Hypothalamo-hypophiseal disorders (part 1)

Lorina Vudu

dr.m., conf.univ

Endocrine System

- Overview
- Endocrine Glands
- Hormones and Their Actions
- Hypothalamus and Pituitary Gland
- Endocrine Disorders

Endocrine System Components

- endocrine system - glands, tissues, and cells that are spread in other organs and tissues (nervous system, digestive tract, pancreas, kidneys, heart, thyroid, etc) that secrete hormones
- endocrinology – is the science that studies the endocrine system's structure and function, and the hormone's physiological and pathological biosynthesis, actions and metabolism, the diagnosis and treatment of its disorders
- endocrine glands – organs that produce hormones
- hormones - are the endocrine system's information messengers, chemical messengers transported by the bloodstream that stimulate responses in another tissue or organ, often far away

Hormones - Overview of functions

- regulate chemical composition and volume of internal environment: water and electrolytes
- regulate metabolism and energy balance
- regulate contraction of smooth and cardiac muscle fibers
- regulate homeostasis despite disruptions
- regulate activities of immune system
- integration of growth and development
- contribute to basic processes of reproduction

NATURE OF HORMONES

Hormones can be divided into five major classes:

(1) *amino acid derivatives* such as dopamine, catecholamines, and thyroid hormone;

(2) *small neuropeptides* such as gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), somatostatin, and vasopressin;

(3) *large proteins* such as insulin, luteinizing hormone (LH), and PTH produced by classic endocrine glands;

(4) *steroid hormones* such as cortisol and estrogen that are synthesized from cholesterol-based precursors; and

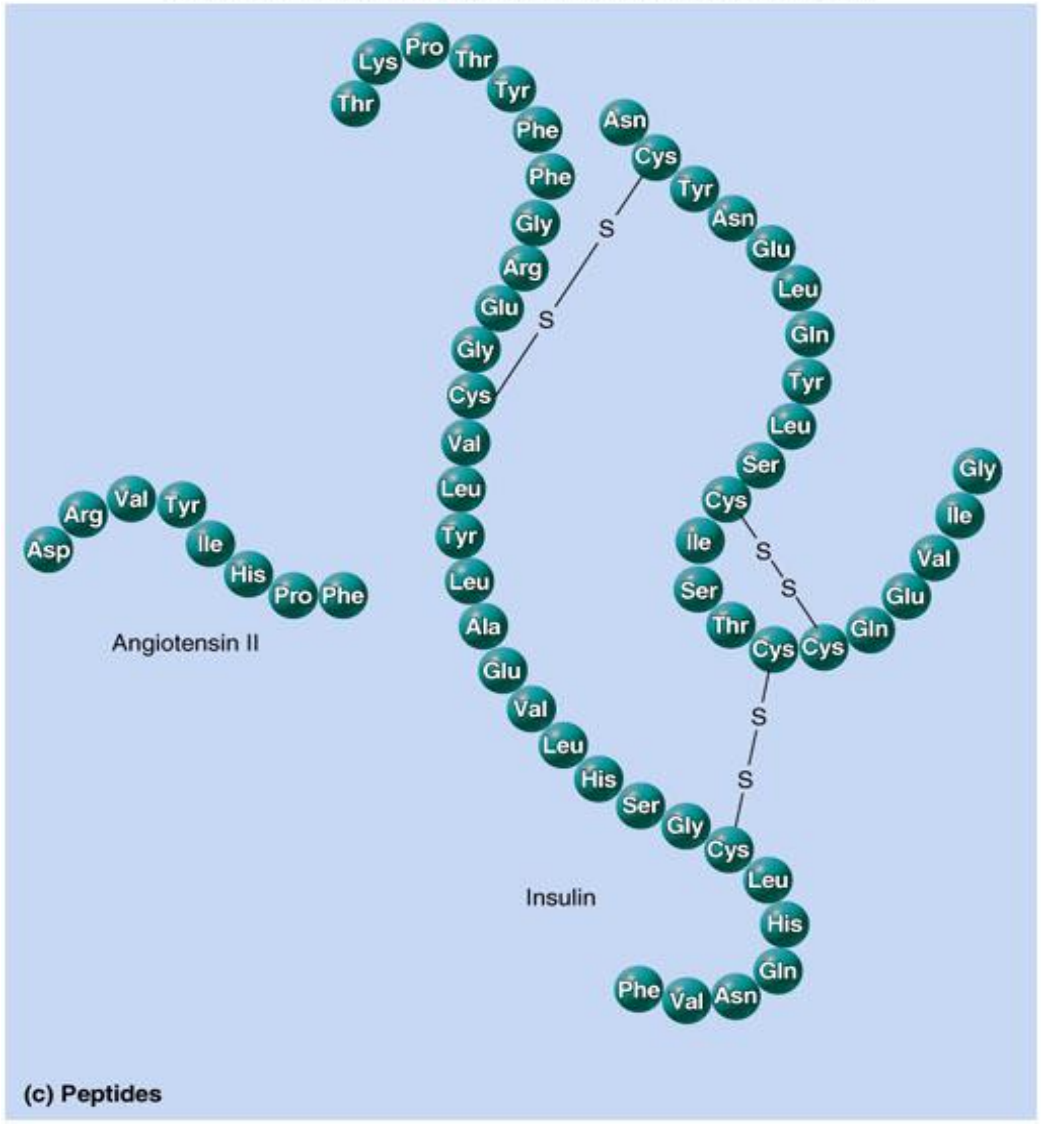
(5) *vitamin derivatives* such as retinoids (vitamin A) and vitamin D.

As a rule, amino acid derivatives and peptide hormones interact with cell-surface membrane receptors. Steroids, thyroid hormones, vitamin D, and retinoids are lipid-soluble and interact with intracellular nuclear receptors.

Amino Acid Based Hormones

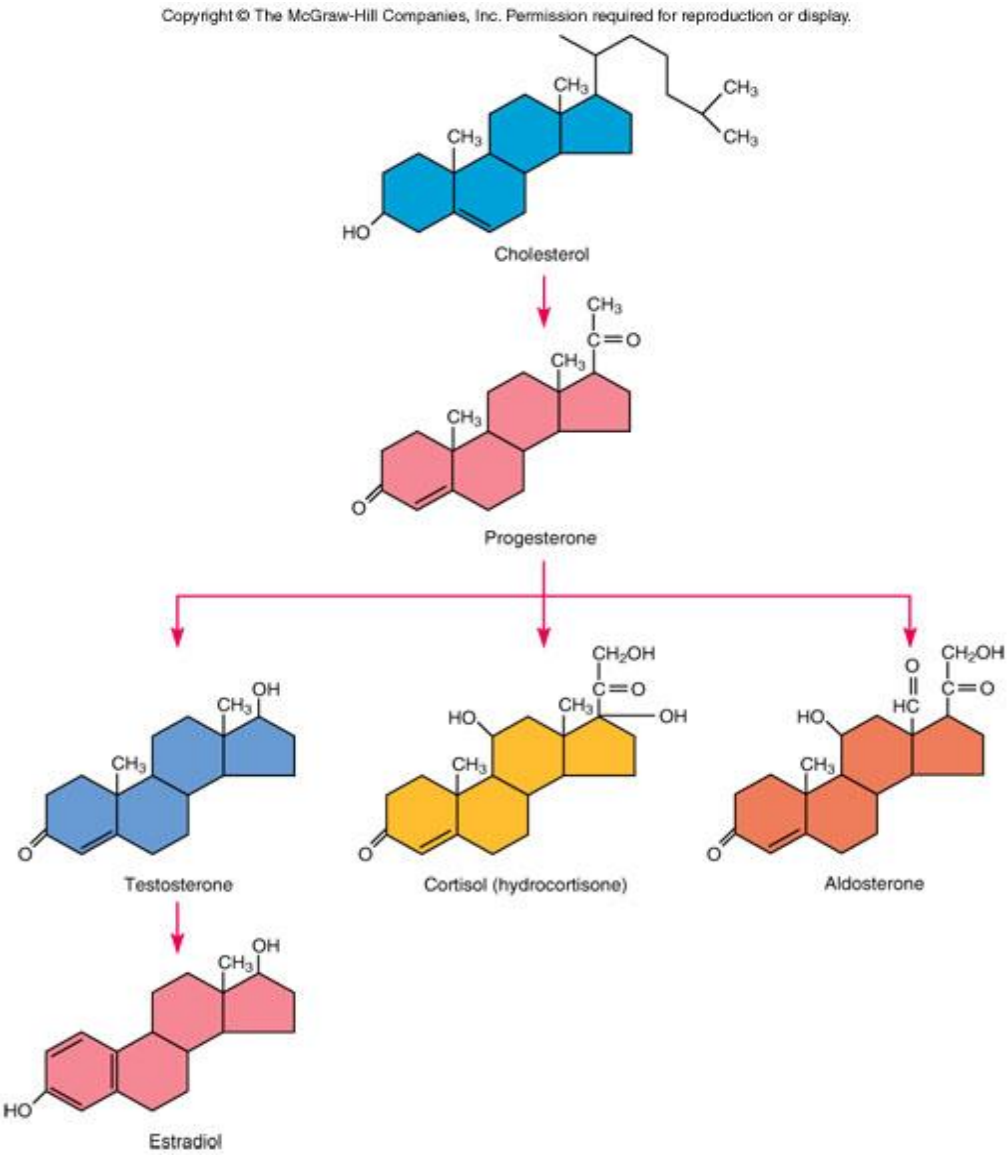
- Most hormones belong to this class, including:
  - Glucagon, Insulin

    are functional polypeptides
  - Specificity of hormone is determined by 3-D configuration.
  - Polar molecules: water soluble allowing them to be transported in the blood.



