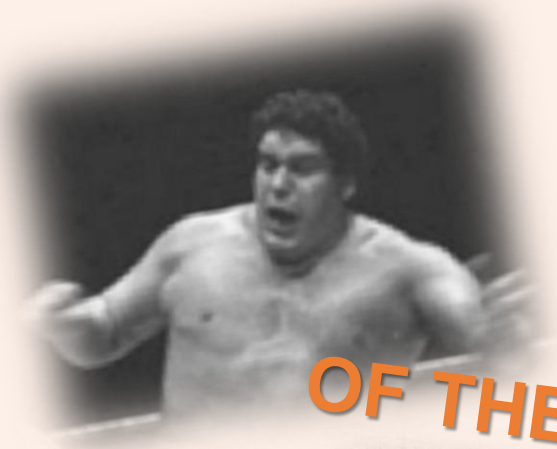
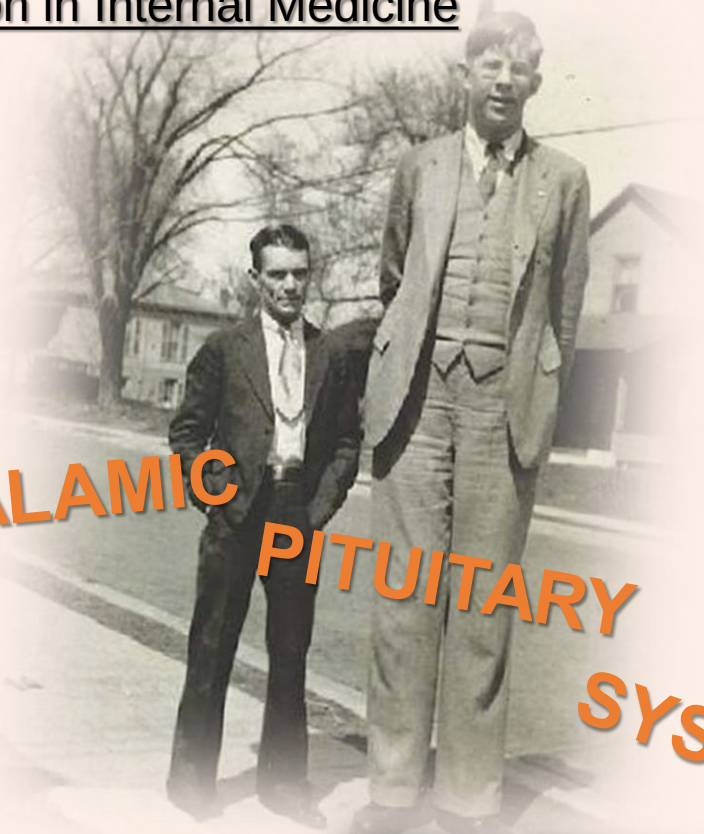
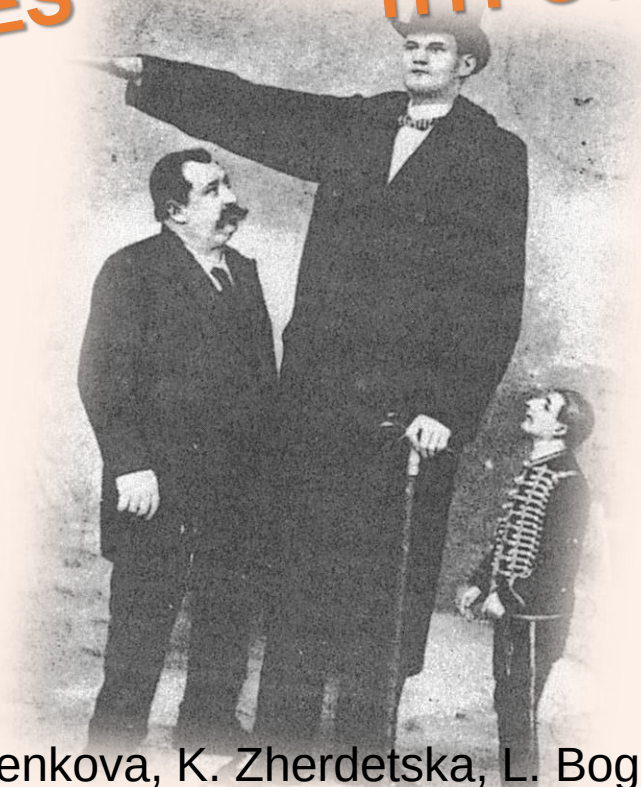
Notes for the Practical lesson in Internal Medicine





DISEASES OF THE HYPOTHALAMIC PITUITARY SYSTEM



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PLAN OF THE NOTES

1.STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM

1.1 HORMONES OF HYPOTHALAMIC-PITUITARY SYSTEM, THEIR FUNCTIONS

2. ACROMEGALY AND HYPOPHYSEAL GIGANTISM

3. HYPOPITUITARYSM: PITUITARY DWARFISM

4. CUSHING DISEASE

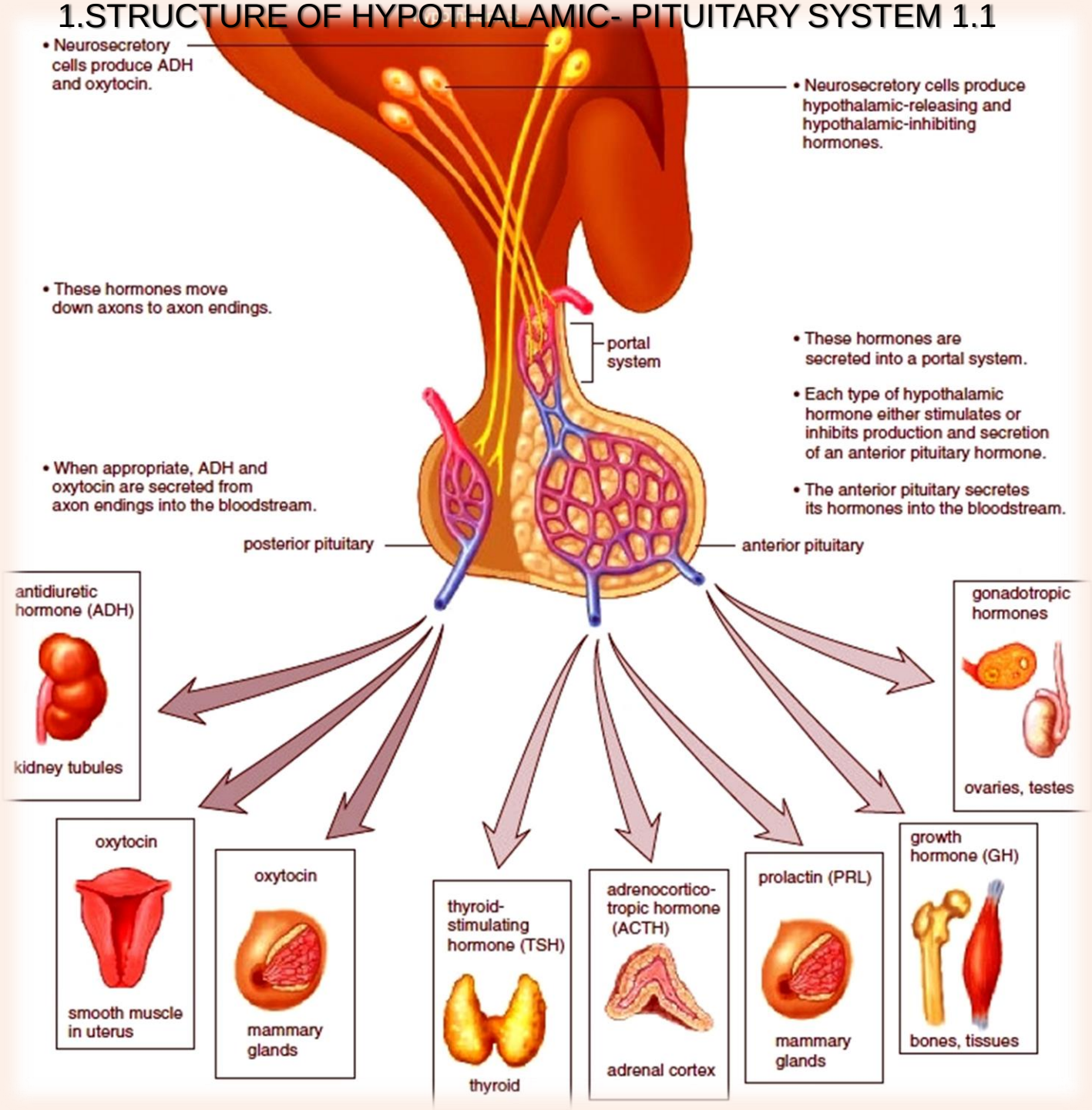
5. SYNDROME OF HYPERPROLACTINEMIA

6. DIABETES INSIPIDUS

7. OBESITY

STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM ?

1.STRUCTURE OF HYPOTHALAMIC- PITUITARY SYSTEM 1.1



1.STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM

1.1 Hormones of hypothalamic-pituitary system, their functions

HORMONES OF HYPOTHALAMIC-PITUITARY SYSTEM, THEIR FUNCTIONS ?

1.STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM

1.1 HORMONS OF HYPOTHALAMIC-PITUITARY SYSTEM, THEIR FUNCTIONS 1.3

HORMONE	MAJOR TARGET ORGAN(S)	MAJOR PHYSIOLOGIC EFFECTS
	ANTERIOR PITUITARY	
Growth hormone	Liver, adipose tissue	Promotes growth (indirectly), control of protein, lipid and carbohydrate metabolism
Thyroid-stimulating hormone	Thyroid gland	Stimulates secretion of thyroid hormones
Adrenocorticotropic hormone	Adrenal gland (cortex)	Stimulates secretion of glucocorticoids
Prolactin	Mammary gland	Milk production
Luteinizing hormone	Ovary and testis	Control of reproductive function
Follicle-stimulating hormone	Ovary and testis	Control of reproductive function

1.STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM

1.1 Hormones of hypothalamic-pituitary system, their functions 2.3

POSTERIOR PITUITARY

Oxytocin has no diurnal rhythm but is released in three reflexes following the influence of several different types of stimuli:

- In the milk let-down reflex the tactile stimuli applied to the breast by the suckling infant are transmitted to the hypothalamus by the spinohypothalamic tract directly to the preoptic and paraventricular nuclei to excite the magnacellular neurons and so provoke the release of hormone into the circulation.
- During parturition ***oxytocin*** induces powerful contractions of the uterine myometrium. ***Oxytocin*** also produces contractions of the uterine myometrium and smooth muscles of the female and male reproductive tract that are important for sperm transport. The stimuli in this reflex are inputs from CNS sympathetic pathways activated with sexual activity.

