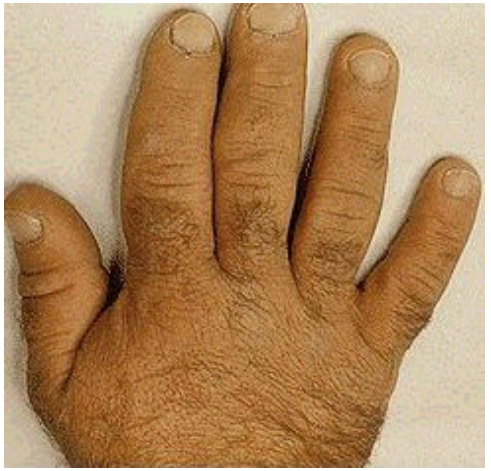


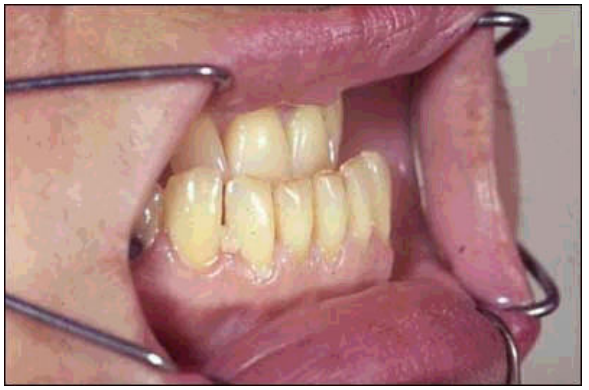
Facio-truncal obesity

Typical clinical features

Acromegaly

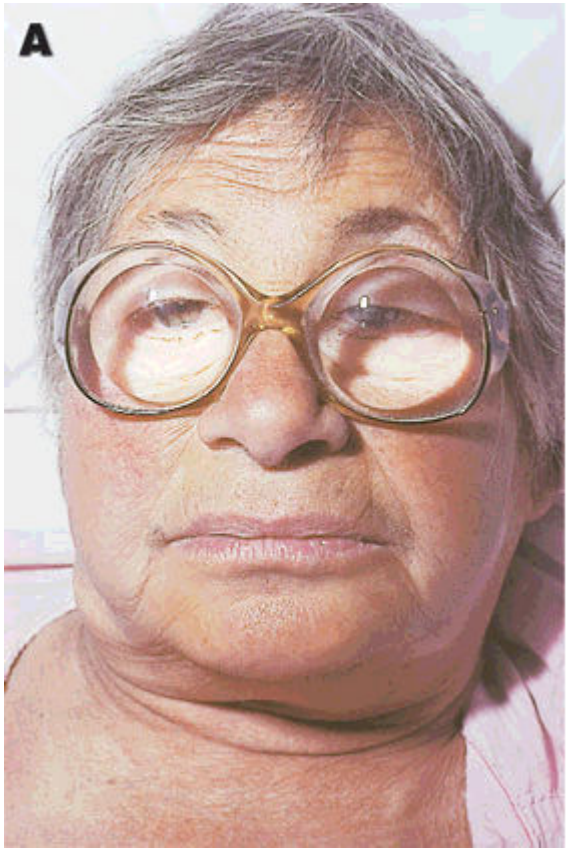


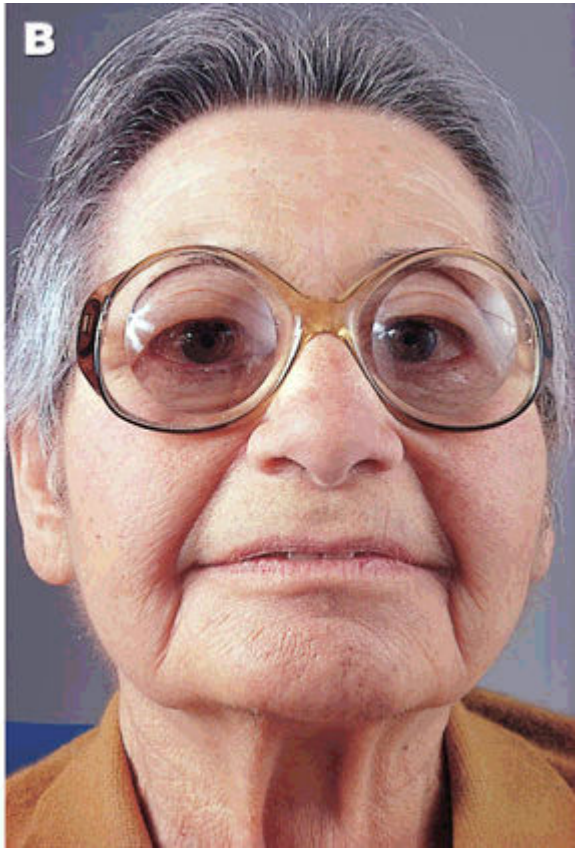


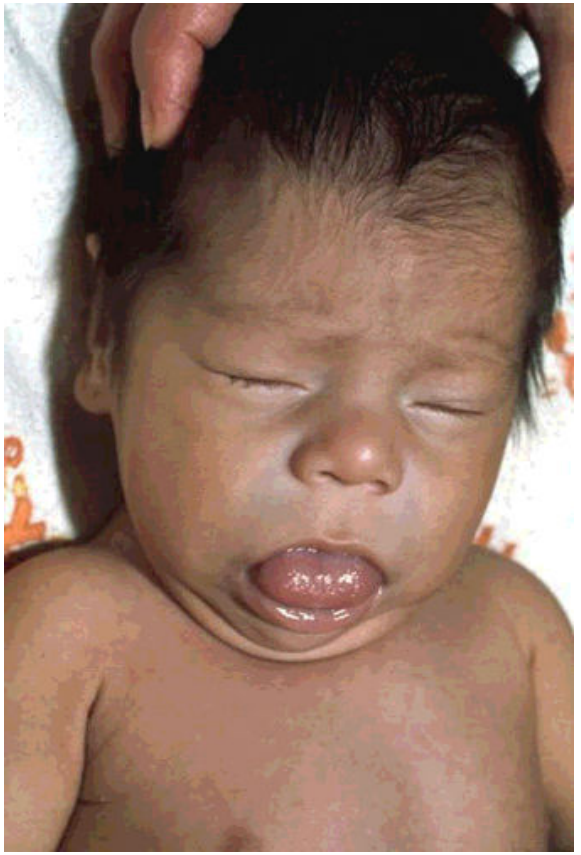


Typical clinical features

Hypothyroidism

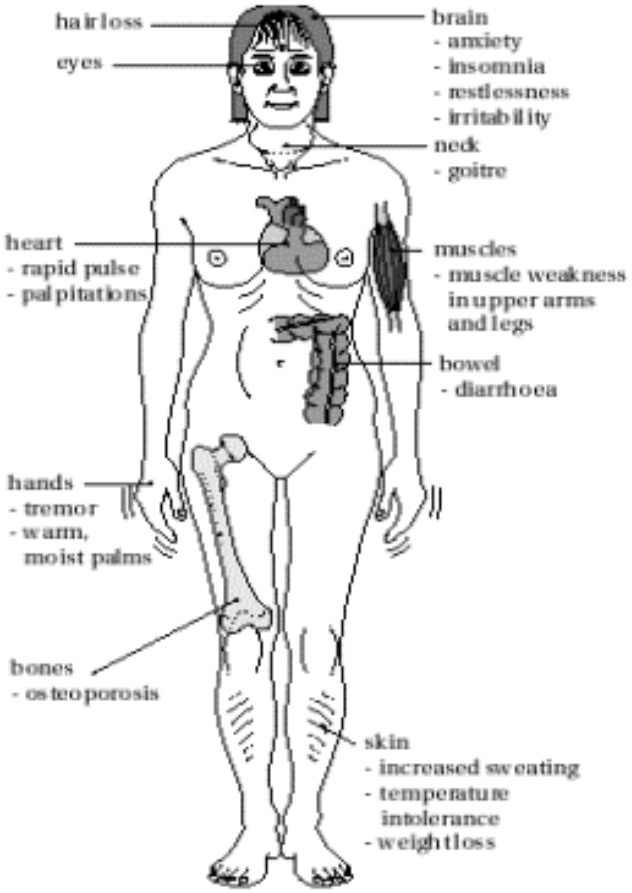


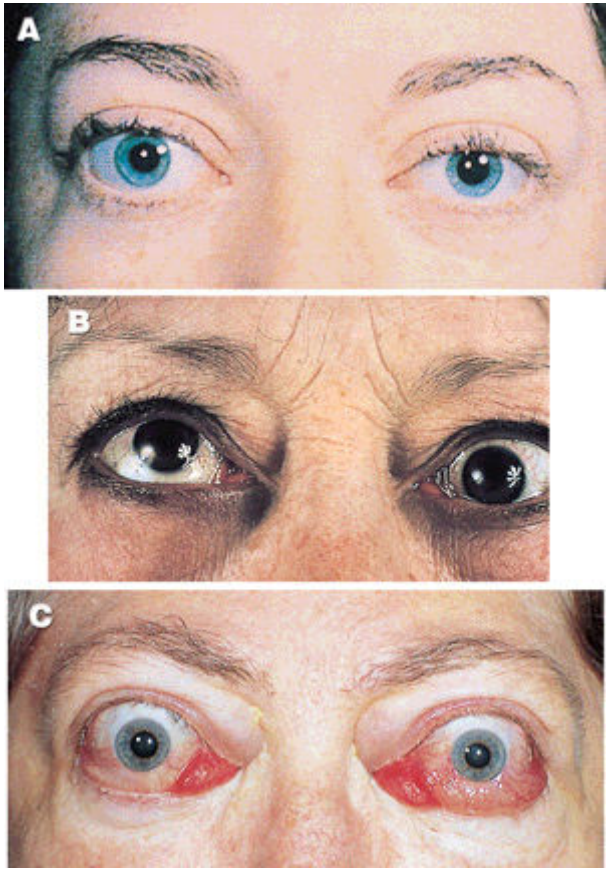




Typical clinical features

Hyperthyroidism

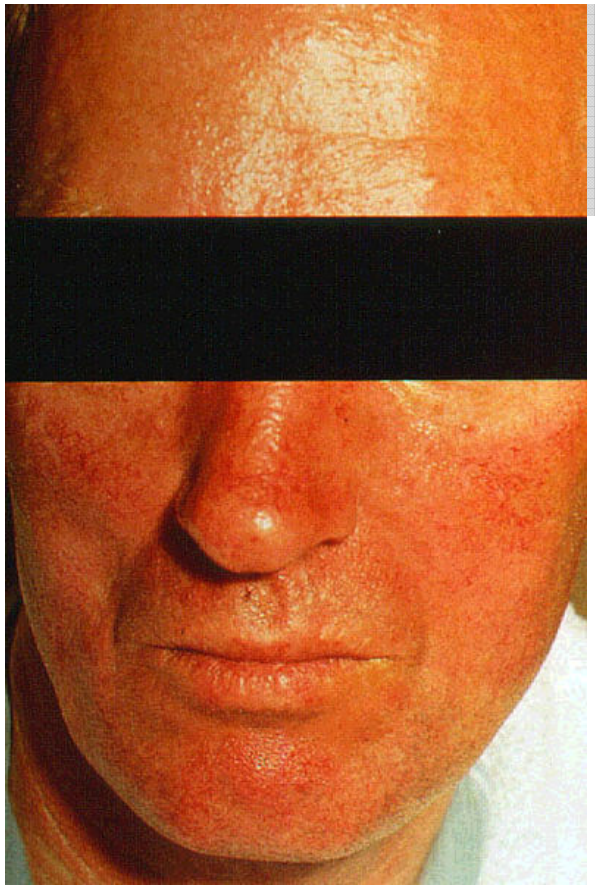




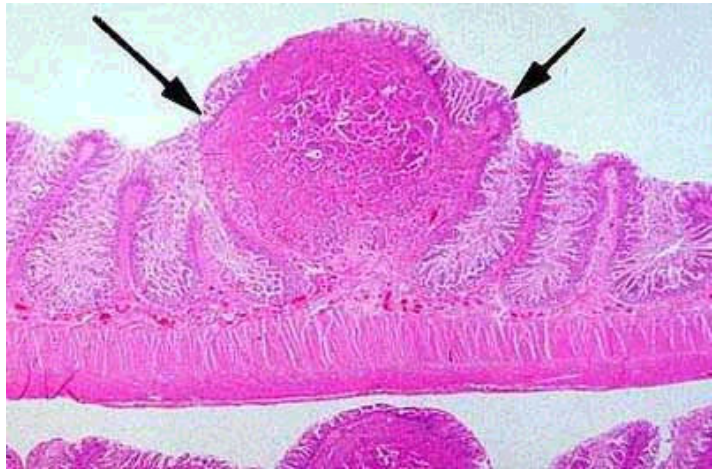
Graves ophthalmopathy

Typical clinical features

Flush syndrome (carcinoid syndrome)



The characteristic flushing rash on the face related to the release of hormones from the carcinoid tumour



Carcinoid tumour of the ileum

Basic biochemistry

(related to endocrinopathies)

Na^+, K^+	... aldosterone, cortisol, ADH
Ca^{2+}	... PTH, vitamin D, (calcitonin)
Glycaemia	... insulin, glucagon, cortisoids, catecholamines, STH ...
Cholesterol	... hypothyroidism, Cushing´s sy
Osmolarity / diuresis	... water / osmotic polyuria (diabetes insipidus, diabetes mellitus...)