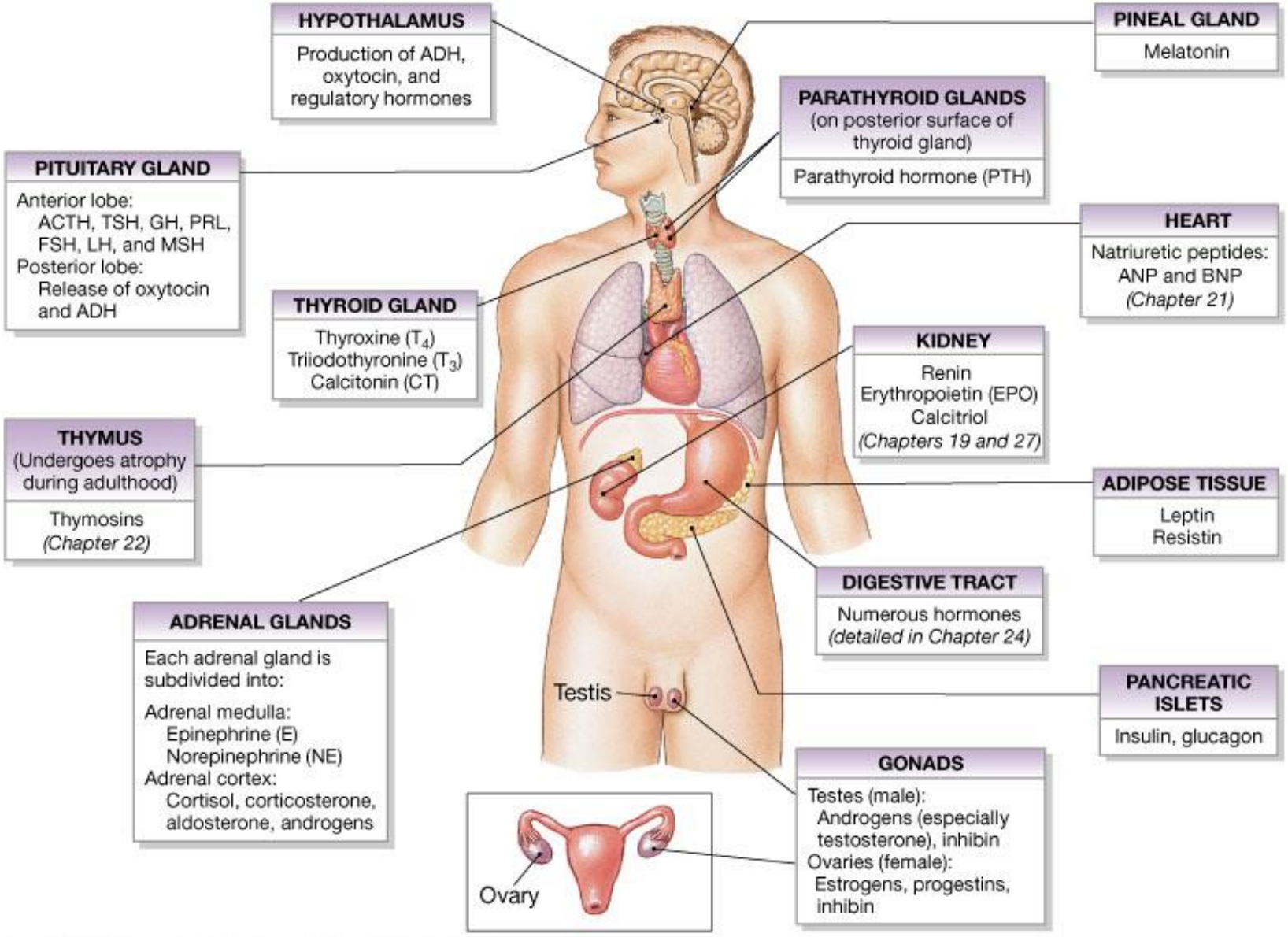
Steroids (Lipid Based Hormones)

- Steroids – derived from cholesterol
  - Non polar molecules: are hydrophobic therefore require a protein carrier to be transported in the blood.
- Adrenocortical hormones
  - Aldosterone
- Gonadal
  - Estrogen, Testosterone



Hormone Action

- Hormones alter target cell activity by one of two mechanisms
  - Second messengers involving:
    - Amino acid–based hormones cannot pass through the membrane.
      - They attach to a specific regulatory G protein on surface of cell membrane.
      - This sets off a series of steps that can activate or inhibit numerous functioning enzymes in the cell.
  - Direct gene activation involving steroid hormones
    - Since steroid based hormones are lipophillic they can diffuse through the cell membrane and enter the nucleus where they can alter gene expression and alter the rate of protein synthesis.


HYPOTHALAMUS
Production of ADH, oxytocin, and regulatory hormones
PINEAL GLAND
Melatonin
PARATHYROID GLANDS
(on posterior surface of thyroid gland)
Parathyroid hormone (PTH)
PITUITARY GLAND
Anterior lobe:
ACTH, TSH, GH, PRL, FSH, LH, and MSH
Posterior lobe:
Release of oxytocin and ADH
HEART
Natriuretic peptides: ANP and BNP
(Chapter 21)
THYROID GLAND
Thyroxine (T_4)
Triiodothyronine (T_3)
Calcitonin (CT)
KIDNEY
Renin
Erythropoietin (EPO)
Calcitriol
(Chapters 19 and 27)
THYMUS
(Undergoes atrophy during adulthood)
Thymosins
(Chapter 22)
ADIPOSE TISSUE
Leptin
Resistin
DIGESTIVE TRACT
Numerous hormones
(detailed in Chapter 24)
ADRENAL GLANDS
Each adrenal gland is subdivided into:
Adrenal medulla:
Epinephrine (E)
Norepinephrine (NE)
Adrenal cortex:
Cortisol, corticosterone, aldosterone, androgens
Testis
PANCREATIC ISLETS
Insulin, glucagon
GONADS
Testes (male):
Androgens (especially testosterone), inhibin
Ovaries (female):
Estrogens, progestins, inhibin
Ovary

Comparison of Endocrine and Exocrine Glands

- exocrine glands
  - ducts carry secretion to an epithelial surface or the mucosa of the digestive tract – 'external secretions'
  - extracellular effects (food digestion)

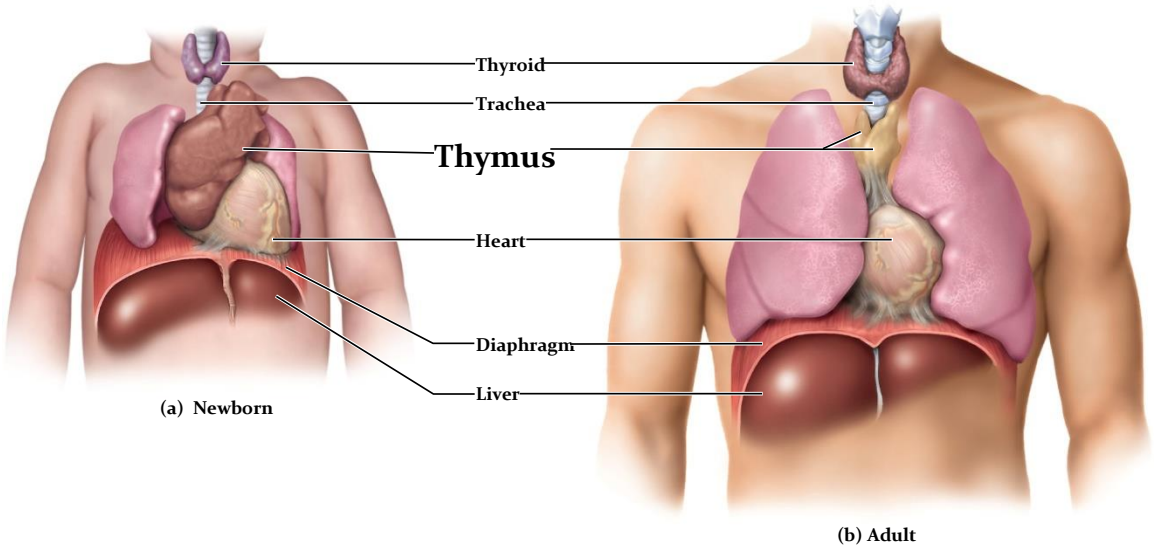
- endocrine glands
  - no ducts
  - contain dense capillary networks to allow easy uptake of hormones into bloodstream
  - 'internal secretions'
  - intracellular effects such as altering target cell metabolism