1.STRUCTURE OF HYPOTHALAMIC-PITUITARY SYSTEM

1.1 Hormones of hypothalamic-pituitary system, their functions 3.3

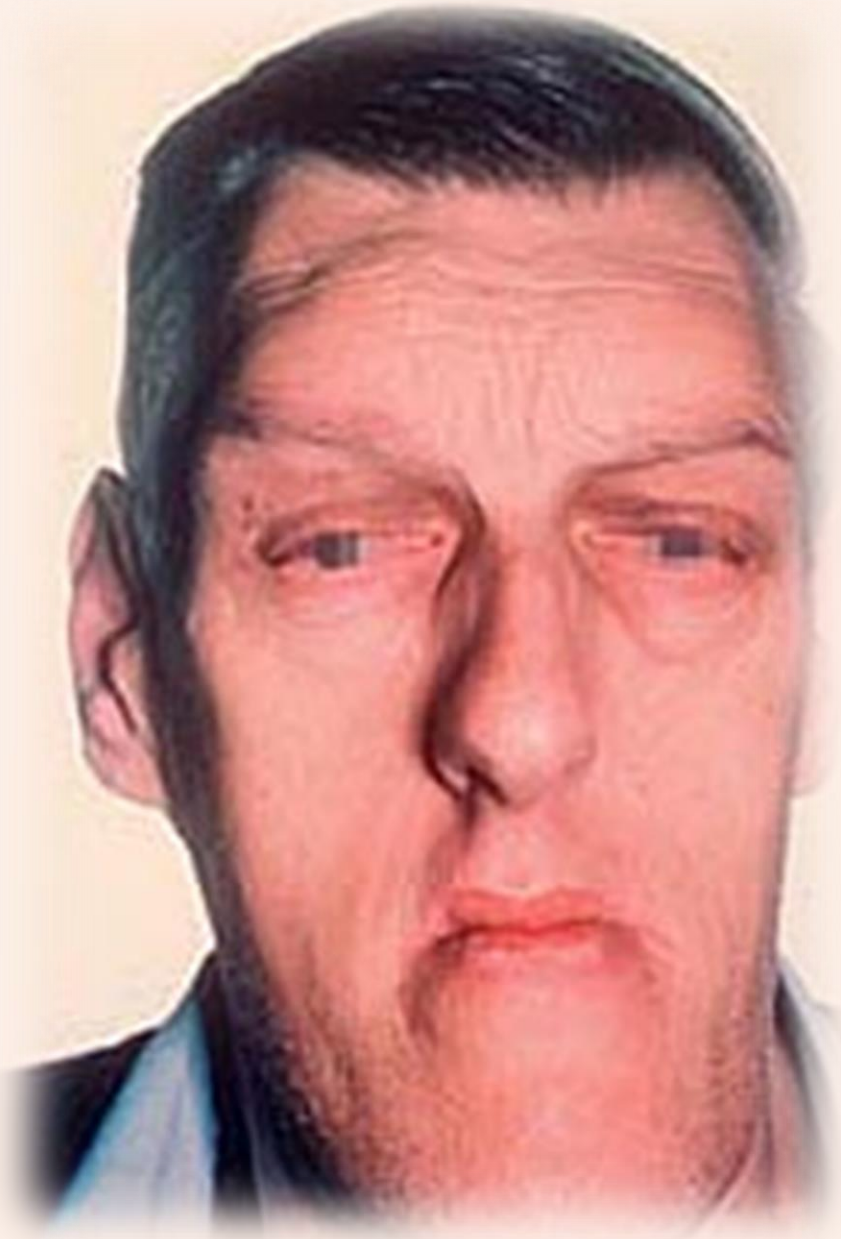
Vasopressin (arginine vasopressin-AVP), acts on V2 receptors on the contraluminal surface of the distal tubular epithelium primarily in the collecting ducts of the kidney to increase permeability and allow reabsorption of water and electrolytes into the circulation

Vasopressin has a diurnal peak late at night and early in the morning and a trough in the mid-afternoon.

Sensors in the subfornical organ for angiotensin II also stimulate the release of ***vasopressin***. Angiotensin II in the blood is elevated following the release of renin from the kidney in response to a decrease in blood pressure.

The carotid and aortic arch bodies that signal the hypothalamus via the vagus and glossopharyngeal nerves via relay in the solitary nucleus also detect a decrease in blood oxygen or pressure and promote the release of ***vasopressin***.

ACROMEGALY



GIGANTISM

DIFFERENCE BETWEEN ACROMEGALY AND GIGANTISM ?

2.ACROMEGALY AND HYPOPHYSEAL GIGANTISM 1.1

Growth hormone(GH) stimulates skeletal and soft tissue growth.

GH excess therefore produces ***GIGANTISM*** in children (if acquired before epiphyseal fusion) and ***ACROMEGALY*** in adults.

Both are due to a pituitary tumour in almost all cases.

Hyperplasia due to GHRH excess is very rare.

Overall incidence is approximately 3–4/million per year and the prevalence is 50–80/million worldwide.

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CAUSES ?

ETIOLOGY 1.1

PITUITARY ADENOMA
primary hypersecretion of ***GH*** by eosinophiles

EXTRA-PITUITARY TUMORS
Hypersecretion of ***GH*** : pancres, lungs, ovarium, mediastenum

EXTRA-PITUITARY TUMORS
hypersecretion of ***GHRH***: carcinoid, pancreatic adenoma, bronchogenious lung cancer

HYPOTHALAMIC TUMORS
Hypersecretion of by ***GHRH***
gamarthroma, ganglioneurinoma

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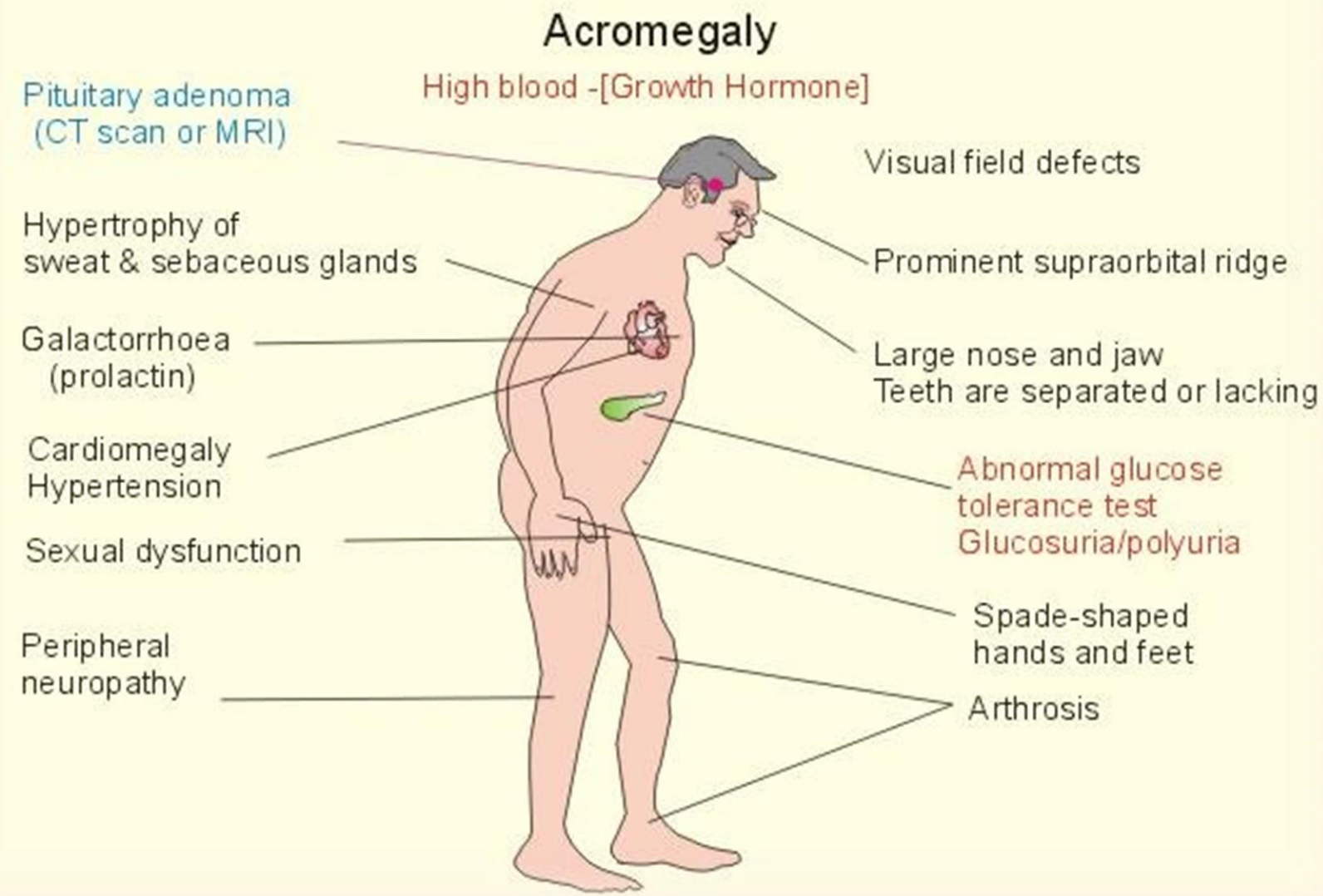
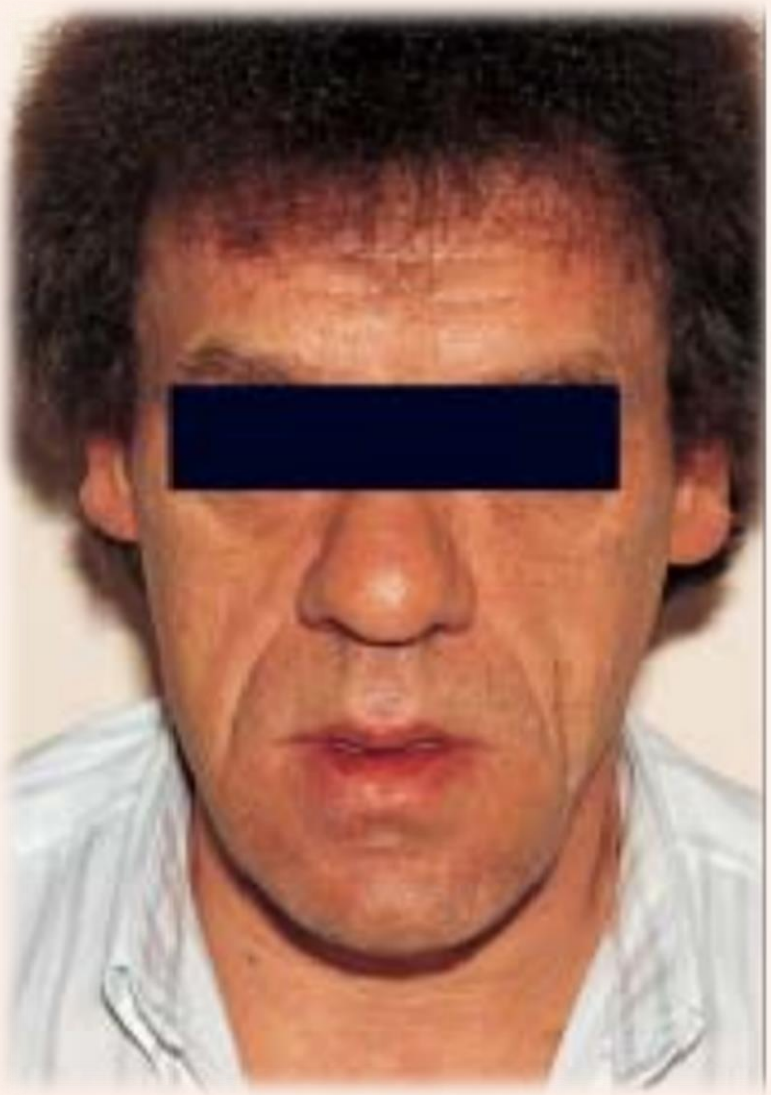
CLINICAL PICTURE OF ACROMEGALY ?