Basic biochemistry

Water and Na^+/K^+ balance

- Aldosterone
- Cortisol
- Vasopressin (ADH)
- Natriuretic peptides (ANP, BNP, CNP)
- Insulin

Basic biochemistry

Differential diagnostics of polyuria

Water diuresis

- diabetes insipidus centralis
- diabetes insipidus renalis
- psychogenic polydipsia

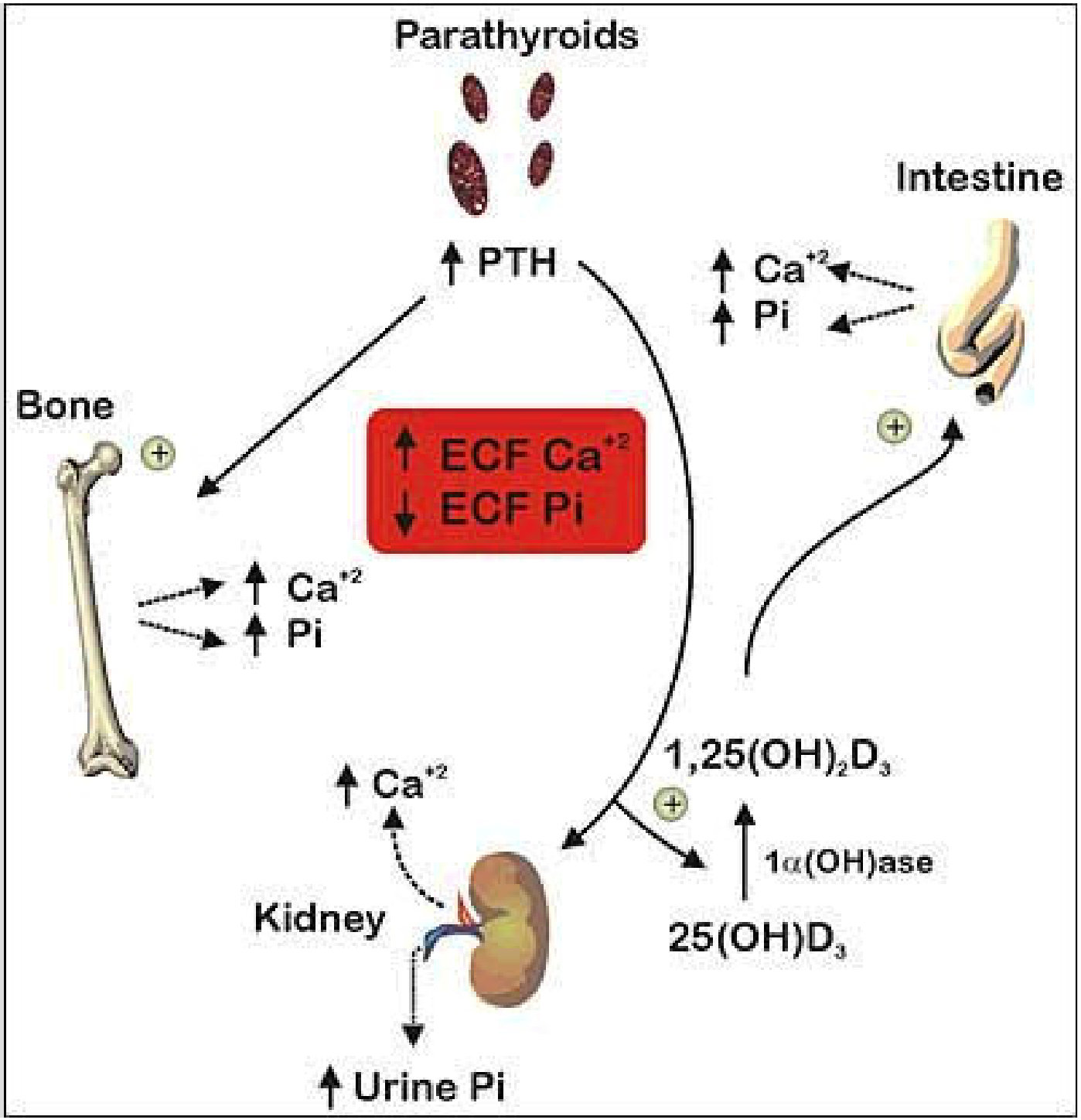
Osmotic diuresis

- glykosuria (DM decompensated)
- calciuria (hyper- PTH, bone metastases, sarcoidosis)
- natriuria (osmotic diuretics, Addison disease)

Ca^{2+}

Regulation:

- **PTH**
- **Vitamin D_3**
- **Calcitonin**



Basic biochemistry

$\downarrow Ca^{2+}$

Etiology:

- **Hypo-PTH ($\downarrow$PTH, $\downarrow Ca^{2+}$, $\uparrow HPO_4^{2-}$)**
- **Vitamin D_3 deficiency ($\uparrow$PTH, $\downarrow Ca^{2+}$, $\downarrow HPO_4^{2-}$)**
- **Pancreatitis**
- **Chronic kidney failure ($\uparrow$PTH, $\downarrow Ca^{2+}$, $\uparrow HPO_4^{2-}$)**
- **Malnutrition ($\uparrow$PTH, low together with Mg^{++})**

Basic biochemistry

↑Ca^{2+}

Etiology:

- **Primary hyperparathyreosis (↑ PTH, ↑Ca^{2+}, ↓HPO_4^{2-})**
- **Vit. D_3 intoxication (↓PTH, ↑Ca^{2+}, ↑HPO_4^{2-})**
- **Adrenal cortex insufficiency**
  (cortisol blocks bowel resorption of Ca^{2+})
- **Malignancy (breast cancer, bronchogenic ca, myeloma)**
  (PTHrP, IL-6 or other cytokine production)
- **Immobilization**
- **Sarcoidosis (production of 1,25-OH-D3 from macrophages**

Secondary hypertension

Endocrine hypertension is the most frequent type of secondary hypertension.

1. Primary hyperaldosteronism (4 % hypertonic patients !)
2. Cushing´s syndrome
3. pheochromocytoma ... possible paroxysmal character

Some other endocrine disorders are linked to a primary hypertension (acromegaly, primary hyper-PTH ...)

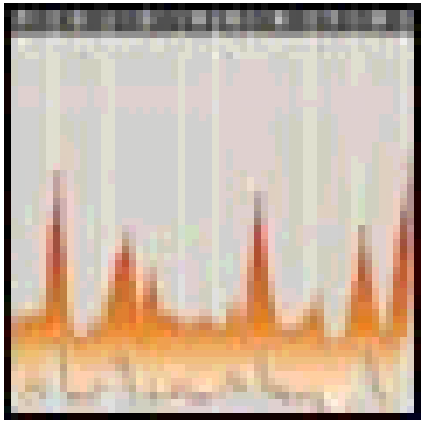
Differences from essentially hypertension:

1. manifestation in younger patients (not necessary)
2. quick development of heavy hypertension
3. low responsiveness on therapy
4. early complications (retinopathy, nephropathy, cardiac hypertrophy)

Secondary hypertension

Paroxysmal hypertension

- typical for 60 % patients with pheochromocytoma

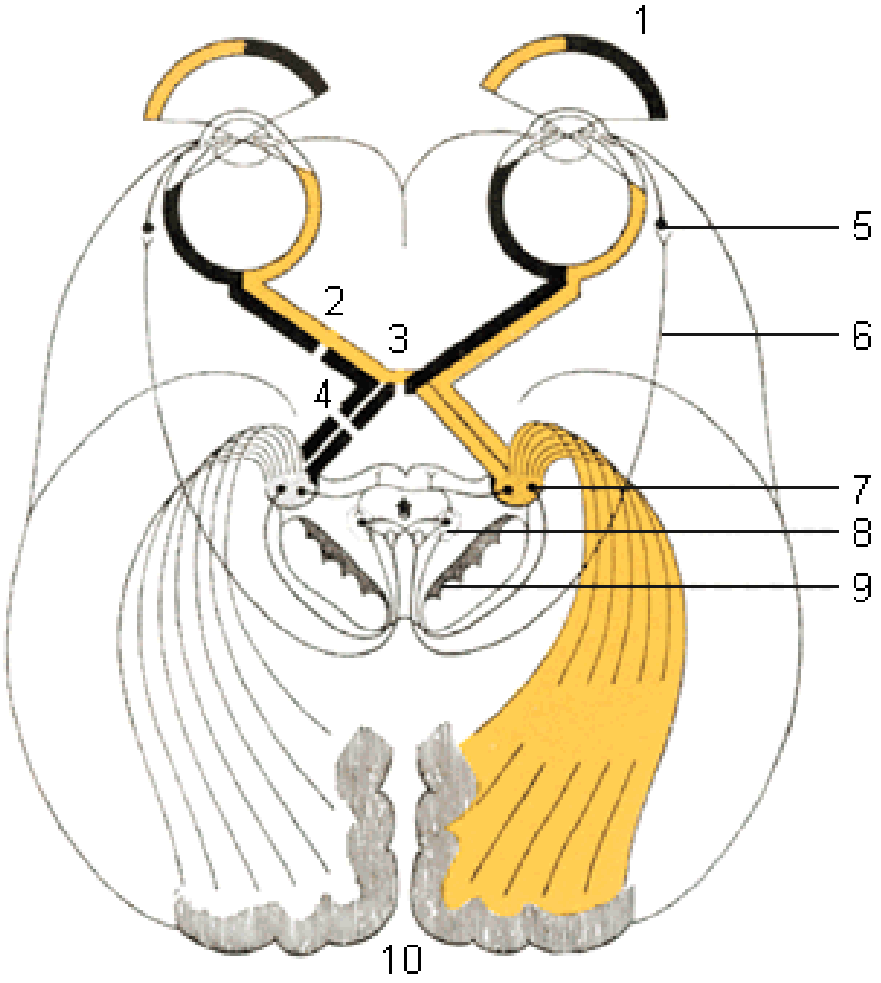


24 h monitoring of blood pressure showing peaks of pressure due to paroxysmal release of catecholamines.

Perimeter

Near contact of pituitary tumours and optical nerve (chiasma n. optici)

Visus alteration
- **vision out of focus**
- **bitemporal hemianopsia**
- **amaurosis**



Hormones

Examination approach

Basal hormonal concentrations

1. Basal plasma levels (one-time examination)
2. Diurnal dynamics of hormone concentrations (e.g. cortisol)
3. Other hormonal cycles (e.g. menstrual phase dynamics)
4. Urinary output
5. Hormonal metabolites - plasma, urine (e.g. C-peptide)
6. Indirect evaluation - measurement of a metabolic response
   (ADH ... diuresis, insulin ... glycaemia etc.)