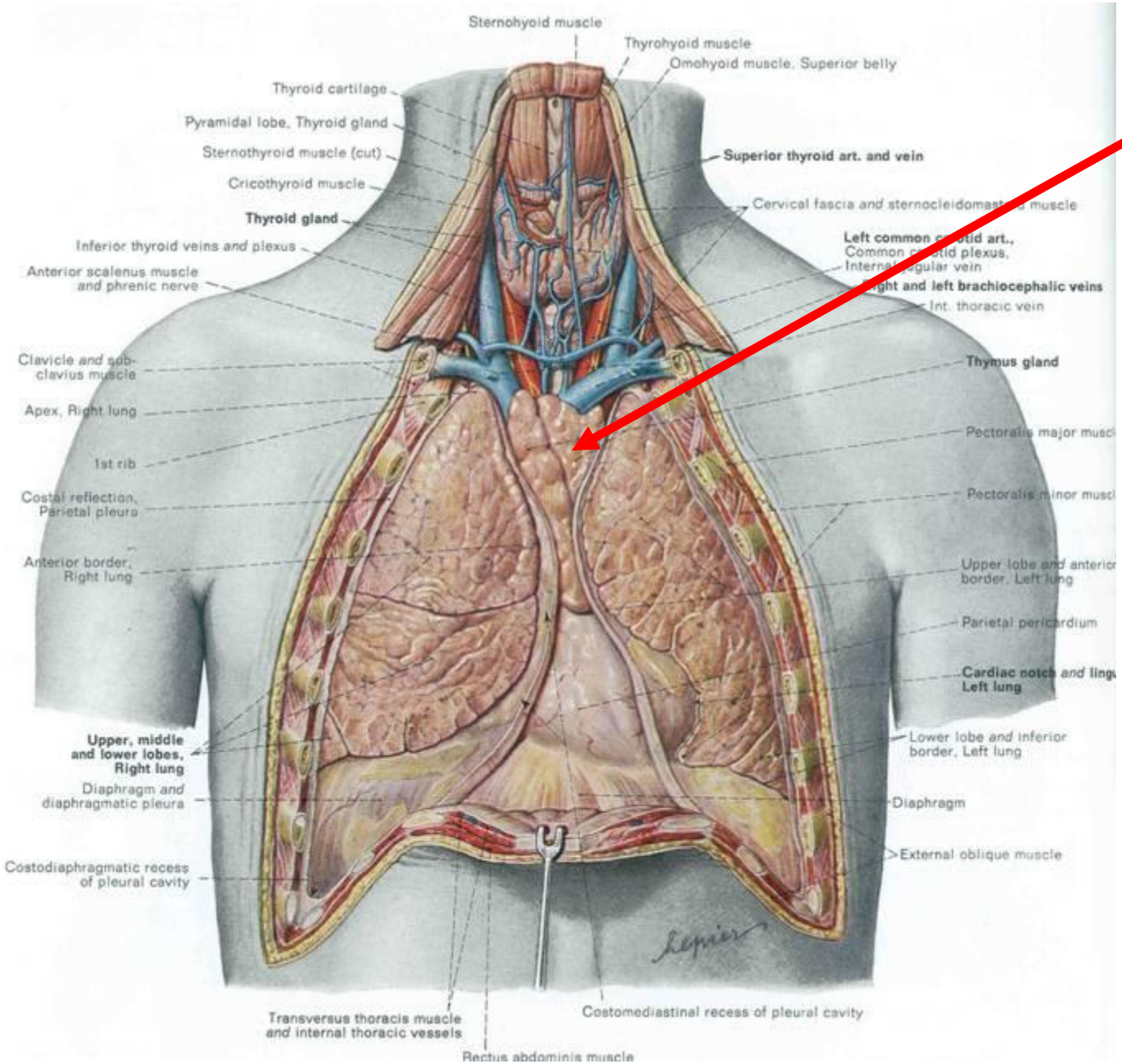
Pineal Gland

- attached to roof of third ventricle beneath the posterior end of corpus callosum
- after age 7, it undergoes involution (shrinkage)
- may synchronize physiological function with 24-hour circadian rhythms of daylight and darkness
  - synthesizes melatonin from serotonin during the night
- may regulate timing of puberty in humans
- seasonal affective disorder (SAD) occurs in winter or northern climates
  - depression, sleepiness, irritability and carbohydrate craving

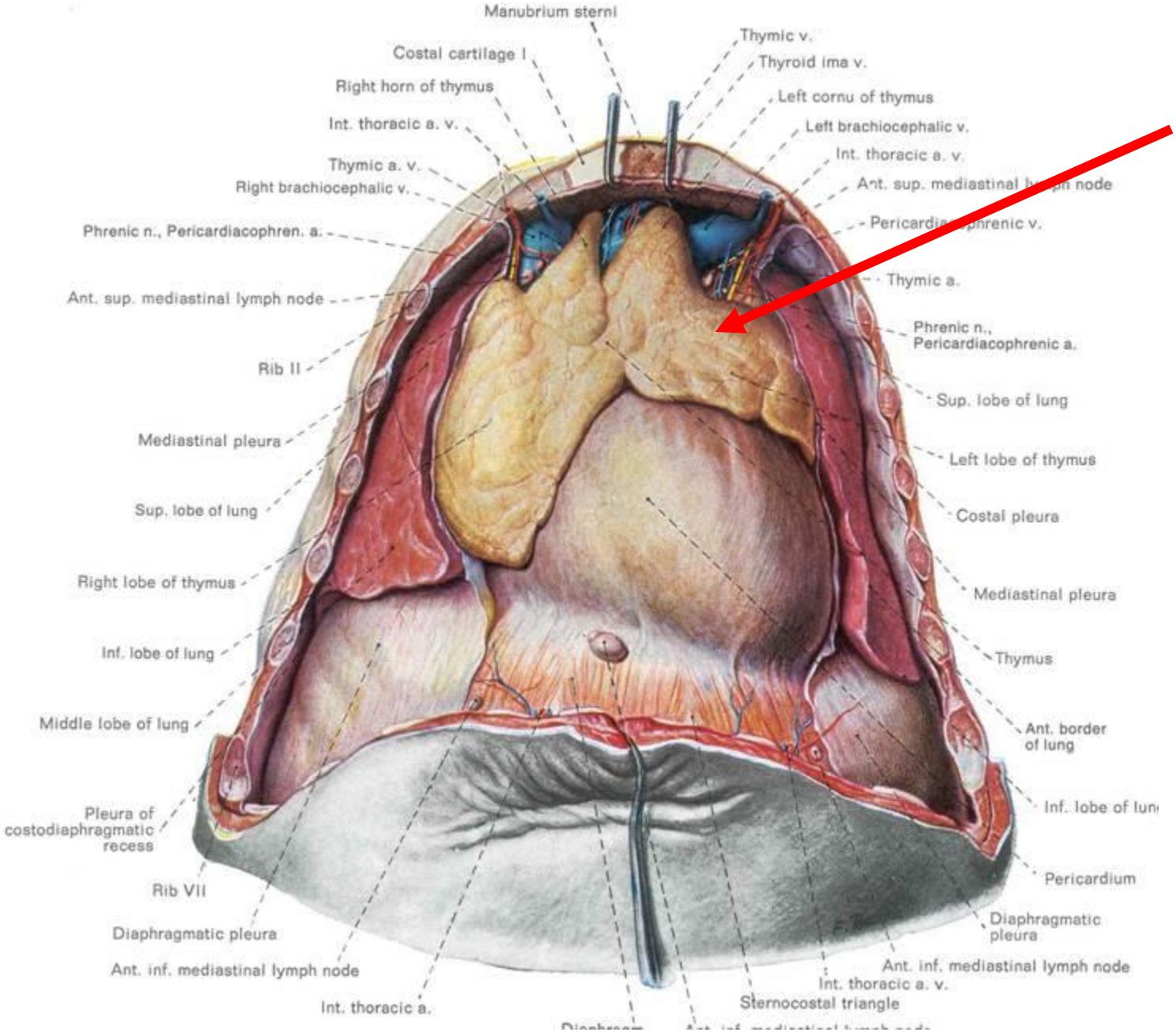
Thymus

- plays a role in three systems: endocrine, lymphatic, and immune
- bilobed gland in the mediastinum superior to the heart
- important in immune defense
- secretes hormones that affect immune activity





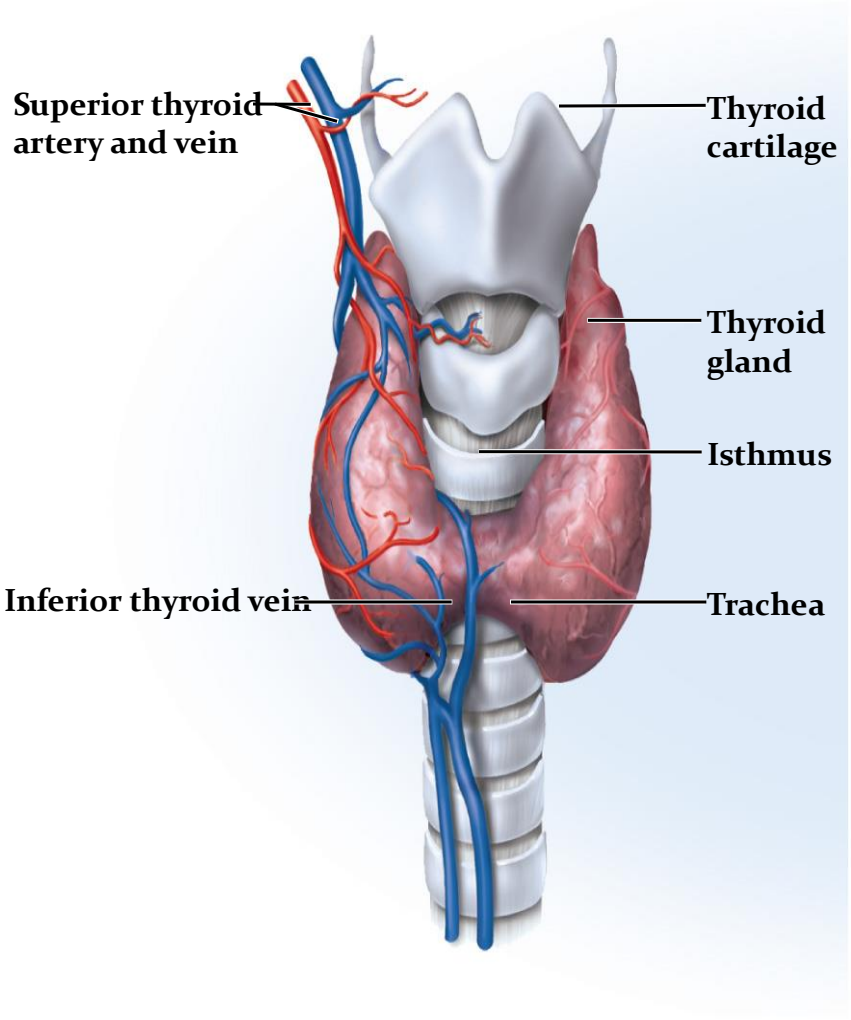
Adult
THYMUS



One-year old THYMUS

Thyroid Gland Anatomy

Butterfly-shaped



secretes thyroxine (T_4: 4 iodine atoms) and triiodothyronine (T_3)

- increases metabolic rate, O_2 consumption, heat production (calorigenic effect), appetite, growth hormone secretion, alertness and quicker reflexes

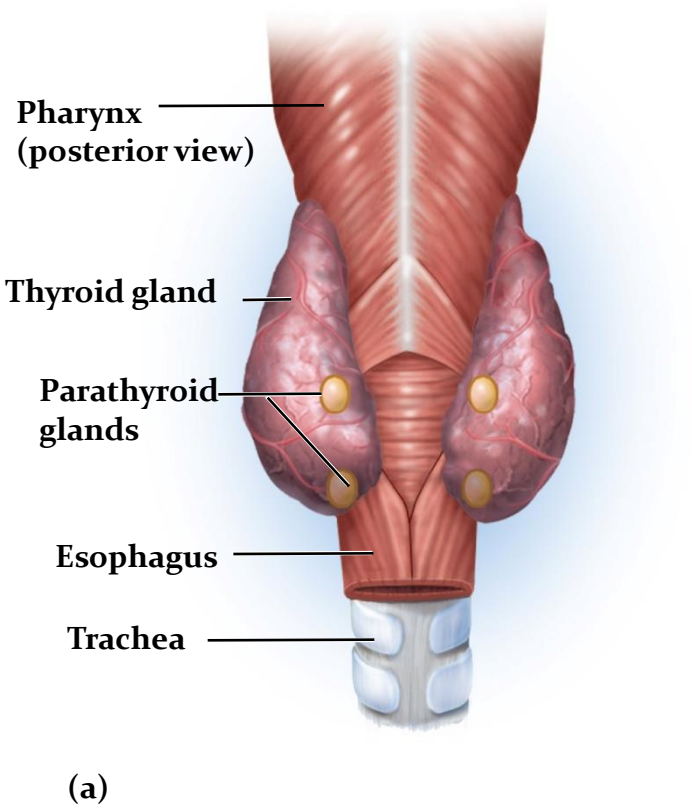
parafollicular (C or clear) cells secrete calcitonin with rising blood calcium