SYMPTOMS & SIGNS 1.4



SYMPTOMS & SIGNS 2.4

- Change in appearance
- Prominent supraorbital ridge
- Increased size of hands/feet
- Prognathism
- Visual deterioration
- Headaches
- Arthropathy
- Excessive sweating
- Interdental separation
- Large tongue
- Tiredness
- Hirsutism



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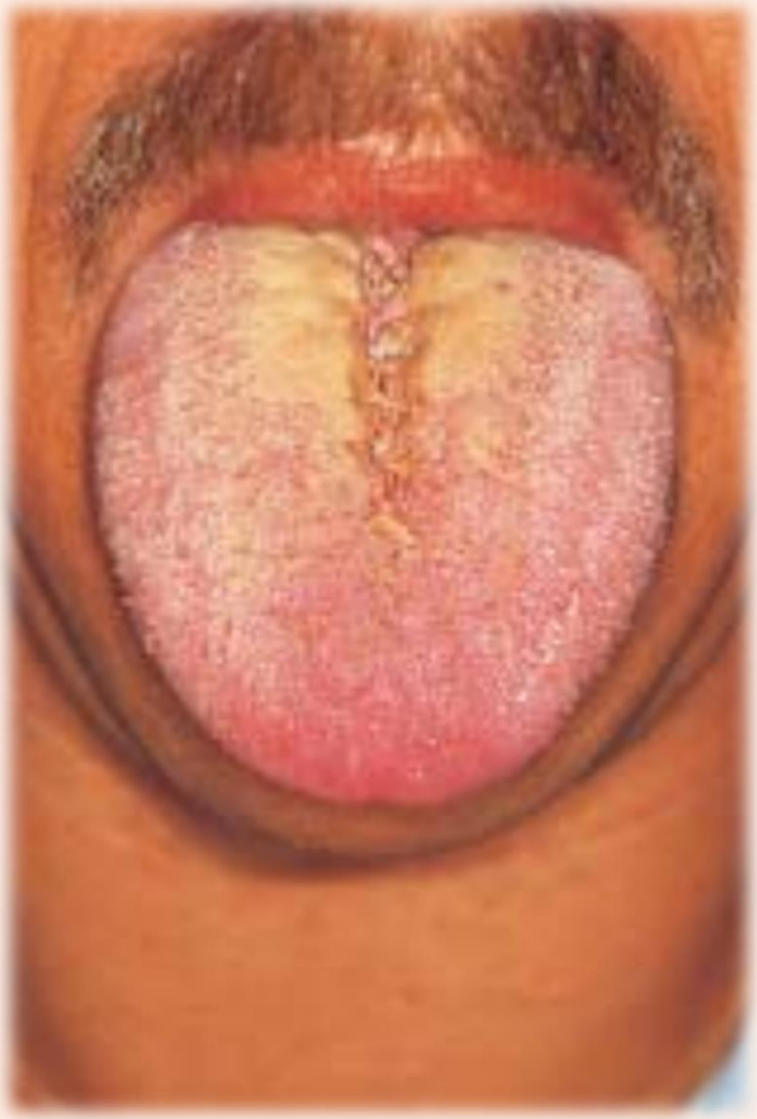
SYMPTOMS & SIGNS 3.4

- Weight gain
- Thick greasy skin
- Amenorrhoea, oligomenorrhoea in women
- Spade-like hands and feet
- Galactorrhoea
- Tight rings
- Impotence or poor libido
- Carpal tunnel syndrome
- Deep voice
- Colonic polyps
- Goitre
- Visual field defects
- Breathlessness
- Pain/tingling in hands
- Galactorrhoea
- Polyuria/polydipsia



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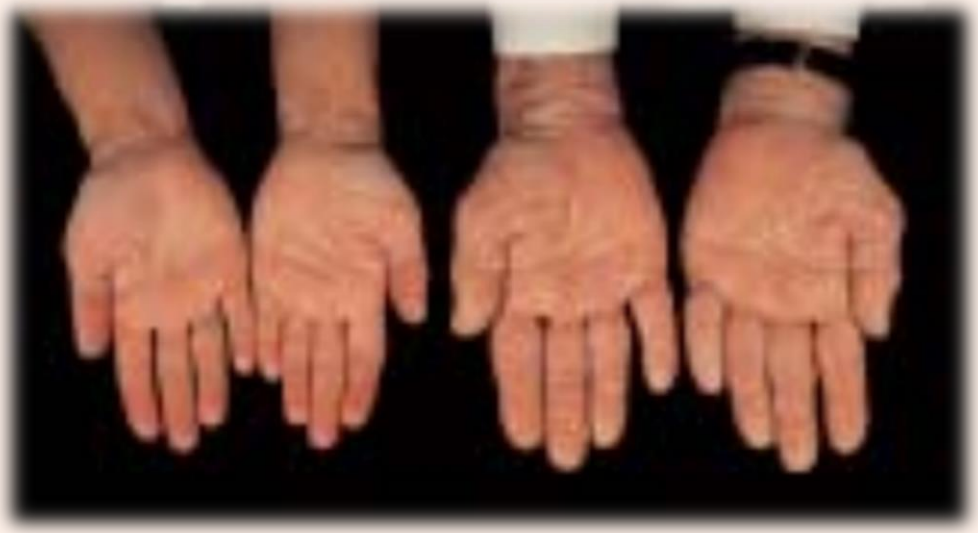
SYMPTOMS & SIGNS 4.4

- Hypertension
- Muscular weakness
- Oedema
- Joint pains
- Heart failure
- Proximal myopathy
- Glycosuria



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HOW DOES ACROMEGALY DEVELOP?

STAGES DEVELOPIND OF ACROMEGALY 1.1

1. PRE-ACROMEGALY
2. HYPERTROPHIC (hypertrophy and hyperplasia of the organs and tissues)
3. TUMOR (increase of intracranial pressure, blindness, neurological disorders)
4. CACHECTIC (severe progression of the disease)

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COMPLICATIONS OF ACROMEGALY?

COMPLICATIONS 1.1

- Arthritis
- Cardiovascular disease
- Carpal tunnel syndrome
- Colonic polyps
- Glucose intolerance or diabetes
- High blood pressure
- Sleep apnea
- Spinal cord compression
- Uterine fibroids
- Vision abnormalities

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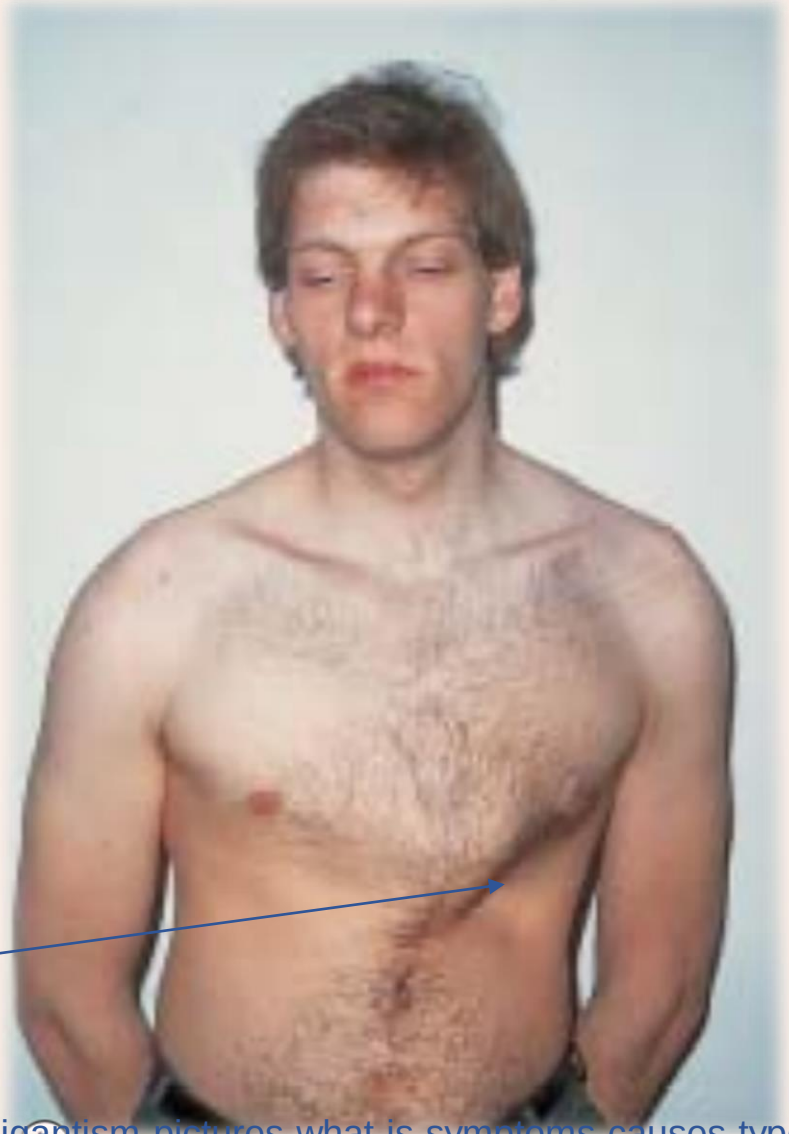
CLINICAL PICTURE OF GIGANTISM ?