Functional tests

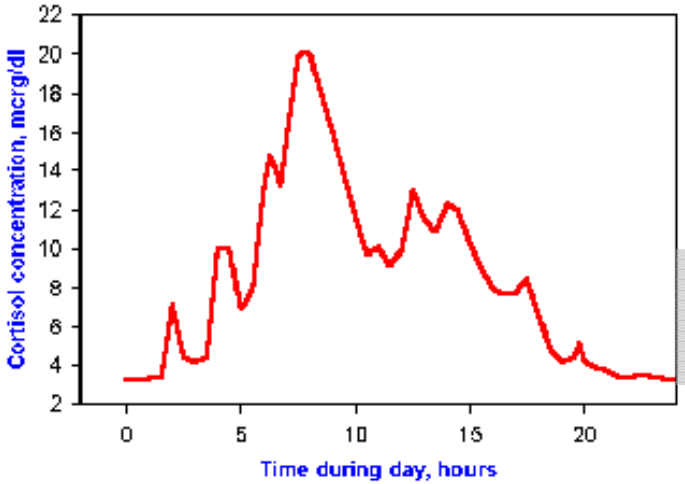
1. Inhibitory tests
2. Stimulatory tests

Hormones

Plasma levels and diurnal variability

One-time blood sample collection is a sufficient procedure for a majority of hormones.

Hormones with diurnal variability - e.g. cortisol, and growth hormone - claim repeating measurement during 24 h period (e.g. every 4 h or every 6 h)



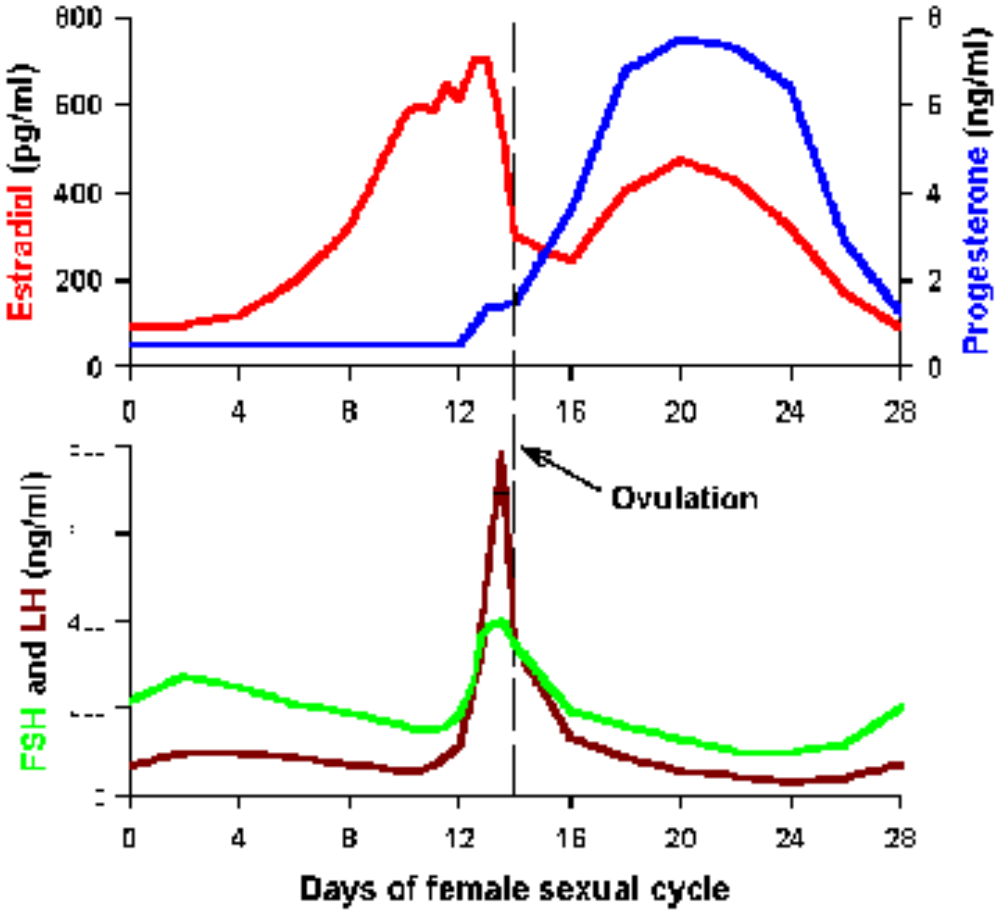
P-cortisol: Physiological diurnal variability with typical overnight decrease more than 50%

Hormones

Other hormonal cycles

Menstrual cycle is related to cyclic changes of LH, FSH, estrogens and progesteron.

The measurement of these hormonal levels - timing of blood collection - must respect a phase of cycle.

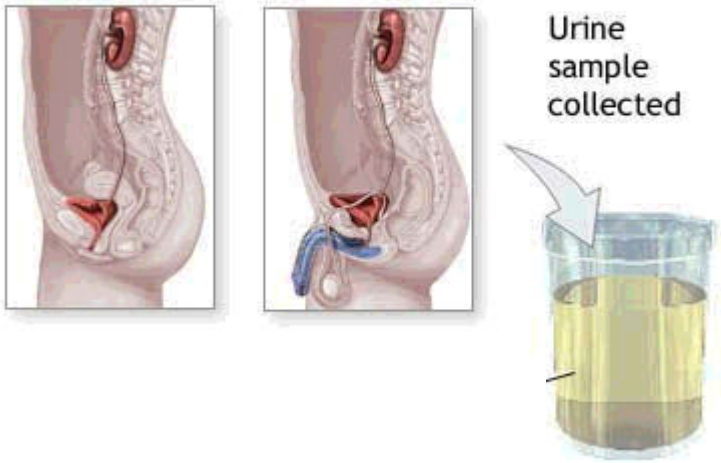


Hormones

Urinary concentrations

24-h collection of urine

Alternative method for hormones with diurnal dynamics (cortisol, aldosterone) or pulsate secretion (catecholamines).

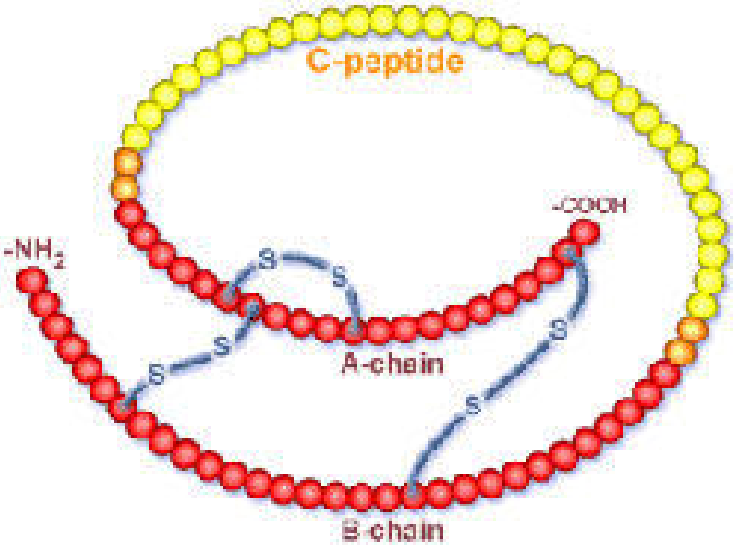


Hormones

Plasma or urinary metabolits

C peptide

Co-product of insulin creating Plasma levels much higher than that of insulin due to longer half-life



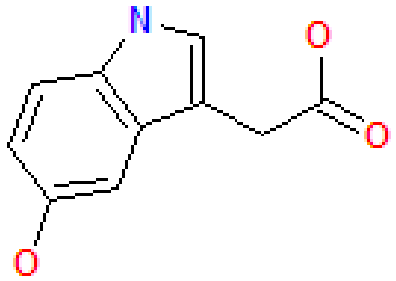
C peptide concentrations reflect insulin production and give the same information as insulin levels.

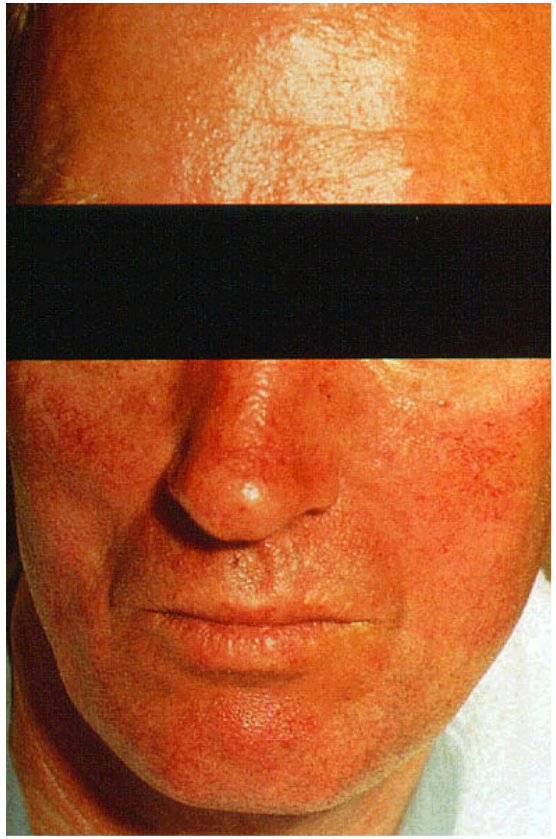
Hormones

Plasma or urinary metabolits

5-HIAA (hydroxyindole acetic acid)

Serotonin metabolite
Urinary excretion measurement in patients with suspicious carcinoid.





Functional tests

Basal hormonal concentration very often don´t allow to establish a diagnosis of hypo- or hyperfunction.

Suspecting hypofunction → Stimulatory tests
= quantification of functional reserve of endocrine gland

Suspecting hyperfunction → Inhibitory tests
= quantification of responsibility of endocrine gland to inhibitory factors

Principles:

- **negative feedback inhibition / stimulation**
- **direct stimulation / inhibition**

Stimulatory tests of pituitary function

Insulin hypoglycemia test

i.v. aplic. insulin (O,1 IU/kg)
to cause hypoglycaemia (2 mmol / L)
stimulation of ACTH + STH secretion
Normal response: STH > 10 ng/mL, P-cortisol > 18 μg / dL
Contra-indications: diabetes mellitus, morbus Addison

Stimulatory tests of pituitary function

Methyrapone (Methopyrone) test

Blocade of cortisol synthesis by metyrapone
negative feedback elevation of ACTH secretion
Secondary elevation of adrenal cortisosteroids (11-deoxycortisol) in plasma
normal: 11-deoxycorticosteroids > 7 μg / dL

Levodopa test

Physiological elevation of STH secretion in pituitary
Normal: STH > 6 ng /mL
(Test is safer than hypoglycemia test)

Stimulatory tests of pituitary function

Clonidin test (modified)

Princip: clonidin (α_2-agonista) stimuluje produkci STH

Postup:
Clonidin 100 μg/m^2 (tj. obvykle Catapressan depot 0,25 mg)
měření STH v čase 0, + 60 a + 90 min.
fyziologicky STH > 10 μg/l

Pozn.:
U hypopituitarismu je vzestup méně výrazný
U Laronova typu je hyperstimulace (vzestup o více než 10 μg/l)

Stimulatory tests of pituitary function

Arginin infusion test

Physiol.: elevation of STH secretion in pituitary
normal: GH > 6 ng / mL

TRH test

i.v. aplication of TRH will evoke TSH and PRL response

GnRH test

i.v. aplication of GnRH (LHRH) stimulates LH elevation (+ slow FSH elevation)

CRH test

i.v. aplication of corticoliberin stimulates POMC response
+ combination with sinus petrosus inferior cathetrization

Inhibitory tests of pituitary function

Glukózový test

Princip:
Hyperglykémie suprimuje sekreci STH a ACTH

Postup:
Na lačno per os 100 g glukózy
Měření STH v čase 0, + 30, +60, +90 min.
fyziologicky STH klesá pod 1 μmol/l

Inhibitory tests of pituitary function

Dopaminergic drugs test

Dopamin = prolactin inhibitory factor

Physiol. inhibition of PRL (+ STH) secretion

Inhibitory tests of pituitary function

Dexamethazone test

Dexamenthazone = synthetic glucocorticoid

Principle: Peroral administration of DEX via negative feedback inhibits ACTH and cortisol production

Basic test variants:
- overnight test (onetime application of 1 or 2 mg p.o.)
- 7-day test (2 days basal cortisol levels, 2 days DEX 2 mg/day, 2 days DEX 8 mg/day)

Local hormonal concentrations

Venous catheterization with selective blood sample collection

1. Catheterization of sinus petrosus inferior

Sinus p.i. = venous drenage of pituitary gland
Principle: Local concentration of ACTH (before and after stimulation with CRH) may distinguish pituitary and paraneoplastic Cushing syndrome)

2. Catheterization of vena cava inferior

Step by step blood sample collection from abdom. veins
Principle: Localization of small (CT/MRI undetectable) abdominal tumour (carcinoid, insulinoma etc.) due to high local concentration of hormone.