- stimulates osteoblast activity and bone formation

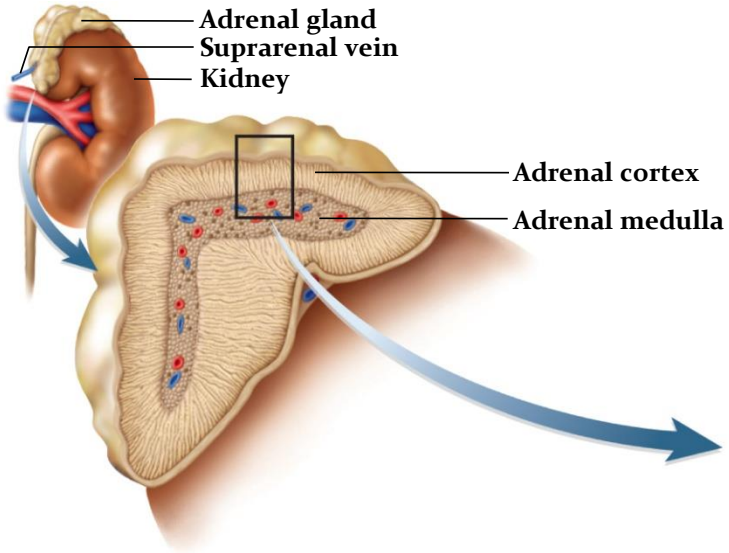
Parathyroid Glands

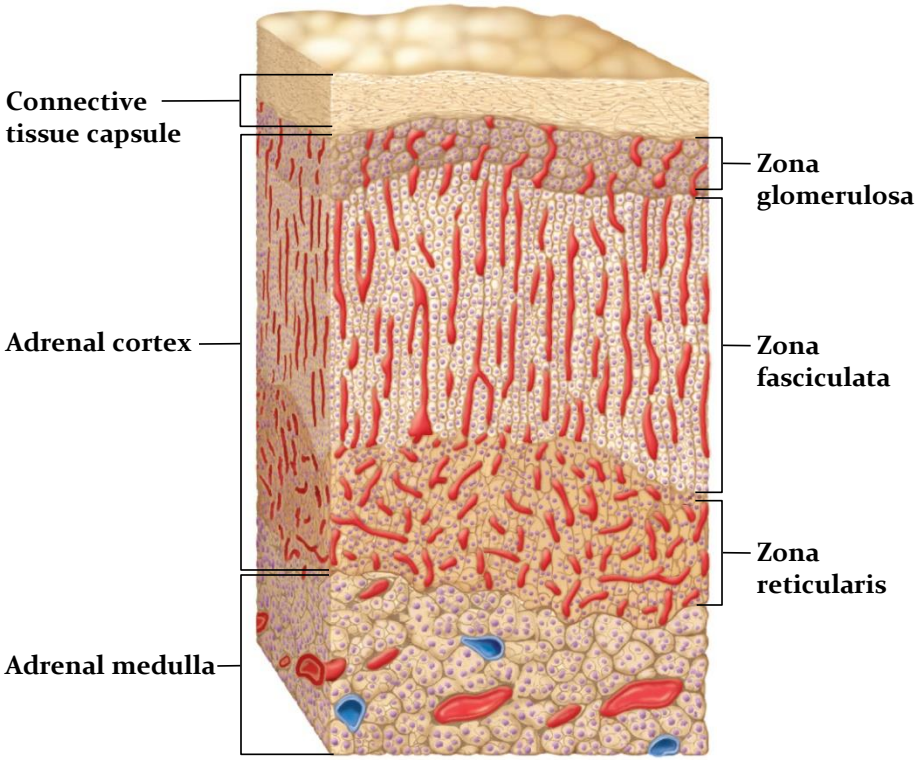
- usually four glands partially embedded in posterior surface of thyroid gland

- secrete parathyroid hormone (PTH)
  - increases blood Ca^{2+} levels
    - promotes synthesis of calcitriol
    - increases absorption of Ca^{2+}
    - decreases urinary excretion
    - increases bone resorption



Adrenal Gland





- small gland that sits on top of each kidney
- adrenal cortex and medulla formed by merger of two fetal glands with different origins and functions

Adrenal Medulla

- adrenal medulla – inner core, 10% to 20% of gland

- has dual nature: endocrine gland and sympathetic ganglion of sympathetic nervous system
  - when stimulated, releases catecholamines (epinephrine and norepinephrine) and a trace of dopamine directly into the bloodstream

- effect is longer lasting than neurotransmitters
  - increases alertness and prepares body for physical activity
    - mobilize high energy fuels, lactate, fatty acids, and glucose
  - increases blood pressure, heart rate, blood flow to muscles, pulmonary air flow and metabolic rate
  - decreases digestion and urine production

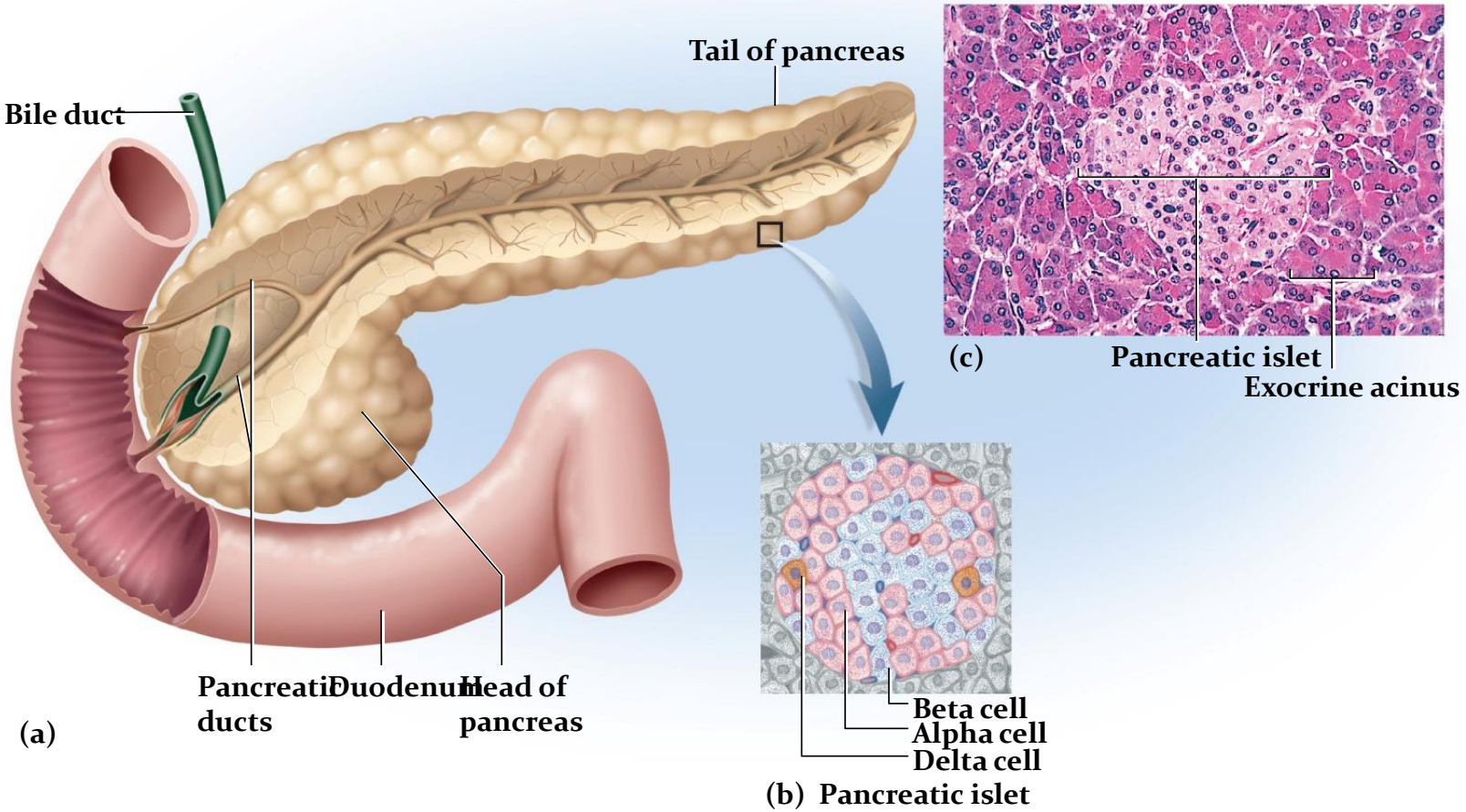
Adrenal Cortex

- surrounds adrenal medulla and produces more than 25 steroid hormones called corticosteroids or corticoids
- secretes 3 classes of steroid hormones
  - mineralocorticoids
  - glucocorticoids
  - sex steroids

Categories of Corticosteroids

- **mineralocorticoids**
  - regulate electrolyte balance
  - aldosterone stimulates Na^+ retention and K^+ excretion, water is retained with sodium by osmosis, so blood volume and blood pressure are maintained
- **glucocorticoids**
  - regulate metabolism of glucose and other fuels
  - especially cortisol, stimulates release of fuels into blood
  - helps body adapt to stress and repair tissues
  - anti-inflammatory effect can become immune suppression in long-term use
- **sex steroids**
  - androgens – sets libido; large role in prenatal male development
  - estradiol – small quantity, but important after menopause for sustaining adult bone mass

Pancreas



- exocrine digestive gland and endocrine cell clusters (pancreatic islets) found inferior and posterior to stomach.