SYMPTOMS & SIGNS 1.2

- Fatigue
- Jaw is large
- Big hands
- Excessive sweating
- Difficulty in visual aspects peripherally
- Puberty retardation



Gigantism with rib cage abnormality

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SYMPTOMS & SIGNS 2.2

- Headache
- Deafness
- Facial features thickens
- Fingers and toes are thick
- Frontal bossing
- Irregular menstrual periods
- Releasing of breast milk or galactorrhea

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COMPLICATIONS OF GIGANTISM ?

COMPLICATIONS 1.1

- Delayed puberty
- Difficulty functioning in everyday life due to large size and unusual features
- Diminished vision or total vision loss
- Embarrassment, isolation, difficulties with relationships, and other social problems
- Hypothyroidism
- Severe chronic headache
- Sleep apnea

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WHICH LABORATORY TESTS DO YOU KHOW?

INVESTIGATIONS 1.1

Biochemistry : hyperphosphatemia, hypercalciuria, hyperlipidemia

Basal secretion of GH in blood is determined at least 3 times at intervals of 1 -2 days. The mean value obtained performance by taking basal level. The contents of growth hormone in the serum of patients with active phase of the disease is 20,51 ± 2,06 ng / mL at a rate of 3,82 ± 0,24 ng / ml

Circadian level of GH *:*increased level 24hours in patients with acromegaly

IGF-1 level is almost always raised in acromegaly – a single plasma level of IGF-1 reflects mean 24-hour GH levels and is useful in diagnosis.

A normal IGF-1 together with GH 5 mU/L (2.5 ng/L) may be taken to exclude acromegaly if the diagnosis is clinically unlikely.

Pituitary function – partial or complete anterior hypopituitarism is common.

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

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

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WHICH TESTS FOR STIMULATION OF GH SECRETION DO YOU KHOW?

INVESTIGATIONS 1.1

Funtional tests for stimulation of GH secretion:

Insulin test (intravenous injection of 0.15 – 0.2 U/kg insulin, blood sample in 30 min and just before injection and after 15, 30, 60, 90,120 min with determination of somatostatin and glucose levels) – positive if glycaemia level decreases below 2 mmol/l.

Thyreoliberin test (injection of 500 mkg of thyreoliberin fasting in the morning, blood sample in 30 min before injection and after 15, 30, 60,120 min) – positive in case of increasing of somatostatin level on 50-100% from initial level, in N – concentration doesn't change

Somatoliberin test (injection of 100mkg of somatoliberin with blood sampling like in previous tests) – sharp increasing of somatotropin levels

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WHICH TESTS FOR SUPPRESSION OF GH SECRETION DO YOU KHOW?

INVESTIGATIONS 1.1

Funtional tests for suppression of GH secretion

A glucose tolerance test is diagnostic if there is no suppression of GH. Acromegalics fail to suppress GH below 1 mU/L and some show a paradoxical rise; about 25% of acromegalics have positive diabetic glucose tolerance test(fasting blood sample and each 30 min during 3 hours after intake of 75g of glucose – determination of GH and glucose – in N hyperglycemia leads to decreasing of GH level)

WHICH INSTRUMENTAL TESTS DO YOU KHOW?

INVESTIGATIONS 1.1

X-ray of skull and cella turcica

CT / MRI acromegaly scan of pituitary if above tests abnormal.

This will almost always reveal the pituitary adenoma.

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TREAMENT ?

TREAMENT 1.5

Surgery

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

TREAMENT 2.5

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

TREAMENT 3.5

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

TREAMENT 4.5

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

TREAMENT 5.5

Pituitary radiotherapy External radiotherapy is normally used after pituitary surgery fails to normalize GH levels rather than as primary therapy. It is often combined with medium-term treatment with a somatostatin analogue or a dopamine agonist because of the slow biochemical response to radiotherapy, which may take 10 years or more and is often associated with hypopituitarism which makes it unattractive in patients of reproductive age. Stereotactic radiotherapy is used in some centres.

Clinical case 1.2

A 38-year-old woman presented with severe headaches to her primary-care physician. The patient had been diagnosed with rheumatoid arthritis and had begun having headache 4 years previously. An MRI scan revealed an 11–12 mm pituitary tumor. Her physical examination was unremarkable and she was referred for neuroendocrine consultation for a presumed nonfunctioning adenoma.

Investigations MRI of the pituitary, and laboratory investigations that included measurement of serum insulin-like growth factor 1 (IGF1) and prolactin levels.

DS?

Clinical cases 2.2

A 25-year-old lady presented with increased statural growth and enlarged body parts noticed since the age of 14 years, primary amenorrhea, and frontal headache for the last 2 years. She has also been suffering from non-inflammatory low back pain with progressive kyphosis and pain in the knees, ankles, and elbows for the last 5 years. There was no history of visual disturbance, vomiting, galactorrhoea, cold intolerance. She had no siblings. Blood pressure was normal. Height 221 cm, weight 138 kg, body mass index (BMI)28. There was coarsening of facial features along with frontal bossing and prognathism, large hands and feet, and small goitre. Patient had severe kyphosis and osteoarthritis of knees. Confrontation perimetry suggested bitemporal hemianopia. Breast and pubic hair were of Tanner stage 1.

Clinical case 2.2 (cont.)

Investigations: Serum insulin like growth factor-1 (IGF1) was 703 ng/ml with all glucose suppressedgrowth hormone (GH)values of >40 ng/ml. Prolactin was 174 ng/ml. Basal serum Lutenising Hormone (LH), follicle stimulating Hormone (FSH) was low. Oral glucose tolerance test (OGTT), liver and renal function tests, basal cortisol and thyroid profile, Calcium, phosphorus and Intact Parathyroid hormone (iPTH) were normal. Computed tomographyscan of brain showed large pituitary macroadenoma. Automated perimetry confirmed bitemporal hemianopia.

DS?

HYPOPITUITARYSM
Growth hormone deficiency

WHAT IS PITUITARY DWARFISM ?

3. HYPOPITUITARYSM: PITUITARY DWARFISM 1.1

Pituitary dwarfism or dwarfism is a condition characterized by growth and development disorders caused by insufficient secretion of pituitary somatotrope hormone (growth hormone or GH).

The condition begins in childhood, but becomes more evident during puberty.

Dwarfism is a condition in which growth is very slowed or delayed.

Pituitary dwarfism is a consequence of decreased function of the pituitary gland occurred early in childhood before the ossification of bone cartilages.

Pituitary dwarfism as retrieved from www.nlm.nih.gov on 30/12/2003 University of Maryland Medical Center

HOW MANY TYPES OF PITUITARY DWARFISM DO YOU KHOW?

3. HYPOPITUITARYSM: PITUITARY DWARFISM

There are two types of pituitary dwarfism 1.1:

•***Pituitary dwarfism type 1*** due to low production of adenohypophysis hormones. When none of the anterior pituitary hormones are properly produced, endocrine failure is manifested on pituitary hormone dependent lines. It is characterized by slow overall growth, and patients do not show signs of normal puberty.

•***Pituitary dwarfism type2*** due to isolated growth hormone deficiency. A common form of dwarfism is caused by deficiency in the production of pituitary growth hormone (GH). Patients are developed proportionally, reach sexual maturity and can reproduce.

Pituitary dwarfism as retrieved from www.nlm.nih.gov on 30/12/2003 University of Maryland Medical Center

WHAT ARE CAUSES OF PITUITARY DWARFISM?

ETIOLOGY 1.1

- Genetics
- Accident-related trauma to the pituitary gland
- Surgical injury of the pituitary
- Central nervous system tumor
- Central nervous system trauma
- Central nervous system radiation
- Leukemia

In most cases, the cause of dwarfism is not known (idiopathic).

Pituitary dwarfism as retrieved from www.nlm.nih.gov on 30/12/2003 University of Maryland Medical Center

CLINICAL PICTURE

OF PITUITARY DWARFISM?

CLINICAL PICTURE 1.2

Due to deficient degradation of fat, fat distribution in patients is much higher than in normal subjects of the same age, especially around the waist. Rarely excess fat deposits in the thighs, abdomen or in the mammary glands can occur.

In patients with pituitary dwarfism, protein synthesis is diminished and the muscle mass is proportionally decreased than in normal individuals of the same age. Studies show that in children with pituitary dwarfism, the skeletal muscle cells are less numerous than normal. Therefore, muscle strength, which can be measured in older children using different exercise tests, is decreased.

Sexual organs are not sufficiently developed, women have the uterus and vagina of reduced dimensions, the mammary glands are also underdeveloped. Amenorrhea is also present. In males the testicles are not descended into the scrotum, the penis and scrotum have infant sizes.

Patients may have a normal sex life but reproduction is quite rare and it usually takes place only in isolated deficiency of somatotropin cases.

CLINICAL PICTURE 2.2

Inadequate degradation of glycogen to glucose can lead to hypoglycemia and seizures in severe and untreated hypoglycemia cases.