Tumour markers in endocrinology

Thyroglobulin (Tg), anti-Tg antibodies

Markers of non-medullar thyroid carcinoma.

Useless as a screening markers (the only indication - systemic metastases of unknown origin)

Higher sensitivity after total thyroidectomy for cancer - for diagnostic of rest thyroid tissue or tumour relapses

CEA (carcinoembryonic antigen)

Marker of non-medullar thyroid carcinoma (and ather malignancy – e.g. colorectal ca)

Diagnostic usage in combination with Tg and anti-Tg Ab

Calcitonin, procalcitonin

Hormonal product and diagnostic marker of medullar thyroid carcinoma (lower sensitivity that Tg for non-medullar thyroid ca)

Auto-antibodies

Endokrinní systém se (spolu s pojivem) vyznačuje nejvyšší frekvencí autoimunitních onemocnění.

Na rozdíl od chorob pojiva se v endokrinologii jedná o protilátky orgánově specifické.

Obě nejčastější endokrinopatie (chronická lymfocytární tyreoiditida a GB choroba) mají autoimunitní podklad.

Autoimunitní tyreopatie jsou 4-8 x častější u žen, u ostatních autoimunitních endokrinopatií tato disproporce není tak výrazná.

Buněčná autoimunita je v patogenezi těchto onemocnění rozhodující, nicméně diagnostika se opírá o markery humorální imunity (autoprotilátky) - Jejich patogenetická úloha je přitom minimální (uvažuje se dokonce o jejich ochranném efektu před působením cytotoxických lymfocytů obsazením cílových antigenů)

Auto-antibodies

Auto-antibodies related to thyroid gland

auto-Ab against TSH-Rec.

váží se na různé epitopy, podle toho:

→ růst strumy

→ stimulace ... Graves-Basedowova n.

→ inhibice ...hypotyreozní idiopat. myxedém

auto-Ab antimikrosomální = proti TPO (tyreoid. peroxidáze)

... chronická lymfocytární tyreoiditis

auto-Ab proti Tg (tyreoglobulinu) ... nejsou patogenetické

auto-Ab proti T_3 ... nacházeny u 40% autoimunních thyreoiditid

Imaging methods

Indications:

1. **Localization of endocrine active tumours, hyperplasia, ectopic hormonal production**
2. **Evaluation of systemic complications**

Native X-ray exams

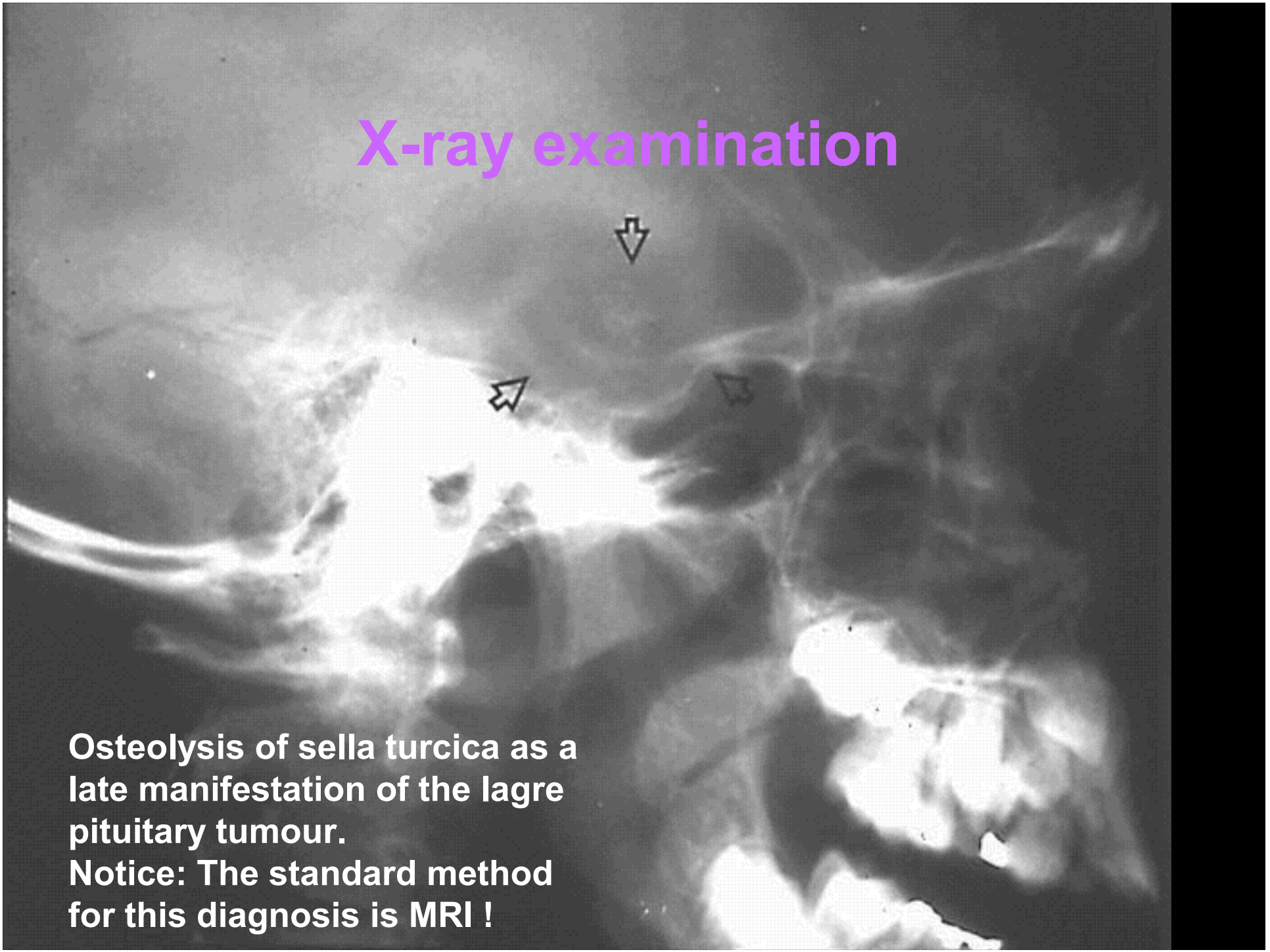
Ultrasonography

CT / MRI

Scintigraphy

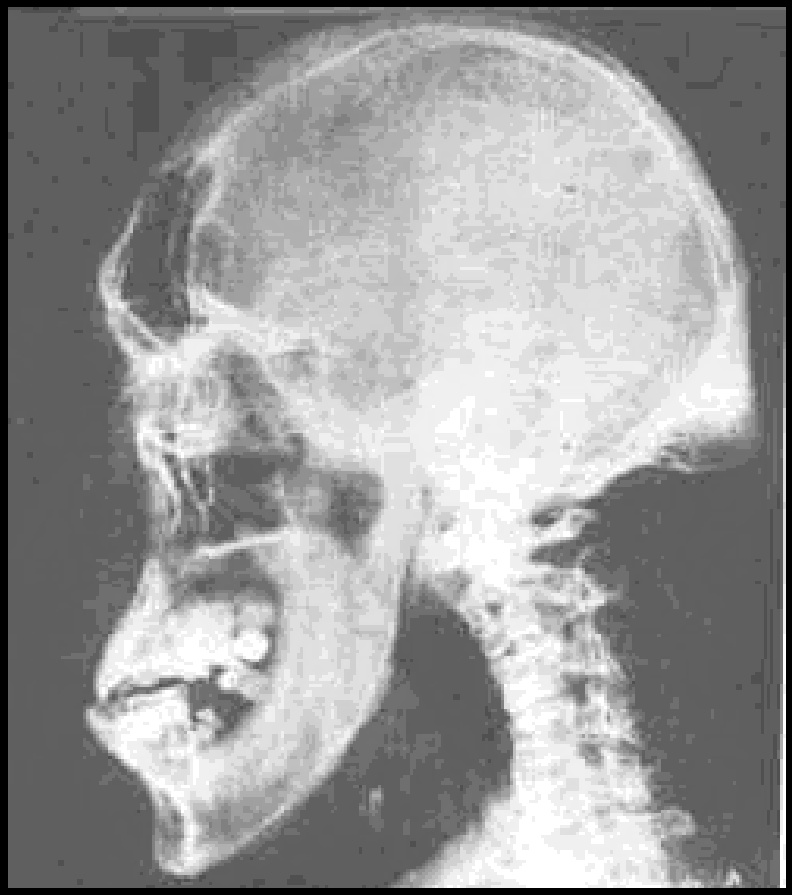
Angiography

X-ray examination



Osteolysis of sella turcica as a late manifestation of the lagre pituitary tumour.
Notice: The standard method for this diagnosis is MRI !