Pancreatic Hormones

- 1-2 million pancreatic islets (Islets of Langerhans) produce hormones
  - other 98% of pancreas cells produce digestive enzymes
- insulin secreted by B or beta (β) cells
  - secreted during and after meal when glucose and amino acid blood levels are rising
  - stimulates cells to absorb these nutrients and store or metabolize them lowering blood glucose levels
    - promotes synthesis of glycogen, fat, and protein
    - suppresses use of already-stored fuels
  - insufficiency or inaction is cause of diabetes mellitus

Pancreatic Hormones

- glucagon – secreted by A or alpha (α) cells
  - released between meals when blood glucose concentration is falling
  - in liver, stimulates release of glucose into the circulation raising blood glucose level
  - in adipose tissue, stimulates fat catabolism
  - glucagon also released to rising amino acid levels in blood, promotes amino acid absorption

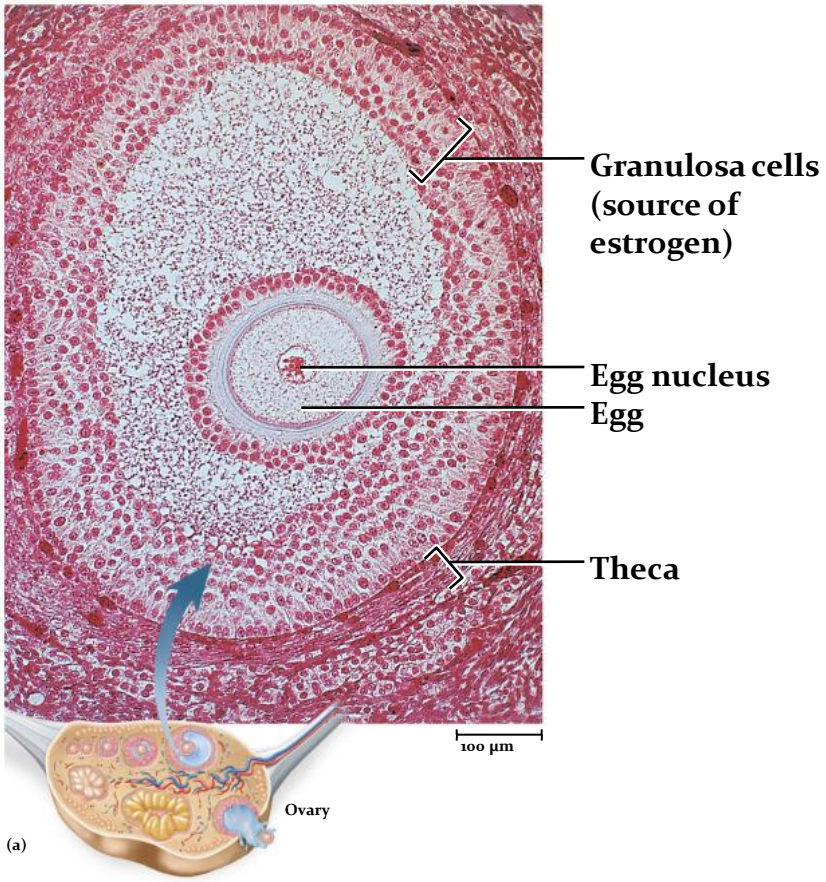
Pancreatic Hormones

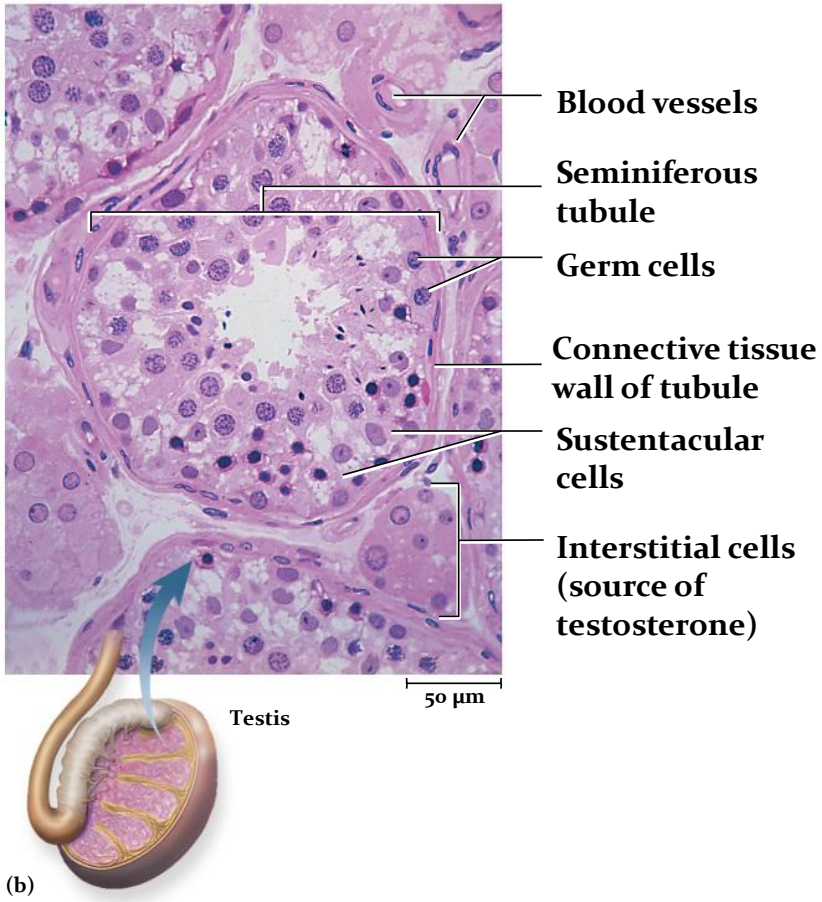
- **somatostatin** secreted by D or delta (δ) cells
  - partially suppresses secretion of glucagon and insulin
  - inhibits nutrient digestion and absorption which prolongs absorption of nutrients
- **pancreatic polypeptide** secreted by PP cells (F cells)
  - inhibits gallbladder contraction and secretion pancreatic digestive enzymes
- **gastrin** secreted by G cells
  - stimulates stomach acid secretion, motility and emptying

Hormones and the Pancreas

- hyperglycemic hormones raise blood glucose concentration
  - glucagon, growth hormone, epinephrine, norepinephrine, cortisol, and corticosterone
- hypoglycemic hormones lower blood glucose
  - insulin

Histology of Gonads





ovaries and testes are both endocrine and exocrine

exocrine product – whole cells - eggs and sperm

endocrine product - gonadal hormones – mostly steroids

Ovary

- secrete estradiol
- after ovulation, the remains of the follicle becomes the corpus luteum
  - secretes progesterone for 12 days following ovulation
  - follicle and corpus luteum secrete inhibin
- functions of estradiol and progesterone
  - development of female reproductive system and physique including adolescent bone growth
  - regulate menstrual cycle, sustain pregnancy
  - prepare mammary glands for lactation
- inhibin suppresses FSH secretion from anterior pituitary

Testes

- microscopic seminiferous tubules produce sperm
  - tubule walls contain sustentacular cells
  - interstitial cells lie in clusters between tubules
- testicular hormones
  - testosterone and other steroids from interstitial cells (cells of Leydig) nestled between the tubules
    - stimulates development of male reproductive system in fetus and adolescent, and sex drive
    - sustains sperm production
  - inhibin from sustentacular (Sertoli) cells
    - limits FSH secretion in order to regulate sperm production

Endocrine Functions of Other Organs

- skin
  - keratinocytes make cholecalciferol using UV from sun
- liver – involved in the production of at least five hormones
  - converts cholecalciferol into calcidiol
  - secretes angiotensinogen (precursor for BP regulation)
  - secretes 15% of erythropoietin (stimulates bone marrow)
  - hepcidin – promotes intestinal absorption of iron
  - source of IGF-I that controls action of growth hormone

Endocrine Functions of Other Organs

- kidneys – plays role in production of three hormones
  - converts calcidiol to calcitriol, the active form of vitamin D
  - secrete renin that converts angiotensinogen to angiotensin I
  - produce 85% of erythropoietin
- heart
  - cardiac muscle secretes atrial and brain natriuretic peptides in response to an increase in blood pressure
  - lowers blood pressure
- stomach and small intestine: at least ten enteric hormones
  - coordinate digestive motility and glandular secretion

Endocrine Functions of Other Organs

- adipose tissue secretes leptin - slows appetite
- osseous tissue – osteocalcin secreted by osteoblasts
  - increases insulin sensitivity of body tissues
  - inhibits weight gain and onset of type 2 diabetes mellit
- placenta
  - secretes estrogen, progesterone and others
    - regulate pregnancy, development of fetus

Hormone Receptors

- hormones only stimulate cells that have receptors for them
- receptors are protein or glycoprotein molecules:
  - on plasma membrane, in cytoplasm, or in nucleus
- receptors act like switches, turning on metabolic pathways when hormone binds to them
- usually each target cell has a few thousand receptors for a given hormone
- receptor-hormone interactions exhibit specificity and saturation
  - specific receptor for each hormone
  - saturated when all receptor molecules are occupied by hormone

Mechanisms of endocrine disease

- Endocrine disorders result from hormone deficiency, hormone excess or hormone resistance
- Almost without exception, hormone deficiency causes disease
  - One notable exception is calcitonin deficiency
- Deficiency usually is due to destructive process occurring at gland in which hormone is produced—infection, infarction, physical compression by tumor growth, autoimmune attack

Type 1 Diabetes

Mechanisms of endocrine disease

- Deficiency can also arise from genetic defects in hormone production—gene deletion or mutation, failure to cleave precursor, specific enzymatic defect (steroid or thyroid hormones)