Intelligence is mostly normal, but behavior remains childish and patients often present asthenic disorders, depression, inferiority complex.

The head and limbs are too small, but proportionate, and this makes the overall appearance of the patient to be harmonic. The face is small, and due to the underdeveloped maxilla and mandible, the small teeth are intercalated. The nose is small, eyes very close to each other, but lively.

Pigmentation spots, freckles and fine wrinkles can be present on the facial skin. Due to these wrinkle, the patient gets an appearance of early aging. Hands and feet are small, the skin is often cyanotic.

Once puberty has passed, the patient retains the appearance of dwarf, skeleton and muscles remain undeveloped. Because of the structure of the infant's larynx, high-pitched voice in present also in adults.

In case of craniopharyngioma (a tumor located near the pituitary gland), children can have neurological symptoms such as headaches, vomiting, and vision problems (blurred vision, double vision).

Pituitary dwarfism as retrieved from www.nlm.nih.gov on 30/12/2003 University of Maryland Medical Center

INVESTIGATIONS

OF PITUITARY DWARFISM?

LABORATORY TESTS 1.2

Basal secretion of growth hormone: reduced less than 3.8 ng / ml.

Tests with stimulation of synthesis of growth hormone:

1. Test with somatoliberin (intravenous / 1 mg / kg, peak within 60 min).
2. Test with insulin (intravenous 0.1 U / kg, peak within 60 min).
3. Test with glucagon (intravenous 0.5-1 mg, peak over 120-180 min).
4. Test with L-arhinynom (intravenous 10% solution 0.5 g / kg, peak after 60 min.)
5. Test with L-DOPA (oral 10 mg / kg, peak through 60-120 min).
6. Test with clonidine (intravenous 0.2 mg / kg, the peak at 30 min.).

Decrease in reserve of somatotropic function - lack of Growth hormone increase in response to stimulation,"*partial*" deficiency of growth hormone: 7 to 10 ng / ml; "*total*" growth hormone deficiency: 5 to 7 ng / ml.

LABORATORY TESTS 2.2

The level of IGF-1 and IGF-2 in serum characterizes biological growth hormone activity.

A test with growth hormone administration for 5 days: in patients with Laron's syndrome - no increase of IGF-1 level.

INSTRUMENTAL INVESTIGATIONS 2.2

CT/MRI AND CEREBRAL ANGIOGRAPHY - the abnormal sella turcica by plain x-ray films of the skull, multidirectional polytomography, pneumoencephalography, computerized cranial axial tomography.

TREATMENT OF PITUITARY DWARFISM ?

TREATMENT 1.2

Induction of growth hormone growth

Indications: deficiency of growth hormone, open epiphyseal growth zones.

Recombinant growth hormone drugs: nordytropin, genotropin, by subcutaneous injection pen. Injections daily or 3 times a week.

Single dose of 0.05 mg / kg, during puberty 0.1 mg / kg. Growth rate - 6.7 cm per year.

Lifetime maintenance therapy prevents early growth hormone aging.

Heksarelin, enkephalin analogue, stimulates secretion of growth hormone.

Recombinant somatoliberyn

Recombinant IGF-1

L-thyroxine in case of concomitant hypothyroidism.

TREATMENT 2.2

Induction of sexual development

Indications: bone age of 12 years, infantilism.

Drugs with gonadotropic action: choroid gonadotropin:

- Boys in 1000-1500 IU 2-3 times a week 3 month break 9 months.

- Girls of 1000-1500 IU 3-5 times a week during the second phase of the alleged sexual cycle.

Preparations of sex steroids:

During the induction of growth by the age of 16:

Boys: testosterone enanthate / m 50-100 mg / m 2 1 time per month

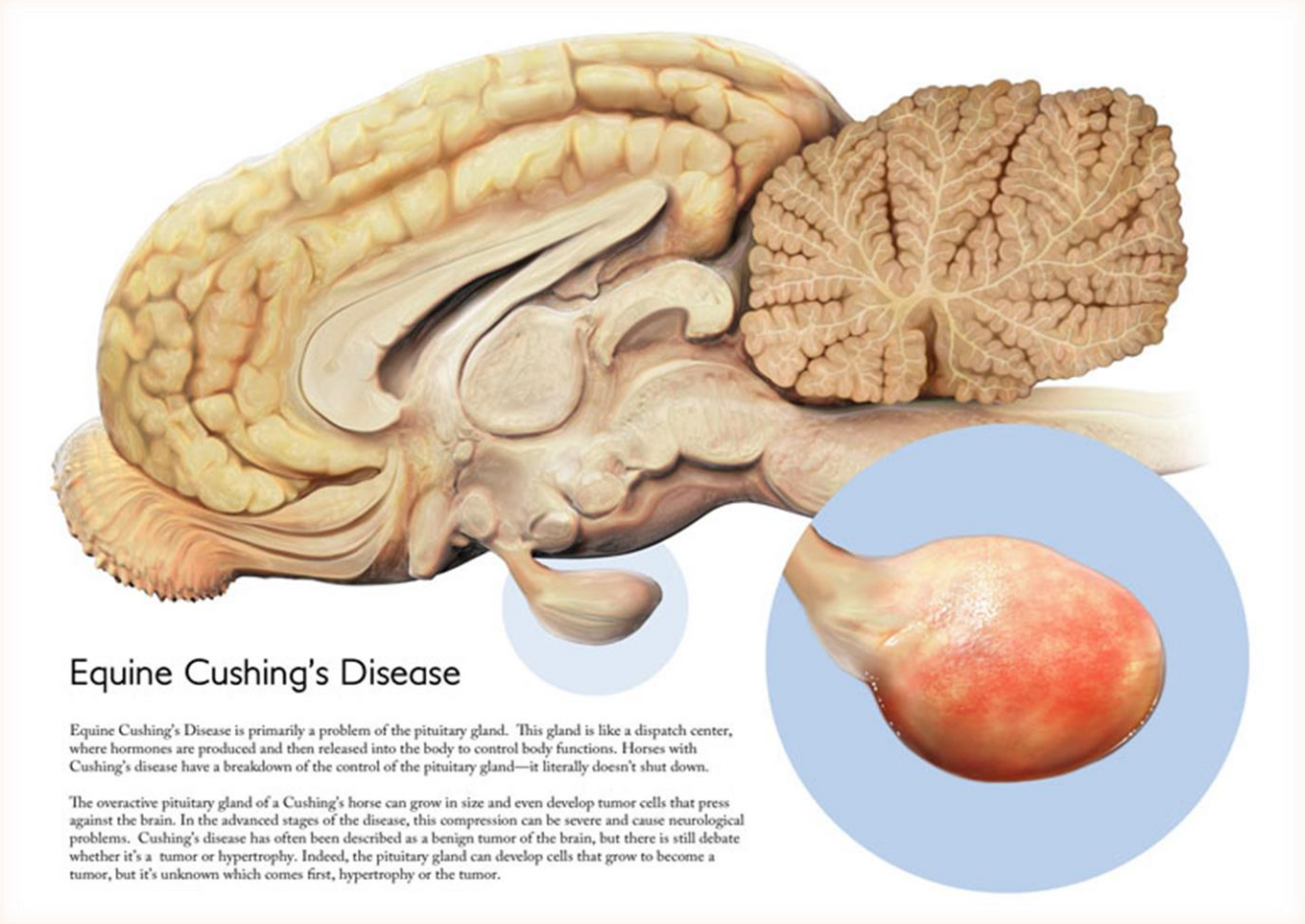
Girls: The first 16-20 days of each month estrogen, next 10 days - progestins

WHAT IS CUSHING DISEASE?

SYMPTOMS ?

4. CUSHING DISEASE 1.4

Cushing disease is a condition in which the pituitary gland releases too much adrenocorticotropic hormone (ACTH)