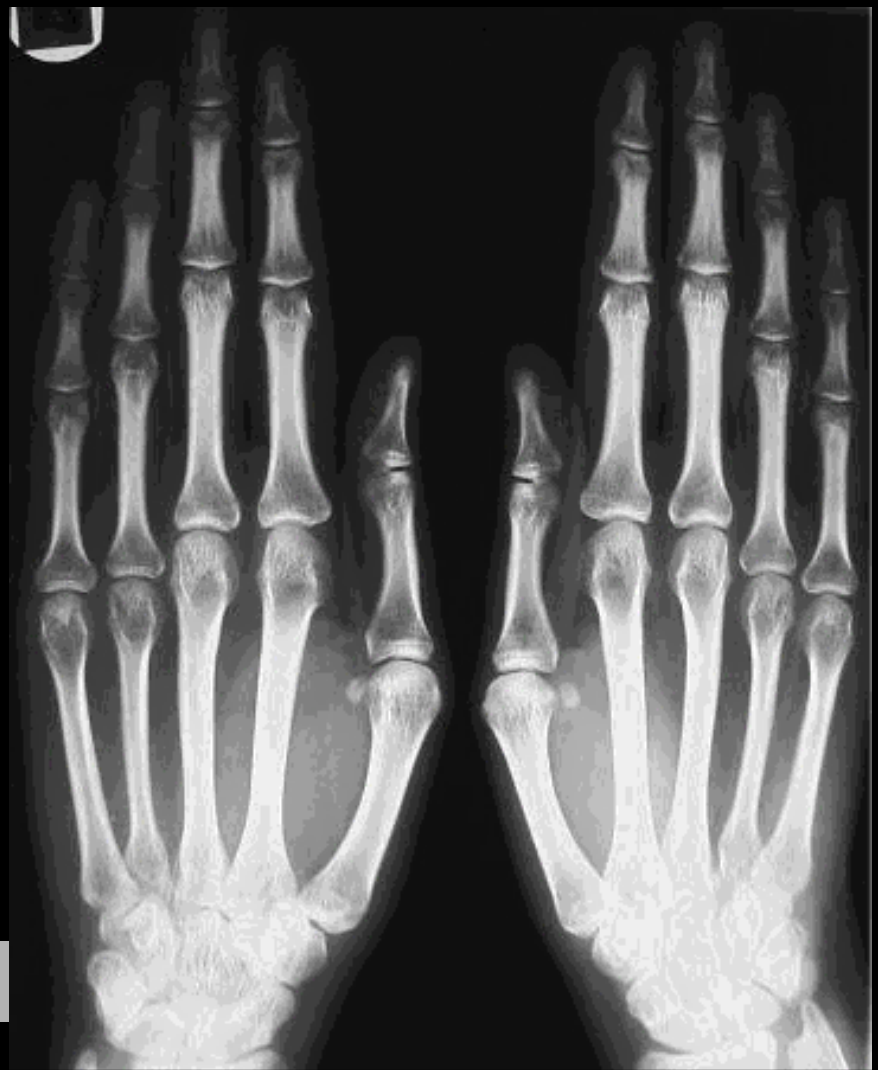
X-ray examination



Acromegaly

X-ray examination

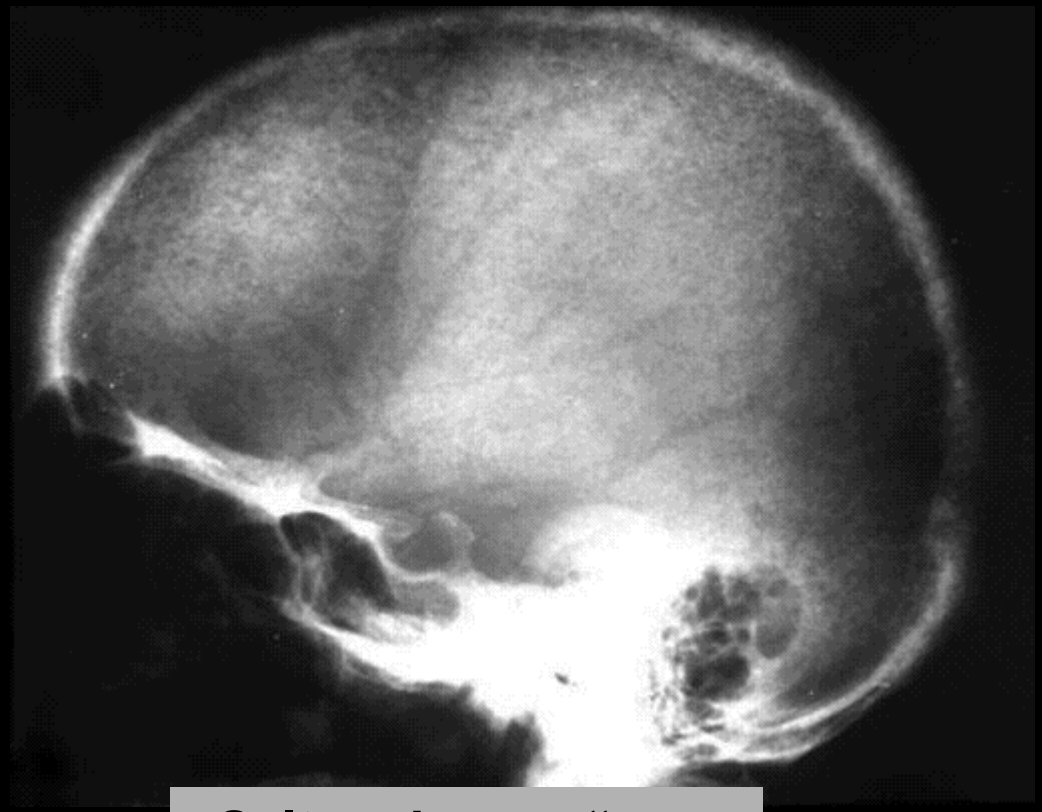
Acromegaly



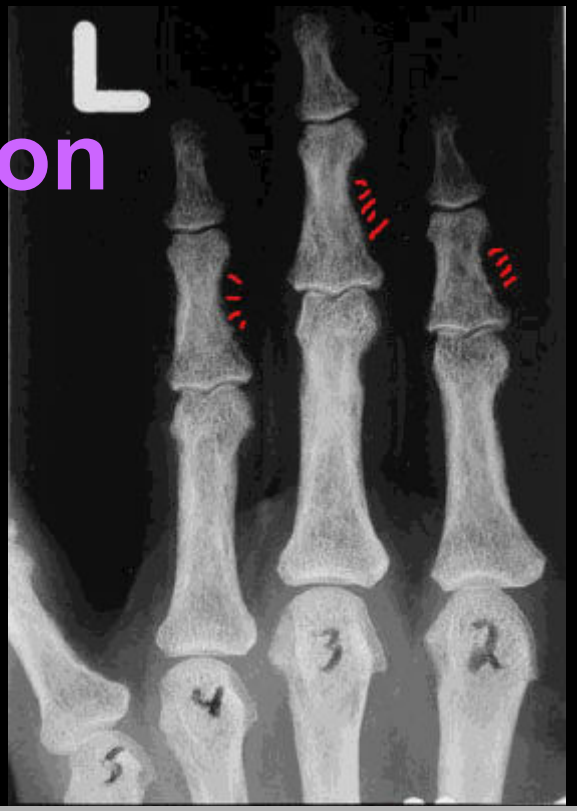
Arachnodactylia

X-ray examination

Hyper-PTH



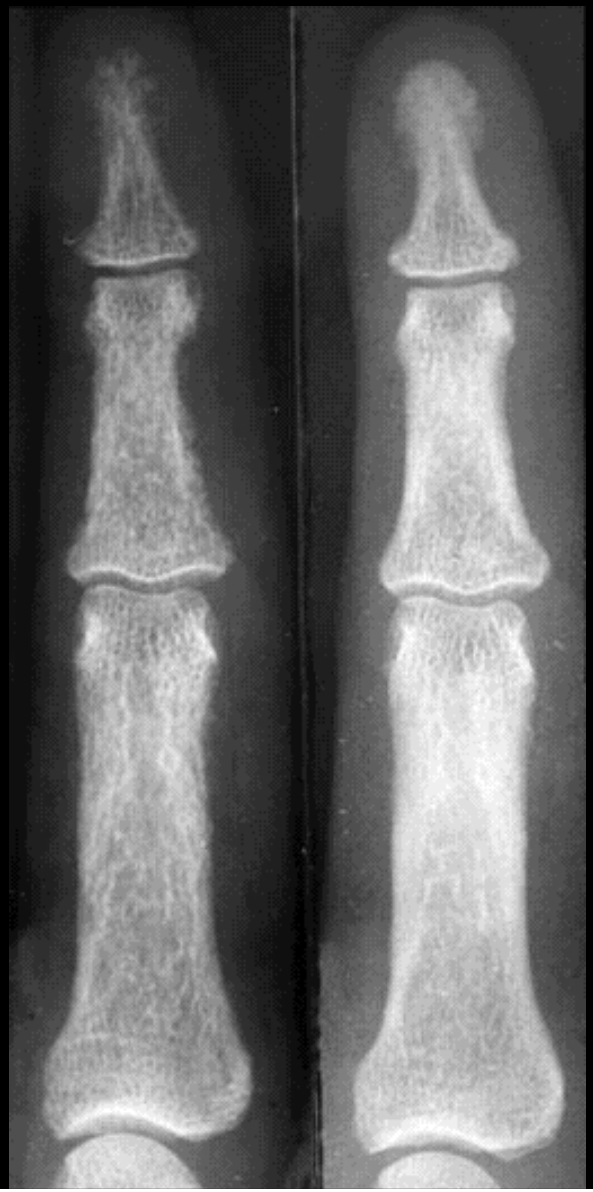
„Salt and peper“ scull



Increased parathyroid activity leading to characteristic subperiosteal resorption

X-ray examination

Hyper-PTH



The bone changes of the same finger after 6 months therapy of primary hyper-PTH.

Ultrasonography

Indications:

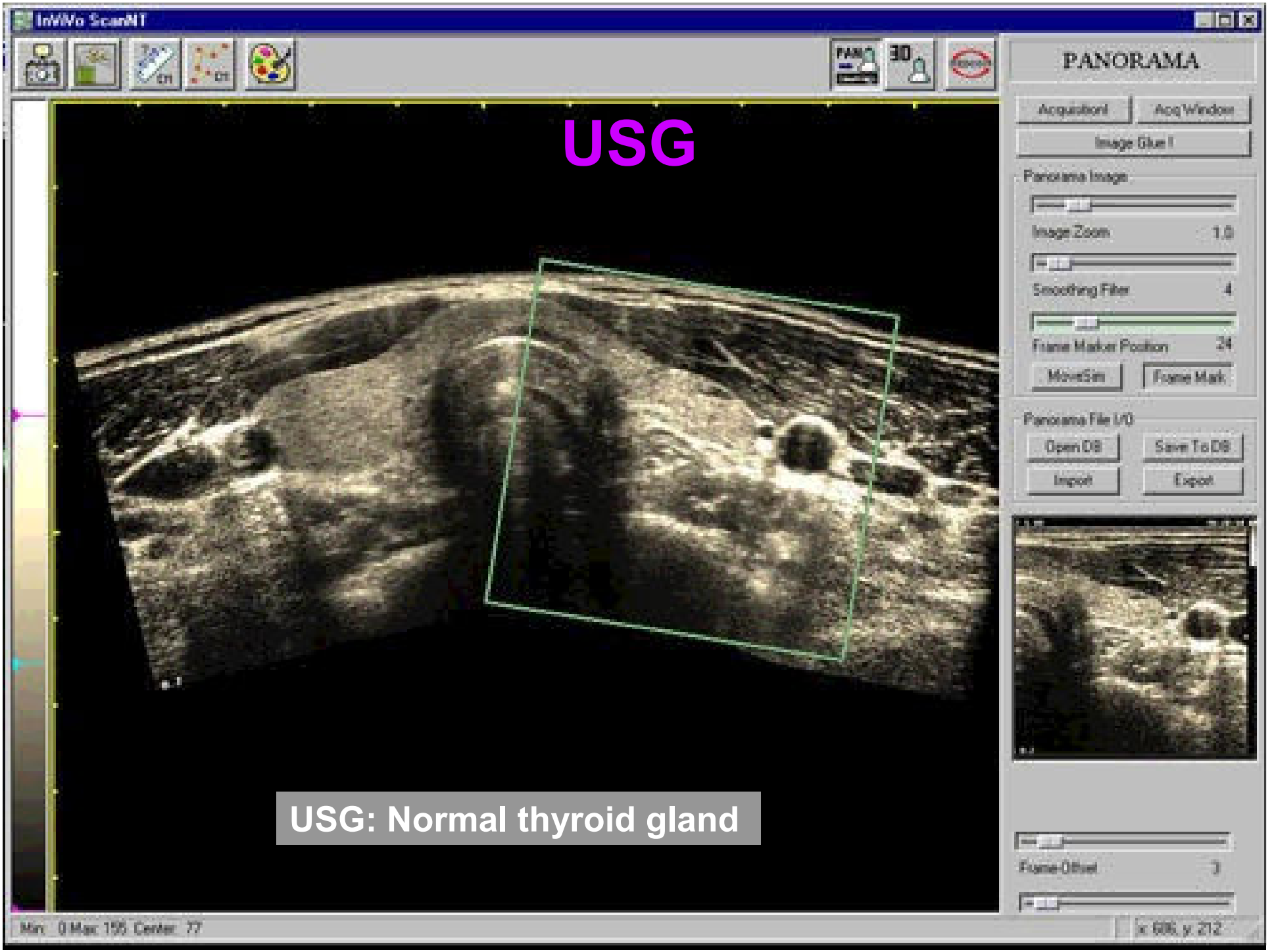
1. Thyroid gland, parathyroid glands disorders
   - basic imaging examination
2. Abdominal endocrinopathy (adrenal gland, endocrine pancreas)
   - orientation examination, replaced now with CT / MRI

Technics:

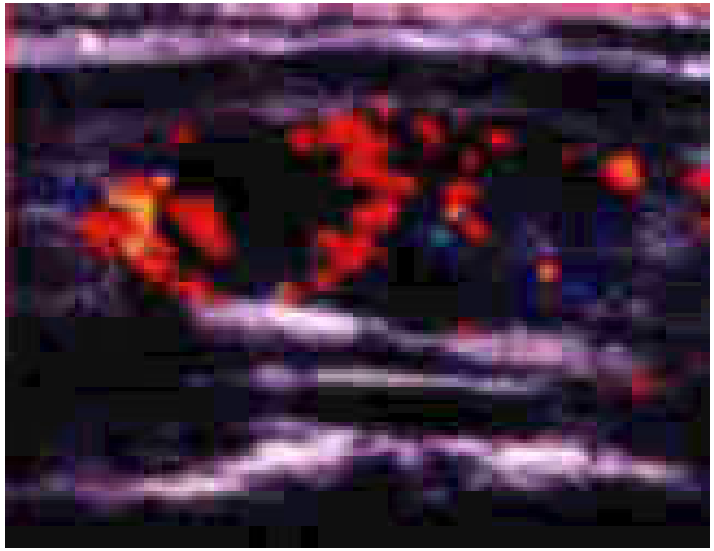
2D USG: Cystic changes and solid conditions as small as 3 to 5 mm can be detected.