Congenital Adrenal Hyperplasia

- Inactivating mutations of receptors can cause hormone deficiency

Testicular Feminization Syndrome

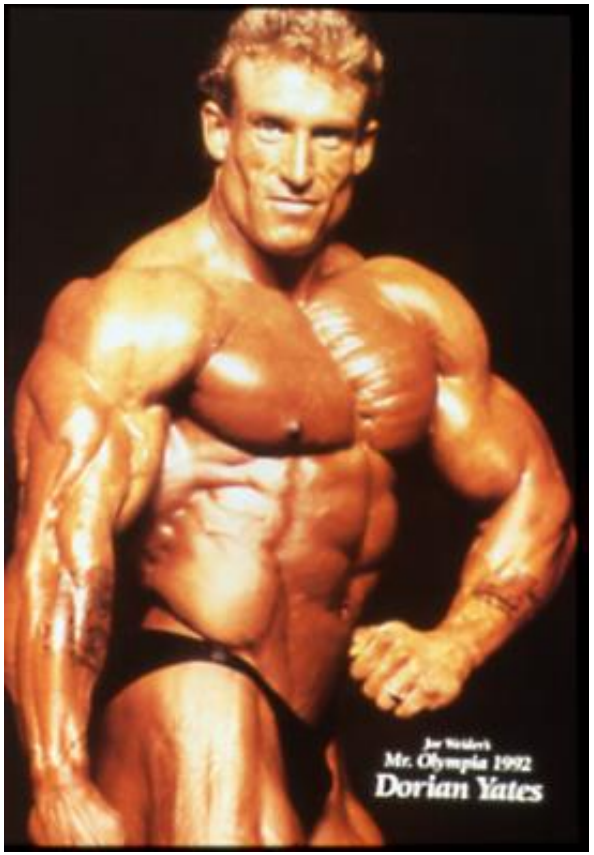
Mechanisms of endocrine disease

- Hormone excess usually results in disease
- Hormone may be overproduced by gland that normally secretes it, or by a tissue that is not an endocrine organ.
- Endocrine gland tumors produce hormone in an unregulated manner.

Cushing's Syndrome

Mechanisms of endocrine disease

- Exogenous ingestion of hormone is the cause of hormone excess—for example, glucocorticoid excess or anabolic steroid abuse



Mechanisms of endocrine disease

- Activating mutations of cell surface receptors cause aberrant stimulation of hormone production by endocrine gland.
  - McCune-Albright syndrome usually caused by mosaicism for a mutation in a gene called GNAS1 (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide 1).
  - The activating mutations render the GNAS1 gene functionally constitutive, turning the gene irreversibly on, so it is constantly active. This occurs in a mosaic pattern, in some tissues and not others.

Mechanisms of endocrine disease

- Malignant transformation of non-endocrine tissue causes dedifferentiation and ectopic production of hormones

- Anti-receptor antibodies stimulate receptor instead of block it, as in the case of the common form of hyperthyrodism.

Grave's Disease

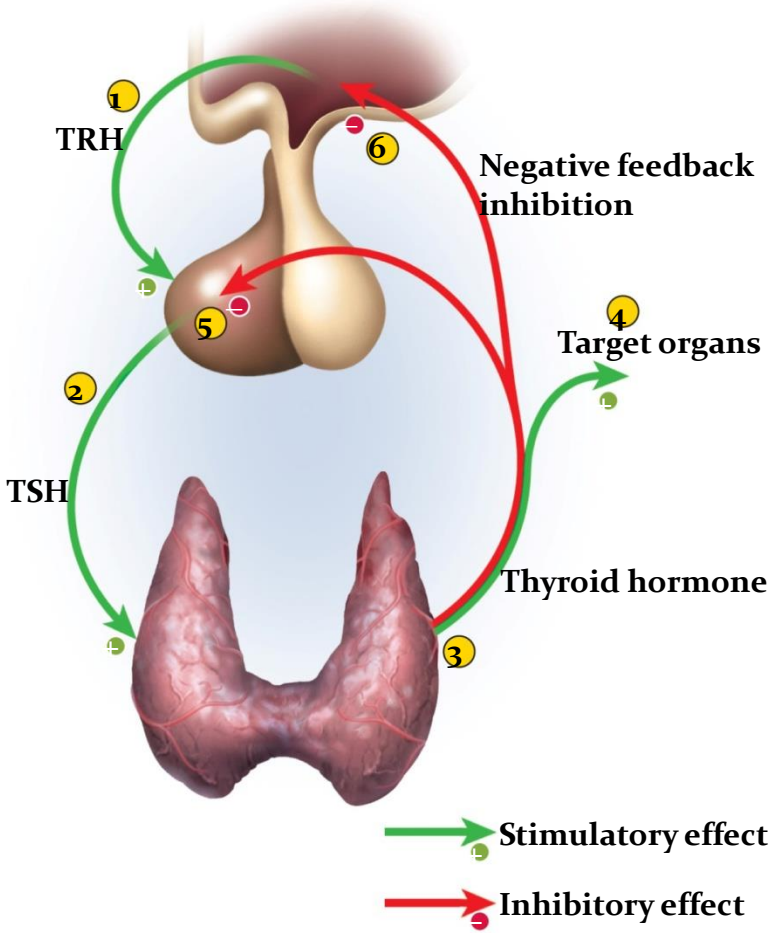
Mechanisms of endocrine disease

- Alterations in receptor number and function result in endocrine disorders
- Most commonly, an aberrant increase in the level of a specific hormone will cause a decrease in available receptors

Type 2 diabetes mellitus

- The activity of endocrine system is regulated at the production level, and at the tissular receptor level.
- **At the production level**, regulation is made by feedback (retro-control), biorhythm and neurogenic influence.
- Feedback can be positive (estradiol-dependent FSH and especially LH increase) or negative (cortisol – depended ACTH inhibition).

Control of Pituitary:
Feedback from Target Organs



- **<u>negative feedback</u>** - increased target organ hormone levels inhibits release of hormones

- **<u>positive feedback</u>** - increased target organ hormone levels stimulates release of hormones

- Hormonal biorhythms are genetically programmed but suffer a synchronization under environmental influence. Biorhythms are ultradian (minute/hour periodicity e.g. gonadotrophin pulsatile secretion), circadian (24 hour periodicity, e.g. cortisol secretion), circatrigintan (every 30 days, e.g. ovulation) , or circannual.
- Neurogenic regulation is insured by “neuroendocrine transducers” (hypothalamus, the medullar adrenal gland, the pineal gland, pancreas) the “cascade regulation” means that the superior centres use much less hormonal quantities than those peripheral response of target glands.

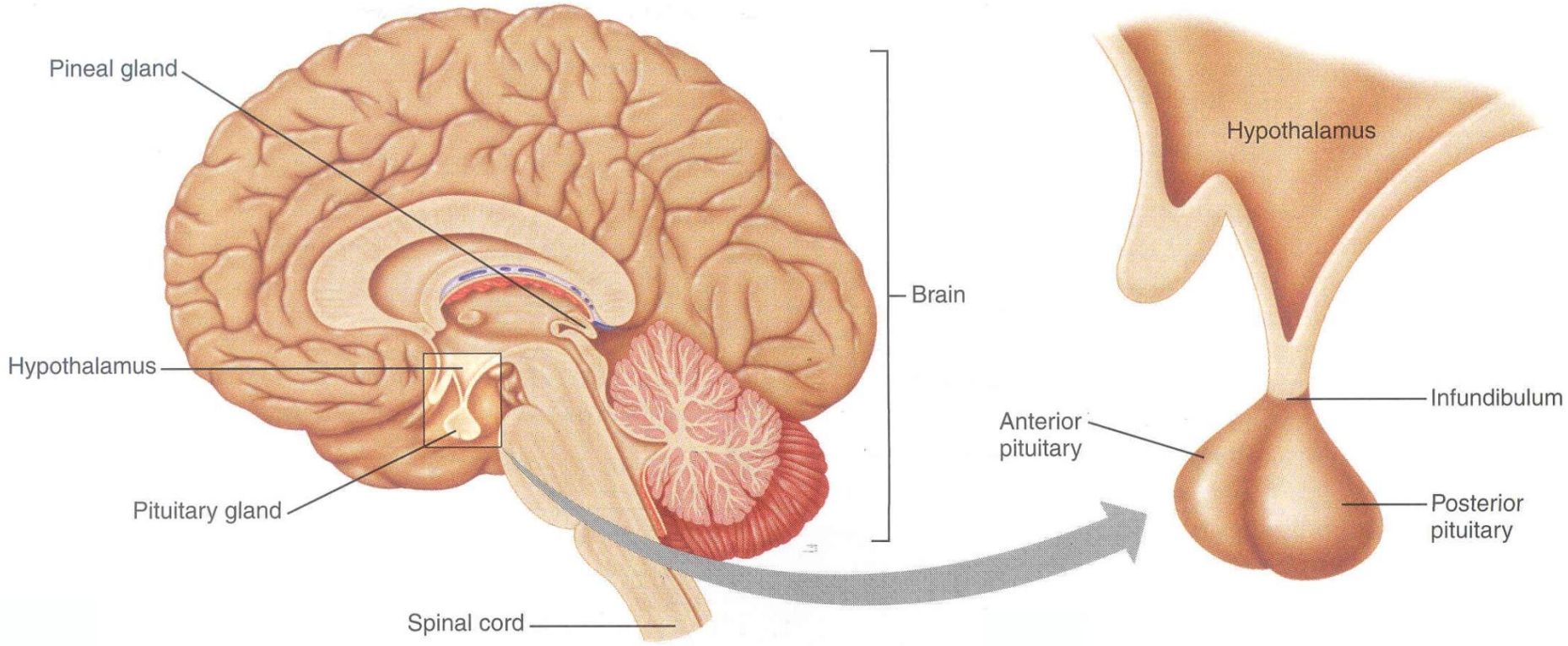
- **At the tissues level,** regulation is made through the modifications in receptor sensibility either in a negative (decrease) or positive (increase) way, i.e. “down regulation” and “up regulation” respectively.
- Other regulatory mechanisms consist in hormone binding to **transport proteins** and thereby the variation of the hormonally active free fraction, as well as **hormonal degradation**, with the possibility of partial modifying their blood concentration.

Hypothalamus and Pituitary

Hypothalamus and Pituitary

- The hypothalamus-pituitary unit is the most dominant portion of the entire endocrine system.
- The output of the hypothalamus-pituitary unit regulates the function of the thyroid, adrenal and reproductive glands and also controls somatic growth, lactation, milk secretion and water metabolism.