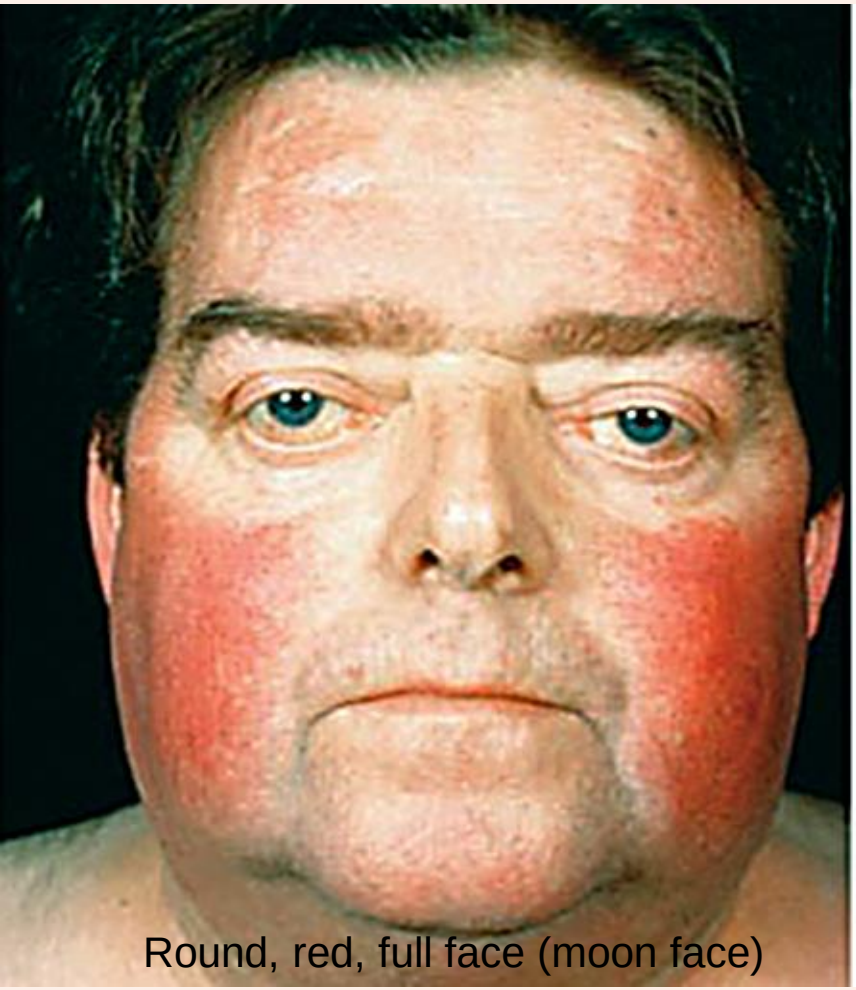
britannica.com›science/Cushing-disease

SYMPTOMS

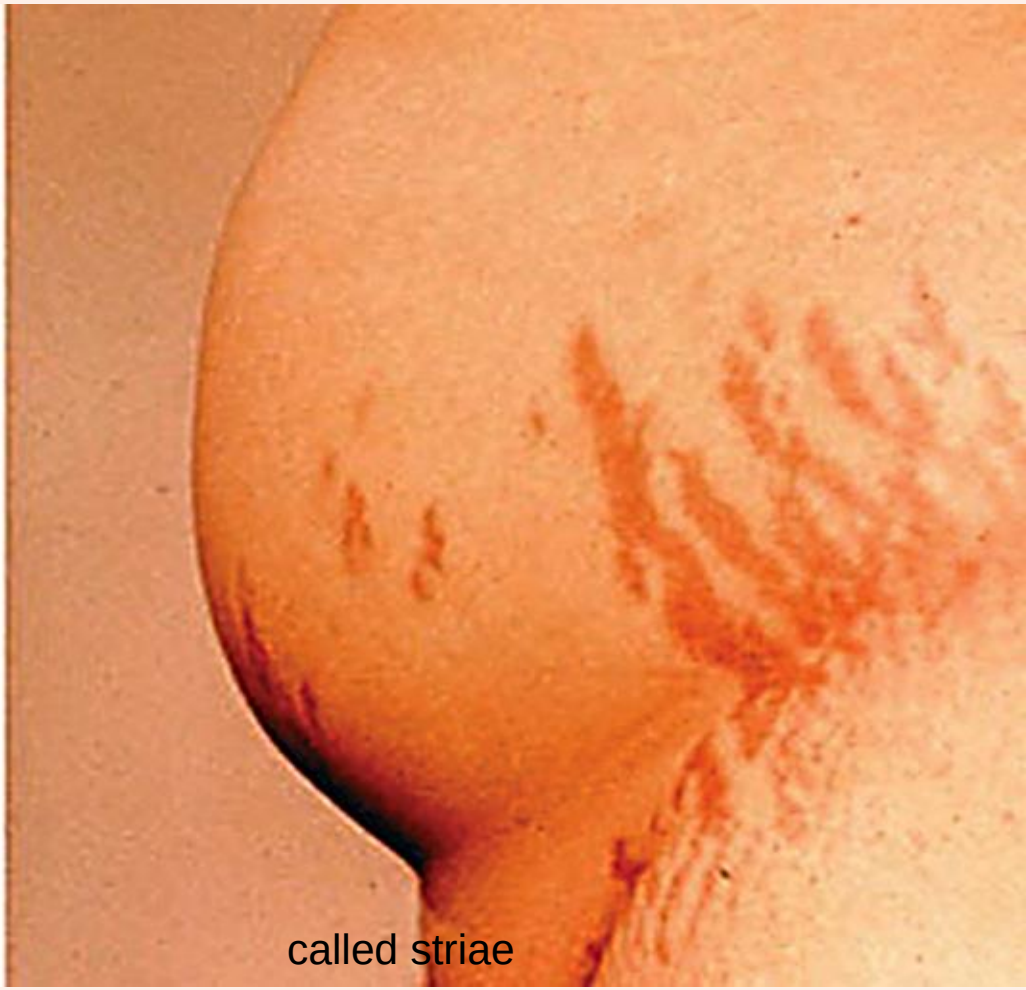
- Upper body obesity (above the waist) and thin arms and legs
- Round, red, full face (moon face)
- Slow growth rate in children
- Skin changes that are often seen include: acne or skin infections, purple marks (1/2 inch or more wide), called striae, on the skin of the abdomen, thighs, and breasts, thin skin with easy bruising, most commonly on the arms and hands
- Muscle and bone changes include: backache, which occurs with routine activities, bone pain or tenderness, collection of fat between the shoulders,(buffalo hump),thinning of the bones, which leads to rib and spine fractures, weak muscles

britannica.com›science/Cushing-disease

SYMPTOMS



Round, red, full face (moon face)



called striae

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SYMPTOMS

Women often have:

- Excess hair growth on the face, neck, chest, abdomen, and thighs
- Menstrual cycle that becomes irregular or stops

Men may have:

- Decreased or no desire for sex
- Impotence

Other symptoms may include:

- Mental changes, such as depression, anxiety, or changes in behavior
- Fatigue
- Headache
- Increased thirst and urination

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COMPLICATIONS OF CUSHING DISEASE?

COMPLICATIONS

- Compression fractures
- Diabetes
- High blood pressure Infections
- Kidney stones
- Mental illness

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WHICH TESTS FOR CUSHING DISEASE DO YOU KHOW?

TESTS

- These tests confirm too much cortisol: 24-hour urine cortisol
- Dexamethasone suppression test (low dose) and (high dose)
- Salivary cortisol levels (early morning and late at night)

These tests determine cause:

- Blood ACTH level
- Brain MRI
- Corticotropin-releasing hormone test, which acts on the pituitary gland to cause the release of ACTH
- Inferior petrosal sinus sampling (IPSS) - measures ACTH levels in the veins that drain the pituitary gland compared to the veins in the chest

britannica.com›science/**Cushing-disease**

TESTS

Other tests that may be done include any of the following:

- Fasting blood glucose and hemoglobin A1c to test diabetes
- Lipid profile testing
- Bone mineral density scan to check for osteoporosis

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TREAMENT ?

TREATMENT 1.1

- Treatment involves surgery to remove the pituitary tumor, if possible
- After surgery, the pituitary gland may slowly start to work again and return to normal
- During the recovery process, patient may need cortisol replacement treatments
- Radiation treatment of the pituitary gland may also be used if the tumor is not completely removed
- If the tumor does not respond to surgery or radiation, patient may need medicines to stop body from making cortisol
- If these treatments are not successful, the adrenal glands may need to be removed to stop the high levels of cortisol from being produced

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WHAT IS HYPERPROLACTINEMIA ?

5. SYNDROME OF HYPERPROLACTINEMIA 1.1

Hyperprolactinemia is the presence of abnormally high levels of prolactin in the blood

- Normal levels are less than 500 mIU/L [20 ng/mL or µg/L] for women, and less than 450 mIU/L for men
- Hyperprolactinaemia may cause galactorrhea (production and spontaneous flow of breast milk) and disruptions in the normal menstrual period in women and hypogonadism, infertility and erectile dysfunction in men

medmantic.com›wiki/Hyperprolactinemia

CLINICAL PICTURE OF HYPERPROLACTINEMIA ?

SIGNS AND SYMPTOMS

- In women, a high blood level of prolactin often causes hypoestrogenism with anovulatory infertility and a decrease in menstruation
- In some women, menstruation may disappear altogether (amenorrhoea)
- In others, menstruation may become irregular or menstrual flow may change
- Women who are not pregnant or nursing may begin producing breast milk
- Some women may experience a loss of libido (interest in sex) and breast pain, especially when prolactin levels begin to rise for the first time, as the hormone promotes tissue changes in the breast
- Intercourse may become difficult or painful because of vaginal dryness

SIGNS AND SYMPTOMS

- In men, the most common symptoms of hyperprolactinaemia are decreased libido, sexual dysfunction (in both men and women), erectile dysfunction, infertility, and gynecomastia
- Because men have no reliable indicator such as menstruation to signal a problem, many men with hyperprolactinaemia being caused by a pituitary adenoma may delay going to the doctor until they have headaches or eye problems caused by the enlarged pituitary pressing against the adjacent optic chiasm
- They may not recognize a gradual loss of sexual function or libido

WHAT CAUSES SYNDROME OF HYPERPROLACTINEMIA?

CAUSES

- Hyperprolactinaemia may be caused by either dysinhibition (e.g., compression of the pituitary stalk or reduced dopamine levels) or excess production from a prolactinoma (a pituitary gland adenoma tumour)
- A blood serum prolactin level of 1000–5000 mIU/L could be from either mechanism, but >5000 mIU/L (>200 μg/L) is likely due to the activity of an adenoma; macroadenomas (large tumours over 10 mm diameter) have levels of prolactin up to 100,000 mIU/L

CAUSES

- Hyperprolactinemia inhibits the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus (by increasing the release of dopamine from the arcuate nucleus), which in turn inhibits the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland and results in diminished gonadal sex hormone production (termed hypogonadism)
- In many people, elevated prolactin levels remain unexplained and may represent a form of hypothalamic-pituitary dysregulation

CAUSES

Physiologic hypersecretion	**Pregnancy** **Lactation** Chest wall stimulation **Sleep** **Stress**
Hypothalamic-pituitary stalk damage	Tumors Craniopharyngioma Suprasellar pituitary mass Meningioma Dysgerminoma Metastases Empty sella Lymphocytic hypophysitis Adenoma with stalk compression Granulomas Rathke's cyst Irradiation Trauma Pituitary stalk section Suprasellar surgery

en.wikipedia.org›Hyperprolactinaemia

CAUSES

Pituitary hypersecretion	**Prolactinoma** **Acromegaly**
Systemic disorders	Chronic renal failure Hypothyroidism Cirrhosis Pseudocyesis Epileptic seizures

en.wikipedia.org›Hyperprolactinaemia

CAUSES

Drug-induced hypersecretion	Dopamine receptor blockers Atypical antipsychotics: **risperidone** **Phenothiazines**: **chlorpromazine**, **perphenazine** **Butyrophenones**: **haloperidol** **Thioxanthenes** **Metoclopramide** Dopamine synthesis inhibitors **α-Methyldopa** Catecholamine depletors **Reserpine** **Opiates** H2 antagonists **Cimetidine**, **ranitidine** Imipramines **Amitriptyline**, **amoxapine** Serotonin reuptake inhibitors **Fluoxetine** Calcium channel blockers **Verapamil** **Estrogens** **TRH**

en.wikipedia.org›Hyperprolactinaemia

CAUSES

Medications

- Prolactin secretion in the pituitary is normally suppressed by the brain chemical dopamine
- Drugs that block the effects of dopamine at the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin
- These drugs include the major tranquillizers (phenothiazines), trifluoperazine (Stelazine), and haloperidol (Haldol); antipsychotic medications, such as risperidone and quetiapine; metoclopramide (Reglan), domperidone, cisapride used to treat gastro-oesophageal reflux; medication-induced nausea(such as cancer drugs); and, less often, alpha-methyldopa and reserpine, used to control hypertension; and estrogens and TRH
- The sleep drug ramelteon (Rozerem) also increases the risk of hyperprolactinaemia
- A benzodiazepine analog, etizolam, can also increase the risk of hyperprolactinaemia