Doppler USG: Blood-flow is present.

USG + Biopsy: USG guided removal of tissue samples


InVivo ScanNT
PANORAMA
Acquisition
Acq Window
Image Glue I
Panorama Image
Image Zoom
1.0
Smoothing Filter
4
Frame Marker Position
24
MoveSim
Frame Mark
Panorama File I/O
Open DB
Save To DB
Import
Export
Frame Offset
3
USG
USG: Normal thyroid gland
Min: 0 Max: 155 Center: 77
x: 686, y: 212

USG



Thyroid gland
Color USG showing blood flow (hirger perfussion typical e.g. for GB disease

CT / MRI

Computed Tomography (CT)
Magnetic Resonance Imaging (MRI)

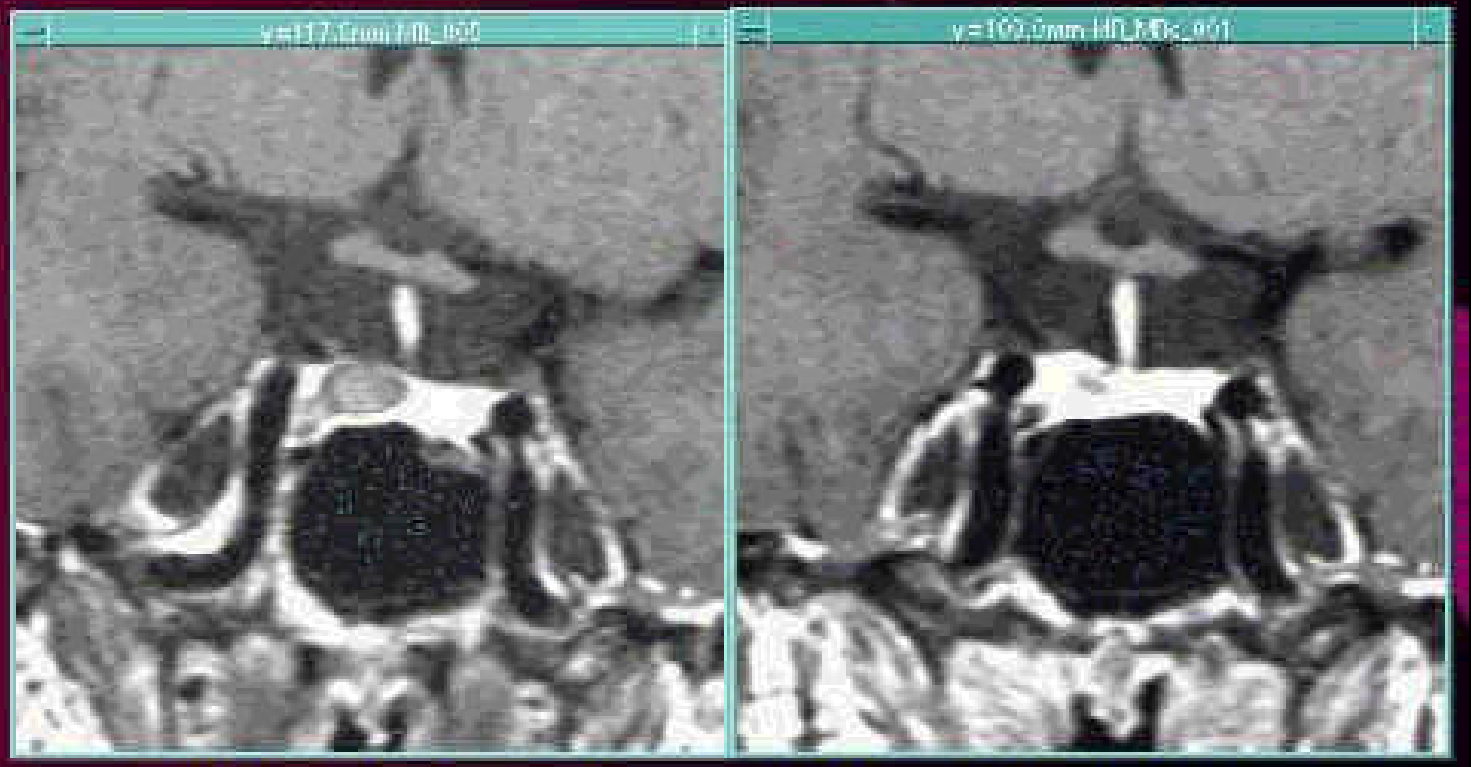
The better degree of contrast in the imaging than in USG.

The comparison of CT and MRI

CT advantages	MRI advantages
Lower cost Better availability Beter resolution of bone structures (e.g. osteolysis)	High resolution of vascular abnorm. (e.g. differentiation of pituit. tumours and hemangiomas) No radiation load