The hypothalamus represents an important link between the nervous and endocrine systems



The endocrine function of the hypothalamus

- The hypothalamus regulates important functions: thermal homeostasis, diuresis, thirst sensation and liquid ingestion, hunger and satiety sensations, food ingestion, sexual function emotional sensations (fright, fury, calmness), partial control of sleep and awakeness, respiration, circulation, metabolism, the learning process: memorization, motivation; the endocrine system activity.

Hypothalamic neurohormones:

- Some hypothalamic hormones are called “hypophysotropes”, controlling the activity of the adenohypophysis (anterior pituitary gland), and reaching it via the port hypothalamo-pituitary system. These hormones are either activators (liberins) or inhibitors (inhibins).
- Other hypothalamic hormones, called “neuropituitary hormones” are syntesised within the supraoptic and paraventricular nuclei and reach the neurohypophysis (posterior pituitary gland) via the hypothalamo-pituitary tract.

Characteristics of hypothalamic releasing hormones

- Secretion in pulses
- Act on specific membrane receptors
- Transduce signals via second messengers
- Stimulate release of stored pituitary hormones
- Stimulate synthesis of pituitary hormones
- Stimulates hyperplasia and hypertophy of target cells
- Regulates its own receptor

Activating hormones:

- TRH (thyrotropin-releasing hormone, thyroliberin), tripeptide, specifically stimulates TSH release. It also stimulates prolactin (PRL) and gonadotropin secretion.

- GnRH or LH-RH (gonadoliberin, gonadotropin-releasing hormone, luteinizing hormone-releasing hormone): decapeptide, stimulates FSH and LH secretion.

Activating hormones:

- CRH (corticoliberin, corticotrophin- releasing hormone): polypeptide made out of 41 aminoacids, stimulates ACTH and LPH (lipotrop hormone) secretion.

- GH-RH or GRH (somatoliberin, growth hormone-releasing hormone): polypeptide formed by 44 aminoacids, stimulates GH/STH secretion.

Inhibitory hormones (inhibins, inhibiting):

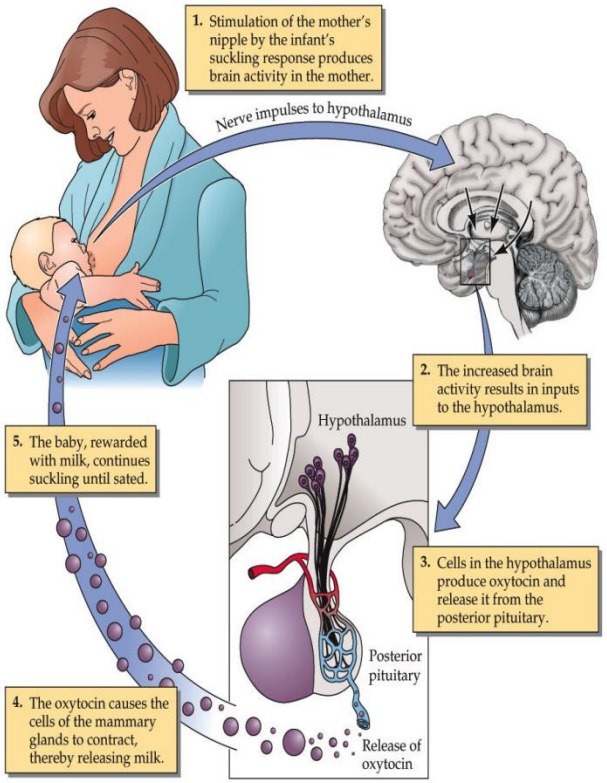
- Somatostatin (GH-IH, GIH, growth hormone inhibiting hormone); peptid formed by 14 aminoacids, inhibits GH secretion. It also inhibits TSH secretion.

- PIF or PIH (prolactin inhibitory factor or hormone): dopamine, inhibits PRL secretion. It also inhibits TSH secretion.

Neuropituitary hypothalamic hormones

The posterior pituitary secretes two principal hormones:

Oxytocine (OXT) or ocytocine (OT): 9 aminoacid-made polypeptide. It is secreted in the paraventricular nucleus. It exerts stimulatory effects upon the uterine muscle and smooth muscular fibers of the mammary gland. It initiates contractions of the resting uterus. It stimulates milk ejection.



Biological Psychology 5e, Figure 5.12

Neuropituitary hypothalamic hormones

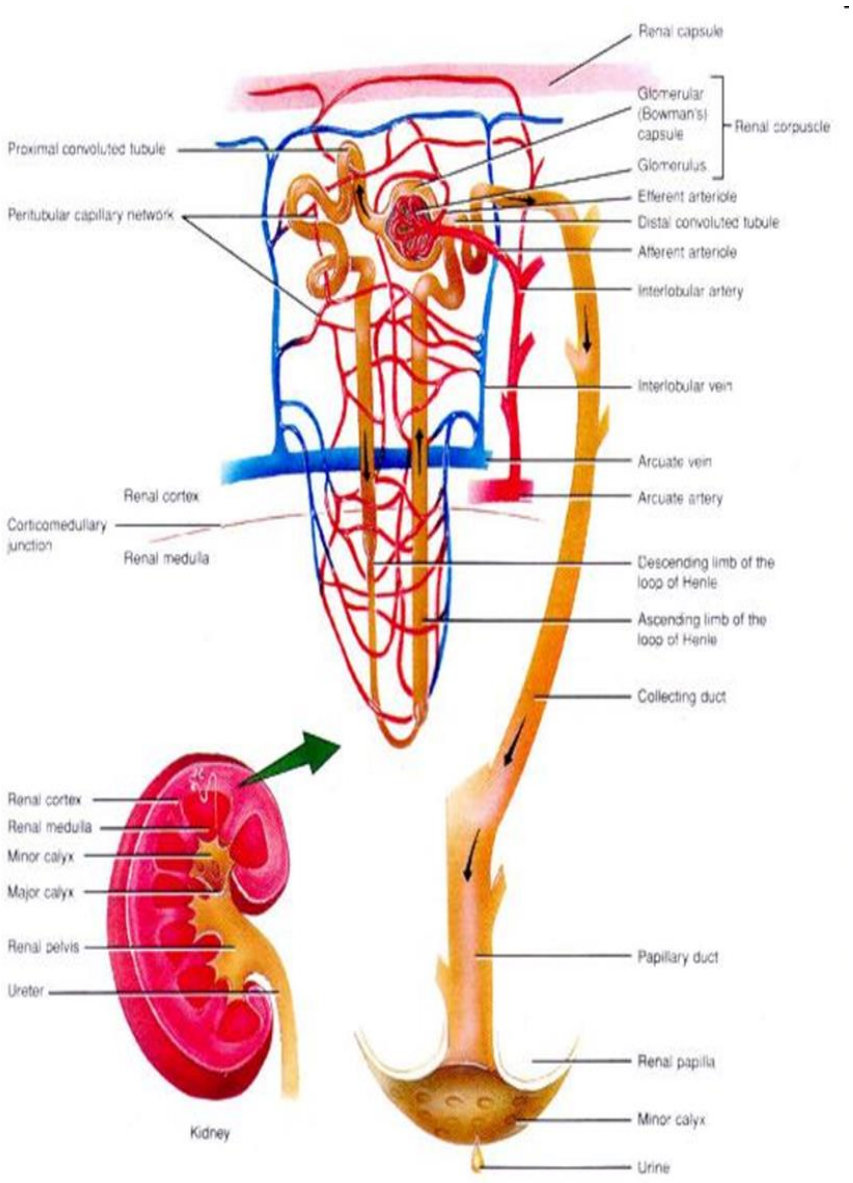
Antidiuretic hormone (ADH, AVP – arginine, vasopresine): 9 aminoacid-made polypeptide.

ADH - favours water reabsorbtion

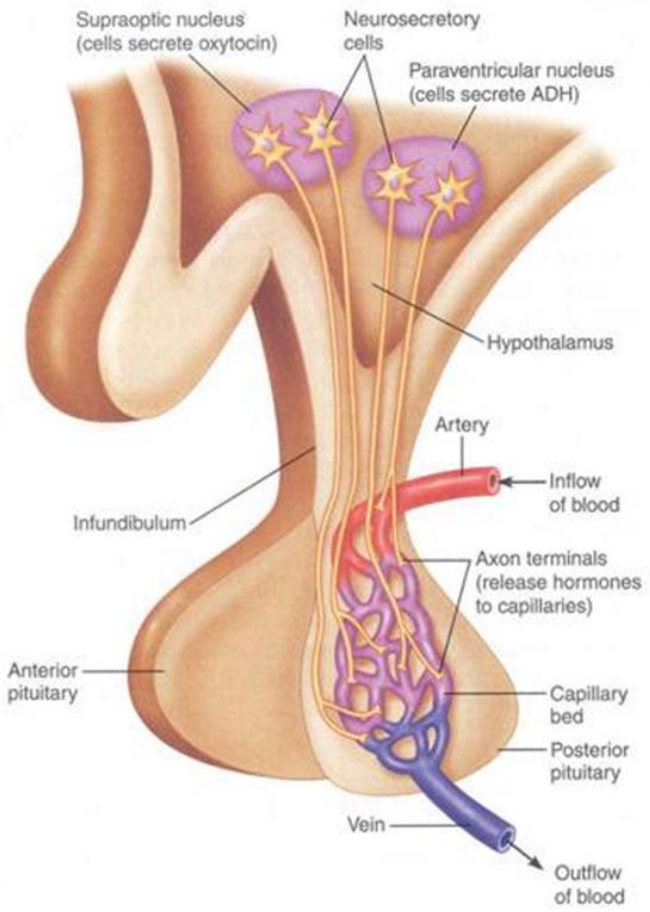
in the distal nephron, intervenes in provoking thirst sensation, diminishes digestive secretions,

decreases sudoral secretion.

It has a role in the learning and memorizing process. In high, pharmacological doses it produces arteriolar vasoconstriction. It also increases erogenic zone sensitivity in both sexes.