CAUSES

Specific diseases

- Prolactinoma or other tumours arising in or near the pituitary — such as those that cause acromegaly may block the flow of dopamine from the brain to the prolactin-secreting cells, likewise, division of the pituitary stalk or hypothalamic disease
- Other causes include chronic renal failure, hypothyroidism, bronchogenic carcinoma and sarcoidosis
- Some women with polycystic ovary syndrome may have mildly-elevated prolactin levels

CAUSES

Specific diseases

- Nonpuerperal mastitis may induce transient hyperprolactinemia (neurogenic hyperprolactinemia) of about three weeks' duration; conversely, hyperprolactinemia may contribute to nonpuerperal mastitis
- Apart from diagnosing hyperprolactinaemia and hypopituitarism, prolactin levels are often checked by physicians in patients that have suffered a seizure, when there is doubt as to whether they have had an epileptic seizure or a non-epileptic seizure
- Shortly after epileptic seizures, prolactin levels often rise, whereas they are normal in non-epileptic seizures

DIAGNOSTICS OF HYPERPROLACTINEMIA?

DIAGNOSTICS

- Test for prolactin blood levels in women with unexplained milk secretion (galactorrhea) or irregular menses or infertility, and in men with impaired sexual function and milk secretion
- While a plain X-ray of the bones surrounding the pituitary may reveal the presence of a large macro-adenoma, the small micro-adenoma will not be apparent
- Magnetic resonance imaging (MRI) is the most sensitive test for detecting pituitary tumours and determining their size
- Computed Tomography (CT scan) also gives an image of the pituitary, but it is less sensitive than the MRI

en.wikipedia.org›Hyperprolactinaemia

TREATMENT OF HYPERPROLACTINEMIA?

TREATMENT

- Treatment usually includes dopamine agonists such as cabergoline, bromocriptine (often preferred when pregnancy is possible), and less frequently lisuride
- A new drug in use is norprolac with the active ingredient quinagolide

WHAT IS DIABETES INSIPIDUS?

6. DIABETES INSIPIDUS 1.1

- Diabetes insipidus (DI) is a condition characterized by excessive thirst and excretion of large amounts of severely dilute urine, with reduction of fluid intake having no effect on the concentration of the urine
- There are different types of DI, each with a different set of causes
- The most common type in humans is the neurological form, called Central DI (CDI), which involves a deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH)
- The second common type of DI is nephrogenic diabetes insipidus (NDI), which is due to kidney or nephron dysfunction caused by an insensitivity of the kidneys or nephrons to ADH
- DI can also be gestational, or caused by alcohol or some types of drug abuse
- DI should not be confused with nocturia

en.academic.ru›dic.nsf/enwiki/28621

CLINICAL PICTURE OF DIABETES INSIPIDUS?

6. DIABETES INSIPIDUS 1.1

SIGNS AND SYMPTOMS

- Excessive urination and also extreme thirst (especially for cold water and sometimes ice or ice water) are typical for DI
- The symptoms of excessive urination and extreme thirst are similar to what is seen in untreated diabetes mellitus, with the distinction that the urine does not contain glucose
- Blurred vision is a rarity
- Signs of dehydration may also appear in some individuals, since the body cannot conserve much (if any) of the water it takes in
- Extreme urination continues throughout the day and the night
- In children, DI can interfere with appetite, eating, weight gain, and growth, as well
- They may present with fever, vomiting, or diarrhea
- Adults with untreated DI may remain healthy for decades as long as enough water is consumed to offset the urinary losses

PATHOPHYSIOLOGY OF DIABETES INSIPIDUS ?

6. DIABETES INSIPIDUS 1.4

PATHOPHYSIOLOGY

- Electrolyte and volume homeostasis is a complex mechanism that balances the body's requirements for blood pressure and the main electrolytes sodium and potassium
- In general, electrolyte regulation precedes volume regulation. When the volume is severely depleted, however, the body will retain water at the expense of deranging electrolyte levels
- The regulation of urine production occurs in the hypothalamus, which produces ADH in the supraoptic and paraventricular nuclei
- After synthesis, the hormone is transported in neurosecretory granules down the axon of the hypothalamic neuron to the posterior lobe of the pituitary gland, where it is stored for later release

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6. DIABETES INSIPIDUS 2.4

PATHOPHYSIOLOGY

- In addition, the hypothalamus regulates the sensation of thirst in the ventromedial nucleus by sensing increases in serum osmolarity and relaying this information to the cortex
- Neurogenic/central DI results from a lack of ADH; occasionally it can present with decreased thirst as regulation of thirst and ADH production occur in close proximity in the hypothalamus
- It is encountered as a result of hypoxic encephalopathy, neurosurgery, autoimmunity or cancer, or sometimes without an underlying cause (idiopathic)

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6. DIABETES INSIPIDUS 3.4

PATHOPHYSIOLOGY

- The main effect or organ for fluid homeostasis is the kidney
- ADH acts by increasing water permeability in the collecting ducts and distal convoluted tubules; specifically, it acts on proteins called aquaporins and more specifically aquaporin 2 in the following cascade
- When released, ADH binds to V2 G-protein coupled receptors within the distal convoluted tubules, increasing cyclic AMP, which couples with protein kinase A stimulating translocation of the aquaporin 2 channel stored in the cytoplasm of the distal convoluted tubules and collecting ducts into the apical membrane
- These transcribed channels allow water into the collecting duct cells

6. DIABETES INSIPIDUS 4.4
PATHOPHYSIOLOGY

- The increase in permeability allows for reabsorption of water into the bloodstream, thus concentrating the urine
- Nephrogenic DI results from lack of Aquaporin channels in the distal collecting duct (decreased surface expression and transcription)
- It is seen in Lithium toxicity, hypercalcemia, hypokalemia
- Hereditary forms of diabetes insipidus account for less than 10% of the cases of diabetes insipidus seen in clinical practice

CLASSIFICATION OF DIABETES INSIPIDUS ?

6. DIABETES INSIPIDUS 1.3
CLASSIFICATION

The several forms of DI are:

- Neurogenic
- Nephrogenic
- Dipsogenic
- Gestational

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6. DIABETES INSIPIDUS 2.3
CLASSIFICATION

Neurogenic

- Main article: Neurogenic diabetes insipidus
- Neurogenic diabetes insipidus, more commonly known as central diabetes insipidus, is due to the lack of vasopressin production in the hypothalamus due to a range of causes
- The underlying causes of Central DI can include vascular, autoimmune, infection, sarcoidosis, some drugs, surgery, head trauma, benign or metastatic pituitary-hypothalamic tumor (particularly originating from breast and lung), although 50% of cases are found to be idiopathic

Nephrogenic

- Main article: Nephrogenic diabetes insipidus
- Nephrogenic diabetes insipidus is due to the inability of the kidney to respond normally to vasopressin

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6. DIABETES INSIPIDUS 3.3

CLASSIFICATION

Dipsogenic

- Dipsogenic DI or primary polydipsia results from excessive intake of fluids as opposed to deficiency of arginine vasopressin. It may be due to a defect or damage to the thirst mechanism, located in the hypothalamus; or due to mental illness

Gestational

- Gestational DI occurs only during pregnancy and the postpartum period
- During pregnancy, women produce vasopressinase in the placenta, which breaks down ADH
- Gestational DI is thought to occur with excessive production and/or impaired clearance of vasopressinase
- Most cases of gestational DI can be treated with desmopressin (ddAVP), but not vasopressin
- In rare cases, however, an abnormality in the thirst mechanism causes gestational DI, and desmopressin should not be used

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DIAGNOSTICS OF DIABETES INSIPIDUS ?

6. DIABETES INSIPIDUS 1.3

DIAGNOSTICS

- To distinguish DI from other causes of excess urination, blood glucose levels, bicarbonate levels, and calcium levels need to be tested. Measurement of blood electrolytes can reveal a high sodium level (hypernatremia as dehydration develops)
- Urinalysis demonstrates a dilute urine with a low specific gravity. Urine osmolarity and electrolyte levels are typically low
- A fluid deprivation test is another way of distinguishing DI from other causes of excessive urination
- It is also used to help determine what DI is caused by:
- a defect in ADH production
- a defect in the kidneys' response to ADH

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6. DIABETES INSIPIDUS 2.3

DIAGNOSTICS

- This test measures the changes in body weight, urine output, and urine composition when fluids are withheld to induce dehydration
- The body's normal response to dehydration is to conserve water by concentrating the urine
- Those with DI continue to urinate large amounts of dilute urine in spite of water deprivation
- In primary polydipsia, the urine osmolality should increase and stabilize at above 280 Osm/kg with fluid restriction, while a stabilization at a lower level indicates diabetes insipidus
- Stabilization in this test means, more specifically, when the increase in urine osmolality is less than 30 Osm/kg per hour for at least 3 hours
- Sometimes measuring blood levels of ADH toward the end of this test is also necessary, but is more time consuming to perform

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6. DIABETES INSIPIDUS 3.3

DIAGNOSTICS

- To distinguish between the main forms, desmopressin stimulation is also used; desmopressin can be taken by injection, a nasal spray, or a tablet
- While taking desmopressin, a patient should drink fluids or water only when thirsty and not at other times, as this can lead to sudden fluid accumulation in the central nervous system
- If desmopressin reduces urine output and increases urine osmolarity, the hypothalamic production of ADH is deficient, and the kidney responds normally to exogenous vasopressin (desmopressin)
- If the DI is due to renal pathology, desmopressin does not change either urine output or osmolarity (since the endogenous vasopressin levels are already high)

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TREATMENT OF DIABETES INSIPIDUS ?