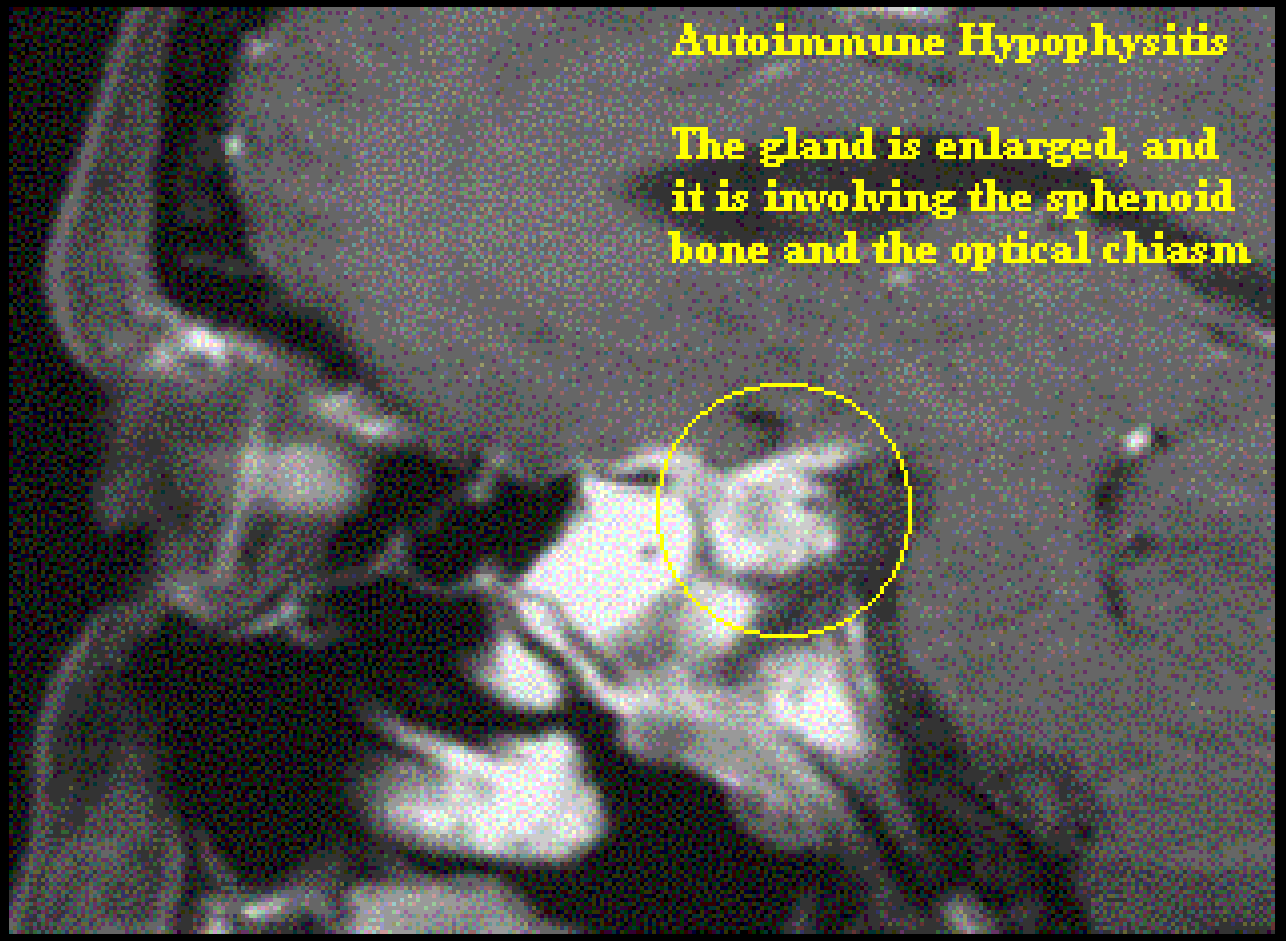
MRI

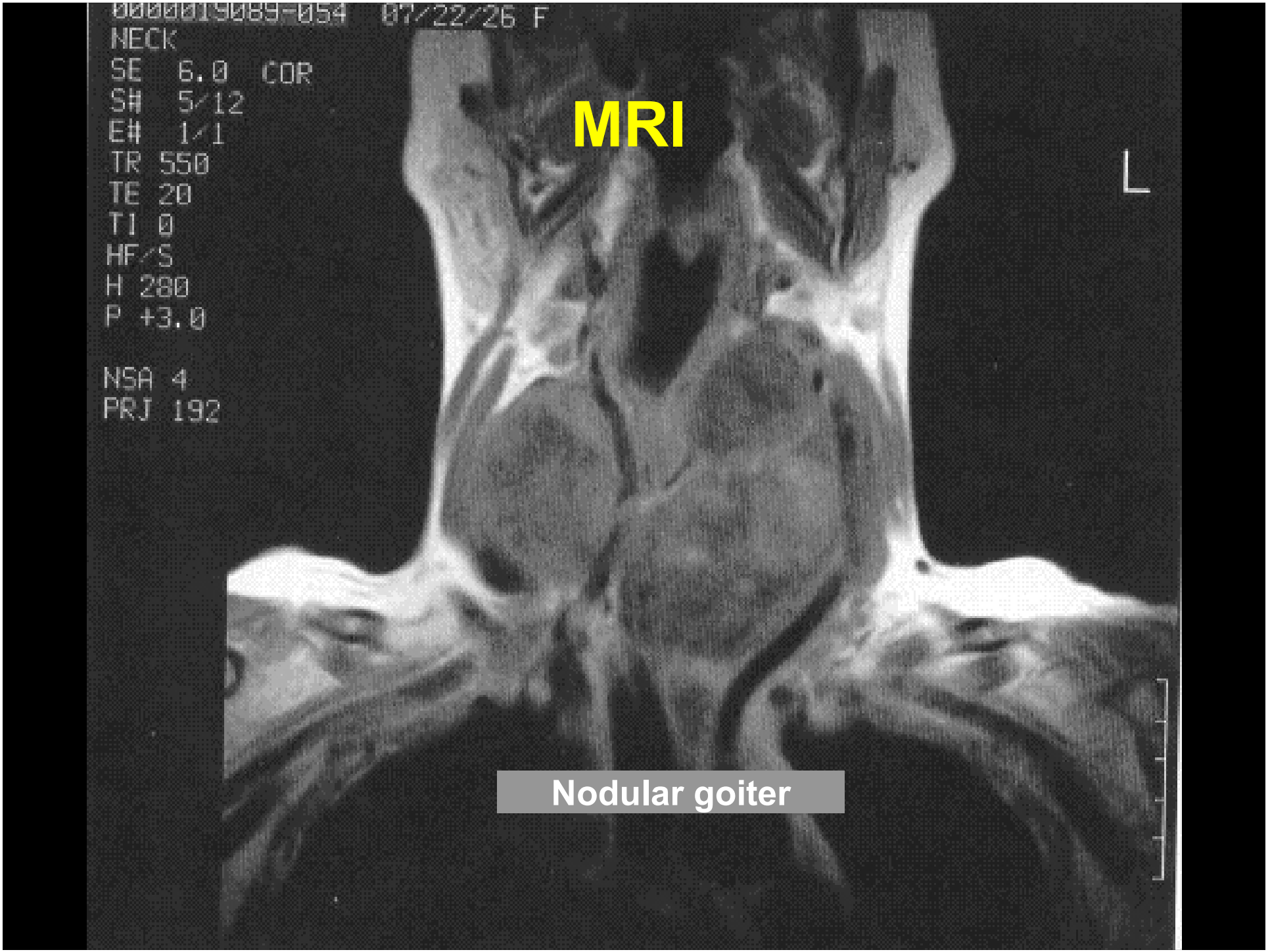
Prolactinoma



Before Treatment 1 Year After Treatment

CT


Autoimmune Hypophysitis
The gland is enlarged, and
it is involving the sphenoid
bone and the optical chiasm


0000019089-054 07/22/26 F
NECK
SE 6.0 COR
S# 5/12
E# 1/1
TR 550
TE 20
TI 0
HF/S
H 280
P +3.0
NSA 4
PRJ 192
MRI
L
Nodular goiter

Scintigraphy

Application of isotope and its uptake in functional parenchyma of endocrine gland. Extracorporal detection of γ-emission.

^{131}I	β+γ emitter
^{125}I	γ-emitter
^{99m}Tc-MIBI	γ-emitter
^{131}I-MIBEG	β+γ emitter
^{99m}Tc-octreotide	γ-emitter

Notice: Despite textbooks, no other isotope is used in diagnosis of endocrine disorders, now.

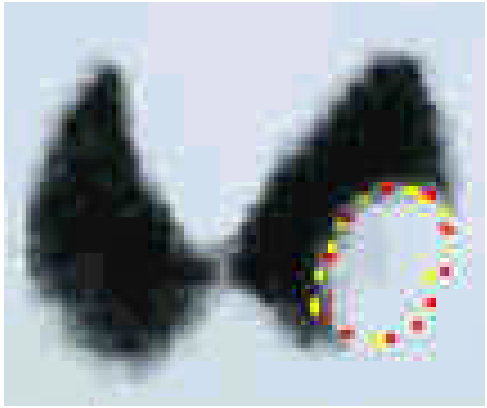
Scintigraphy

^{131}I **^{125}I**

^{125}I is a combined β+γ emitter - for both diagnostics (γ ray) and local irradiation (β activity) of tumour or goiter.

^{125}I as a γ emitter is used for diagnostics only.

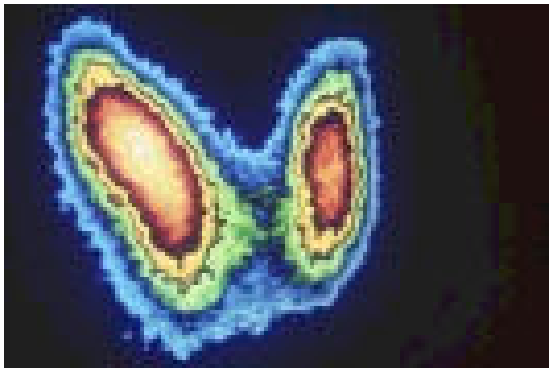
Uptake of iodine is limited to thyroid, salivate glands and breasts (cave lactation !)



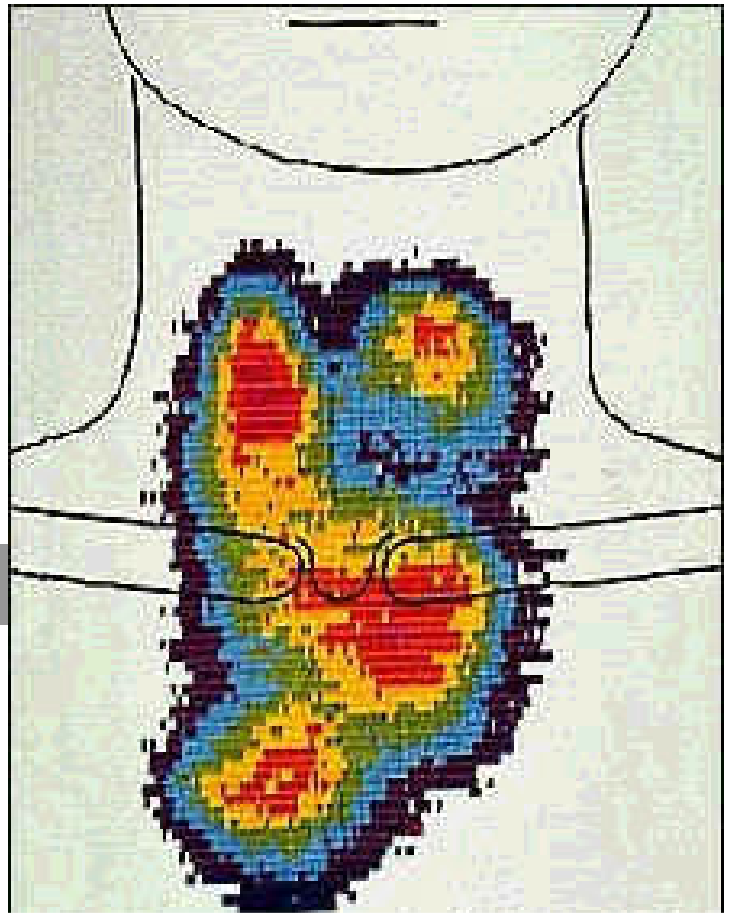
Thyroid cancer - „cold“ nodule

Scintigraphy

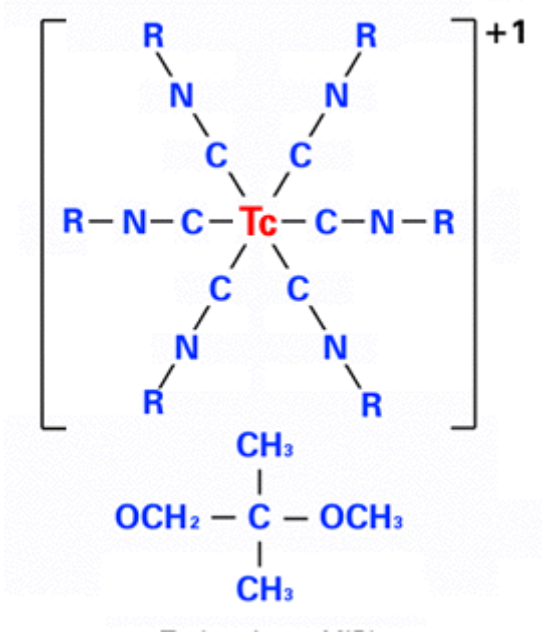
^{131}I



Retrosternal goiter



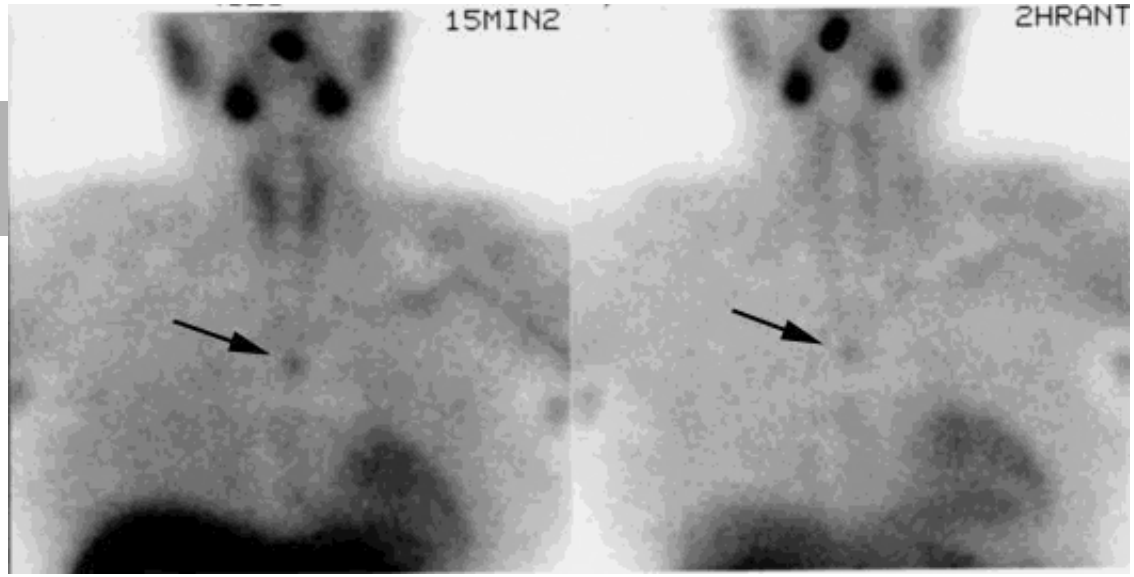
Scintigraphy



^{99m}Tc-MIBI = methoxy isobuthyl isonitril

The molecule passes cells membranes passively, once intracellular it further accumulates in the mitrochondrias. Detection of ^{99m}Tc gamma emission