TREATMENT

Central DI

- Central DI and gestational DI respond to desmopressin which is given as intranasal or oral tablets
- Carbamazepine, an anticonvulsive medication, has also had some success in this type of DI. Also, gestational DI tends to abate on its own four to six weeks following labor, though some women may develop it again in subsequent pregnancies
- In dipsogenic DI, desmopressin is not usually an option

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TREATMENT

Nephrogenic DI

- Desmopressin will be ineffective in nephrogenic DI and it is treated by reversing the underlying cause and replacing the free water deficit
- The diuretic hydrochlorothiazide (a thiazide diuretic) or indomethacin can be used to create mild hypovolemia which encourages salt and water uptake in proximal tubule and thus improve nephrogenic diabetes insipidus
- Amiloride has additional benefit of blocking Li uptake
- Thiazide diuretics are sometimes combined with amiloride to prevent hypokalemia
- It seems paradoxical to treat an extreme diuresis with a diuretic, and the exact mechanism of action is unknown but the thiazide diuretics will decrease distal convoluted tubule reabsorption of sodium and water, thereby causing diuresis
- This decreases plasma volume, thus lowering the glomerular filtration rate and enhancing the absorption of sodium and water in the proximal nephron
- Less fluid reaches the distal nephron, so overall fluid conservation is obtained

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6. DIABETES INSIPIDUS 3.3

TREATMENT

- Lithium-induced nephrogenic DI may be effectively managed with the administration of amiloride, a potassium-sparing diuretic often used in conjunction with thiazide or loop diuretics
- Clinicians have been aware of lithium toxicity for many years, and traditionally have administered thiazide diuretics for lithium-induced polyuria and nephrogenic diabetes insipidus
- However, amiloride has recently been shown to be a successful treatment for this condition

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WHAT ARE OVERWEIGHT AND OBESITY?

7. OBESITY

7. OBESITY 1.4

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2).

The WHO definition is:

- a BMI greater than or equal to 25 is overweight
- a BMI greater than or equal to 30 is obesity.

medical-dictionary.thefreedictionary.com›**obesity**

EPIDERMIOLOGY

- In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.
- Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2014.
- In 2014, 39% of adults aged 18 years and over (38% of men and 40% of women) were overweight.
- The worldwide prevalence of obesity more than doubled between 1980 and 2014.

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SOME REASONS FOR THE INCREASING PREVALENCE OF OBESITY – THE 'OBESOGENIC' ENVIRONMENT

Increasing energy intake

- ↑ Portion sizes
- ↑ Snacking and loss of regular meals
- ↑ Energy-dense food (mainly fat)
- ↑ Affluence

Decreasing energy expenditure

- ↑ Car ownership
- ↓ Walking to school/work
- ↑ Automation; ↓ manual labour
- ↓ Sports in schools
- ↑ Time spent on computer games and watching TV
- ↑ Central heating

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AETIOLOGY

Accumulation of fat results from a discrepancy between energy consumption and energy expenditure that is too large to be defended by the hypothalamic regulation of BMR.

A continuous small daily positive energy balance of only 0.2–0.8 MJ (50–200 kcal; < 10% of intake) would lead to weight gain of 2–20 kg over a period of 4–10 years.

The pandemic of obesity reflects changes in both energy intake and energy expenditure.

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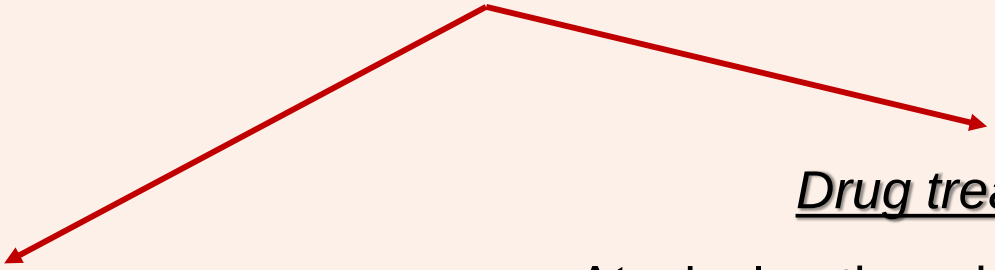
CAUSES OF OBESITY

REVERSIBLE CAUSES OF OBESITY



Endocrine factors

- Hypothyroidism
- Cushing's syndrome
- Insulinoma
- Hypothalamic tumours or Injury

Drug treatments

- Atypical antipsychotics (e.g. olanzapine)
- Sulphonylureas, thiazolidinediones, insulin
- Pizotifen
- Corticosteroids
- Sodium valproate
- β-blockers

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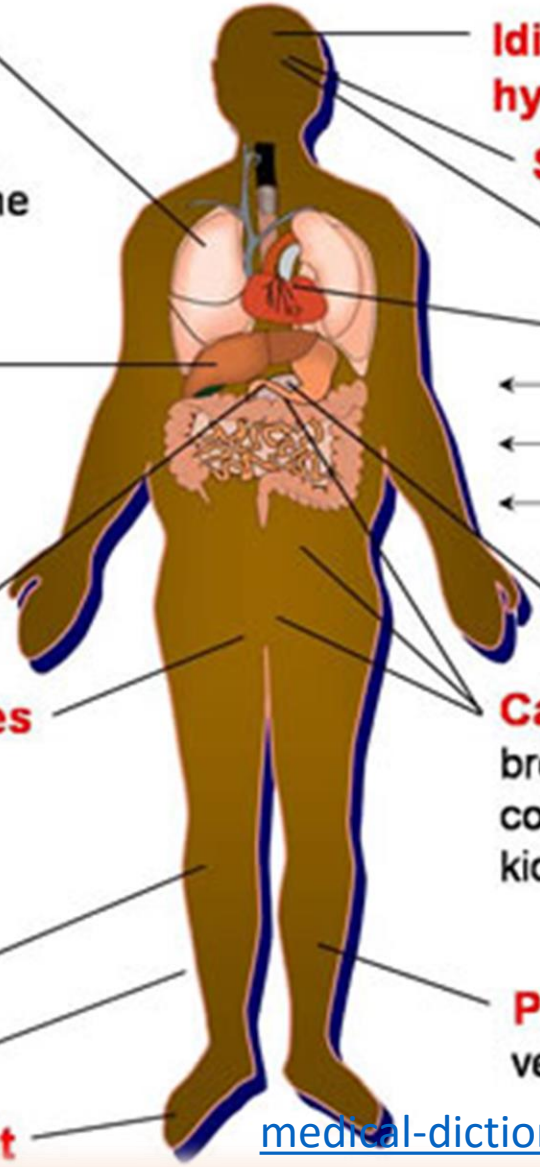
7. OBESITY

Table 1: Nutritional status based on the WHO and "Asian criteria" values		
Nutritional Status	WHO criteria BMI cut-off	"Asian criteria" BMI cut-off
Underweight	<18.5	<18.5
Normal	18.5 – 24.9	18.5 – 22.9
Overweight	25 – 29.9	23 – 24.9
Pre-Obese	-	25 – 29.9
Obese	≥30	≥30
Obese Type 1 (obese)	30 – 40	30 – 40
Obese Type 2 (morbid obese)	40.1 – 50	40.1 – 50
Obese Type 3 (super obese)	>50	>50

emedicinehealth.com›**obesity**/article_em.htm

COMPLICATIONS OF OBESITY

Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

Severe pancreatitis

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Phlebitis
venous stasis

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OTHER COMPLICATIONS

- Psychological morbidity (low self-esteem, depression)
- Socioeconomic disadvantage (lower income, less likely to be promoted)
- Gallstones
- Colorectal cancer
- Skin infections (groin and submammary candidiasis, hidradenitis)

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WEIGHT-LOSS–ASSOCIATED MORBIDITY

Although obesity in itself is associated with increased morbidity and mortality, massive, poorly monitored weight loss and/or weight cycling can have equally dire consequences.

Among the important potential complications to watch out for in the setting of weight loss are the following:

- Cardiac arrhythmias → Electrolyte derangements :hypokalemia is the most important of these, hyperuricemia
- Psychological sequelae → depression and the development of eating disorders (particularly binge-eating disorders)
- Cholelithiasis

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TREATMENT OF OBESITY ?

TREATMENT

MANAGEMENT OF OBESITY

The management plan will vary according to the severity of the obesity and the associated risk factors and complications.

It will also be influenced by availability of resources; health-care providers and regulators have generally been careful not to recommend expensive interventions (especially long-term drug therapy and surgery) for everyone who is overweight.

Instead, most guidelines focus resources on short-term interventions in those who have high health risks and comorbidities associated with their obesity, and who have demonstrated their capacity to alter their lifestyle to achieve weight loss.

TREATMENT

MANAGEMENT(Lifestyle advice)

Treatment of obesity starts with comprehensive lifestyle management (ie, diet, physical activity, behavior modification), which should include the following:

- Self-monitoring of caloric intake and physical activity
- Goal setting
- Stimulus control
- Nonfood rewards
- Relapse prevention

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TREATMENT

MANAGEMENT OF OBESITY

In January, 2015, the Endocrine Society released new guidelines on the treatment of obesity to include the following:

Diet, exercise, and behavioral modification should be included in all obesity management approaches for body mass index (BMI) of 25 kg/m ^{2} or higher.

Other tools, such as pharmacotherapy for BMI of 27 kg/m ^{2} or higher with comorbidity or BMI over 30 kg/m2 and bariatric surgery for BMI of 35 kg/m ^{2}with comorbidity or BMI over 40 kg/m ^{2}, should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when this is possible.

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TREATMENT

To promote long-term weight maintenance, the use of approved weight loss medication (over no pharmacological therapy) is suggested to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI of 30 kg/m ^{2} or higher or in individuals with a BME of 27 kg/m ^{2} and at least one associated comorbid medical condition (eg, hypertension, dyslipidemia, type 2 diabetes mellitus, and obstructive sleep apnea)

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TREATMENT

Surgery

In patients with morbid obesity associated with comorbidities, bariatric surgery is the only available therapeutic modality associated with clinically significant and relatively sustained weight loss.

Well-performed bariatric surgery, in carefully selected patients and with a good multidisciplinary support team, substantially ameliorates the morbidities associated with severe obesity.

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