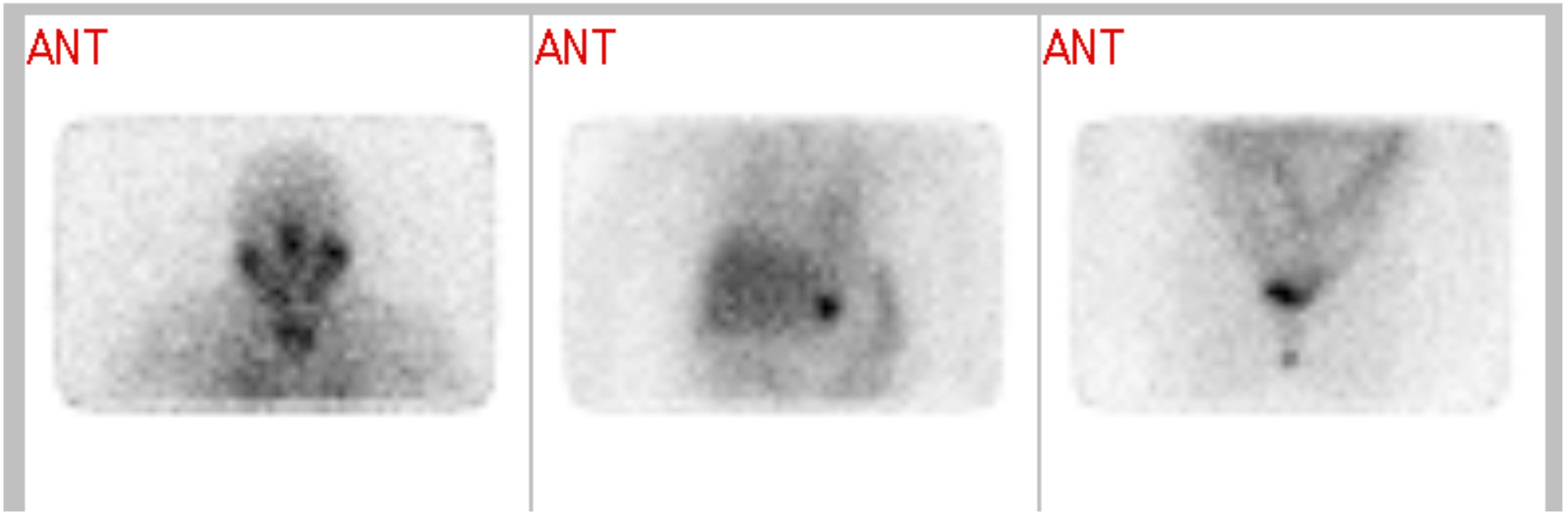
Atypical retrosternal PTH adenoma



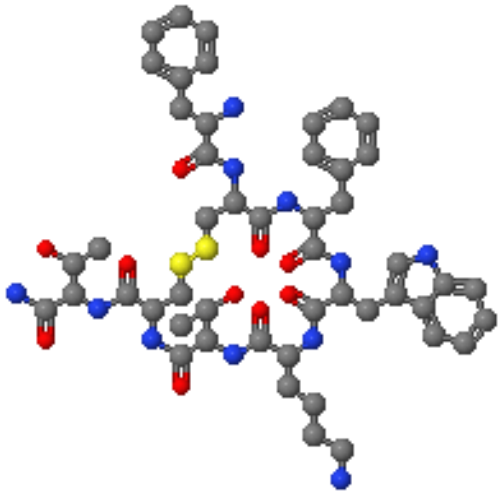
Scintigraphy

^{131}I-MIBEG = metaiodobenzyl-guanidin

Isotope uptake in APUD tumours (e.g. insulinoma, gastrinoma), pheochromocytoma (see image) and some other tumours

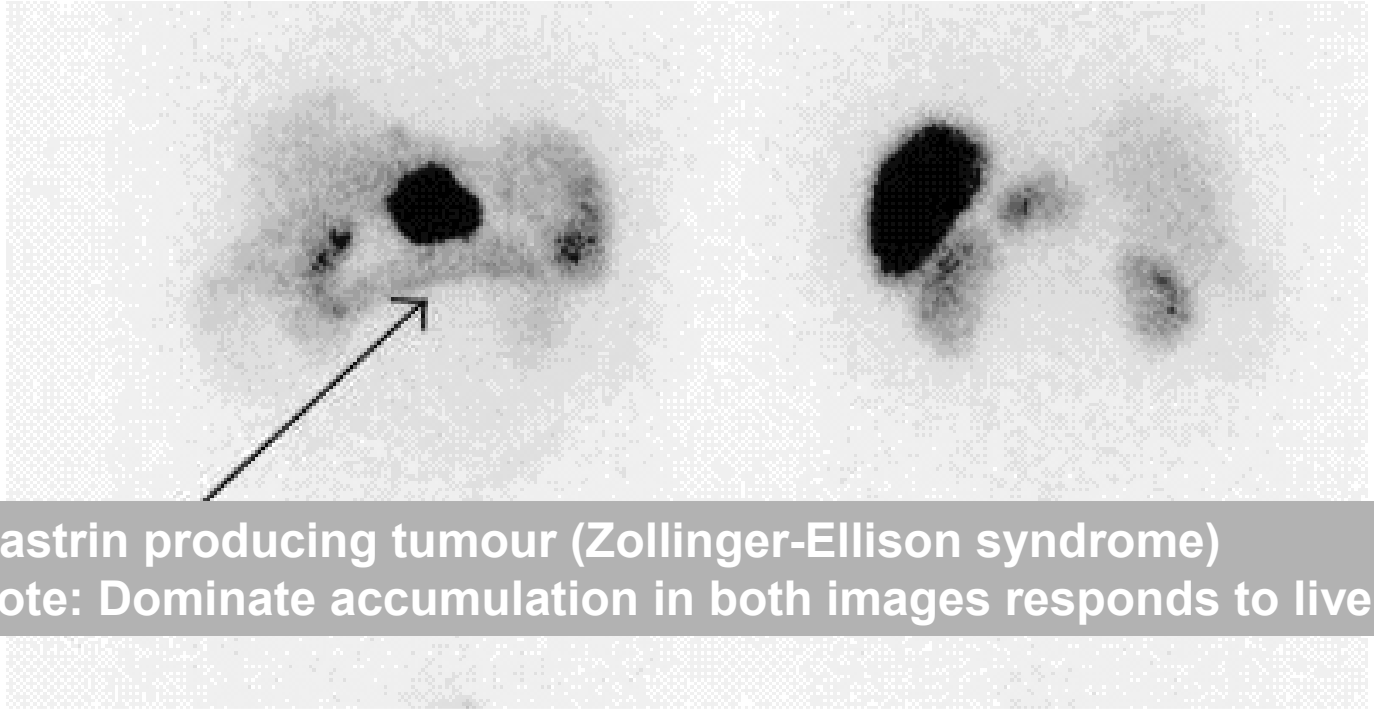


Scintigraphy



^{99m}Tc-octreotide

Octreotide = somatostatin analog
“Octreoscan”: Molecule binds to somatostatin receptors on different endocrine tumours (STH producing pituitary adenoma, APUD tumours, pheochromocytoma ...)

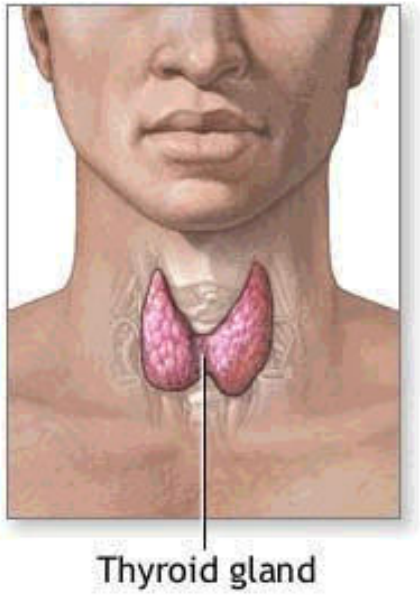


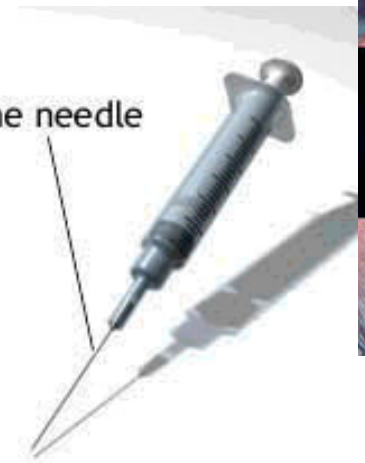
Gastrin producing tumour (Zollinger-Ellison syndrome)
Note: Dominate accumulation in both images responds to liver

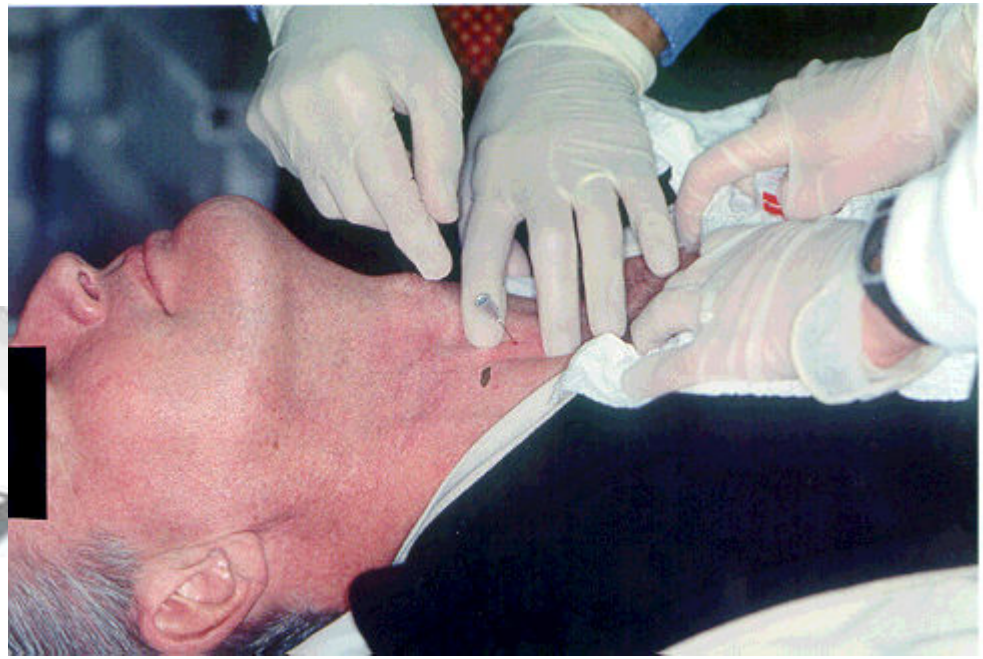
Biopsy

1. Thyroid gland - unclear solitary nodule, tumours
2. Adrenal glands - rarely

Thyroid gland - Fine needle aspiration biopsy (FNAB)



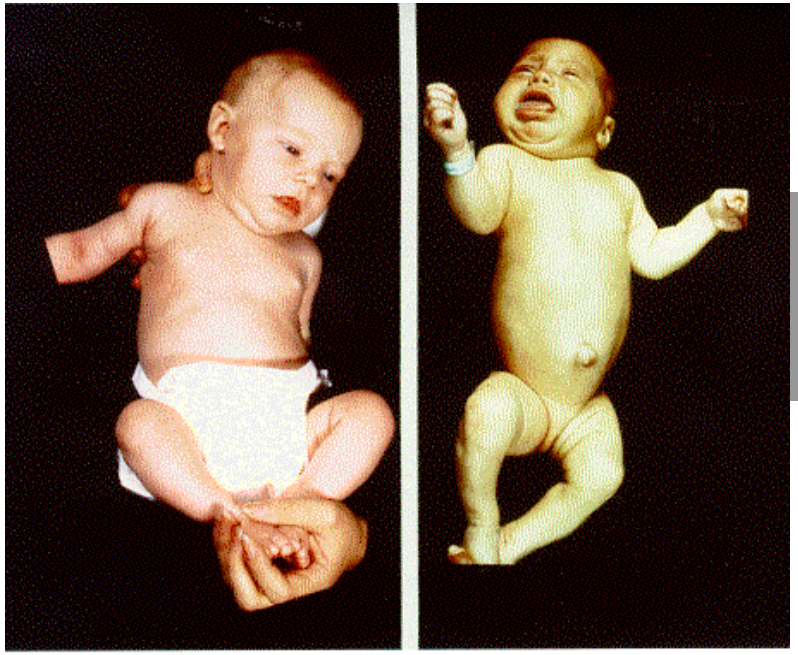




Newborn screening

Three obligatory newborn screening in Czech Republic:

1. **Congenital hypothyroidism - incidence 1 : 5000**
   screening based on elevation of TSH
2. **Congenital adrenal hyperplasia (CAH) - incidence 1 : 10-14000**
   screening based on elevation of 17-OH-progesterone
3. **Phenylketonuria**



Infant with severe, untreated congenital hypothyroidism diagnosed prior to the advent of newborn screening

Genetics of endocrine disorders

MEN 1 ... gene MEN1, 11q chrom.
tumour suppressor gene
PPP syndrome (PTH adenoma + pituitary + endocrine pancreas)

MEN 2 ...RET protooncogene, 10th chrom.
receptor of neurotrophic growth factors
thyroid medullar ca + PTH adenoma + pheochromocytoma

von Hippel-Lindau syndrome ... VHL gene, 3p chrom.
tumour suppressor gene (controling hypoxia-inducible factor)
pheochromocytoma + retinal hemangioblastoma + Grawitz tumour etc.