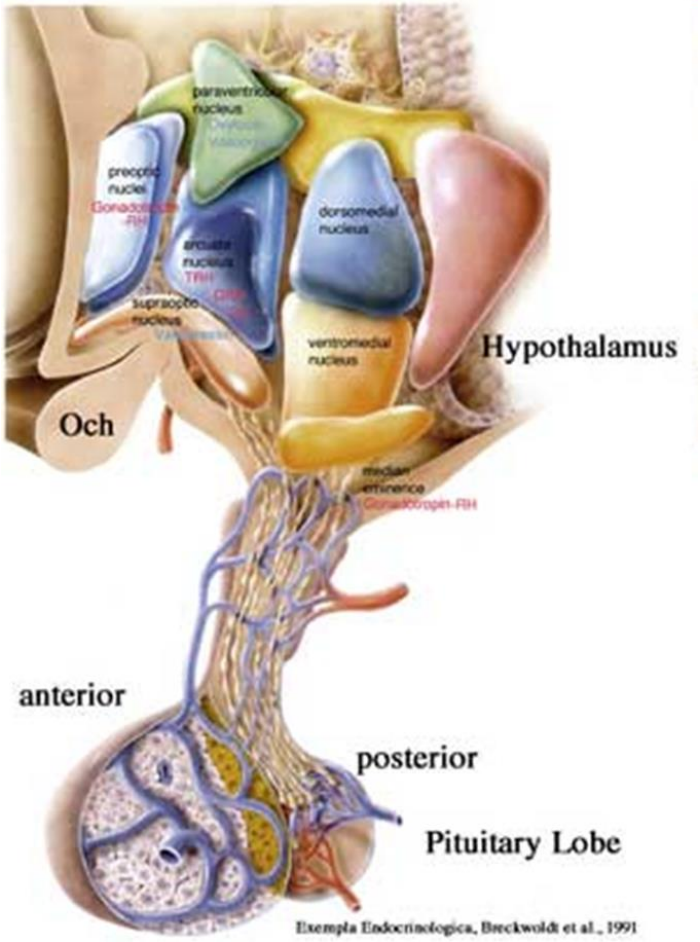


Oxytocin and Vasopressin are manufactured in the hypothalamus, but released in the posterior pituitary



- ADH is a nonapeptide synthesized at the supraoptic and paraventricular nuclei. After being stored as a prehormone in intracytoplasmic granules, ADH is transported along axons in the median eminence to the neurohypophysis, where it is converted into the native hormone. Once released together with neurophysin II, it is bound to specific V2 receptors located in the basal portion of collecting tubule cells. This interaction results in displacement to the apical membrane of aquaporin 2 preformed in the cytoplasm and in passive water reabsorption.

Pituitary gland



- The “Master Gland”
- The pituitary gland (or hypophysis) releases important hormones

Parts

- pars distalis (anterior) - Anterior pituitary (adenohypophysis)- releases about 7 hormones
- pars intermedia - unknown function in humans
- pars nervosa (posterior) - Posterior pituitary (neurohypophysis) - releases but does not produce

- The two parts of the pituitary gland are separate in function: adenohypophysis and neurohypophysis.

- Anterior pituitary (adenohypophysis)
- Posterior pituitary (neurohypophysis)
- The pituitary stalk, or infundibulum, connects the pituitary to the hypothalamus. The stalk contains blood vessels and many axons, which only extend to the posterior pituitary

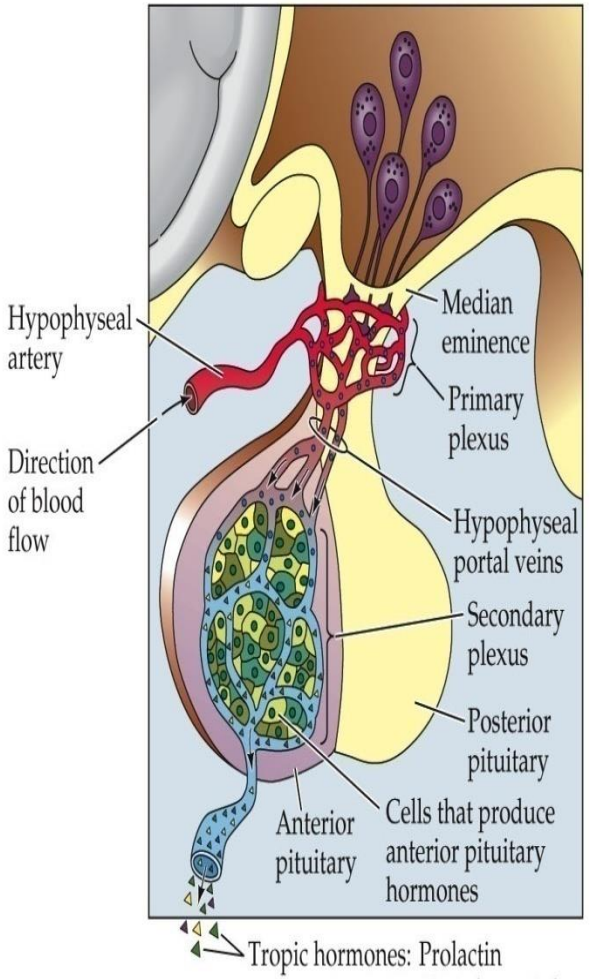
Hypothalamic neurons synthesize releasing hormones.

Axons from these cells converge on the **median eminence**, above the pituitary stalk.

Releasing hormones are secreted into local blood vessels, called the **hypophyseal portal system**.

Releasing hormones are carried to the anterior pituitary, which then releases tropic hormones.

The hypothalamus is influenced by *circulating messages*, such as other hormones, and by *synaptic inputs* from other brain areas.



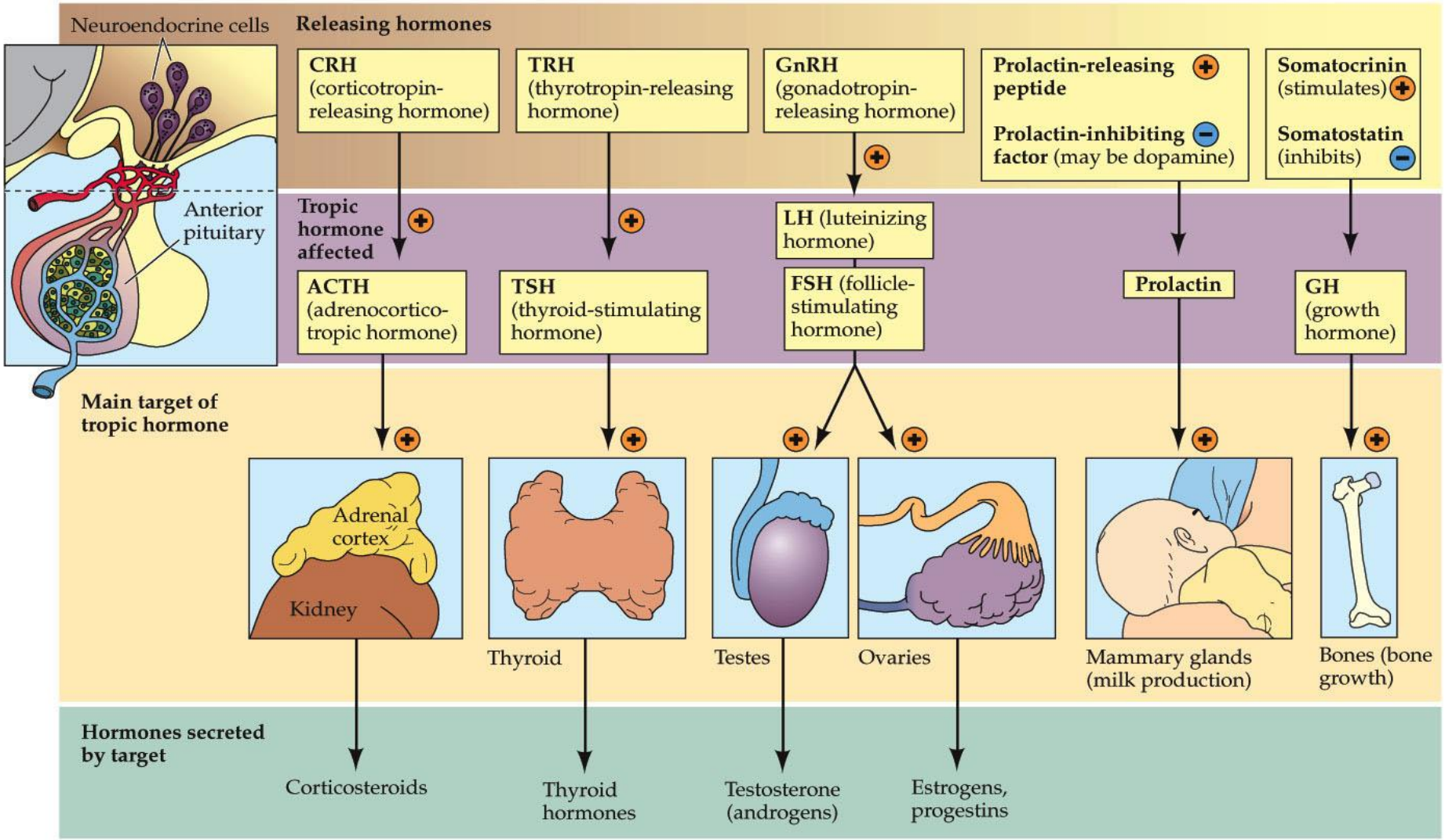
Biological Psychology 5e, Figure 5.14

1. **Adrenocorticotropic hormone (ACTH)** controls adrenal cortex and steroid hormone release.
2. **Thyroid-stimulating hormone (TSH)** increases thyroid hormone release.

Gonadotropins influence the gonads.

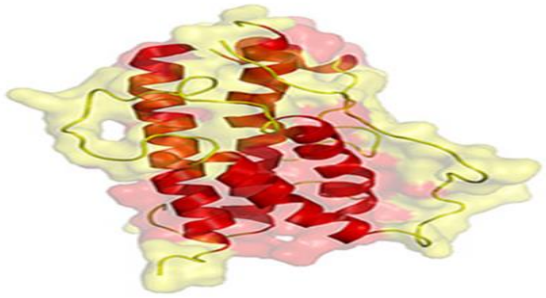
3. **Follicle-stimulating hormone (FSH)** stimulates egg-containing follicles or sperm production.
4. **Luteinizing hormone (LH)** stimulates follicles to form the **corpora lutea.**
5. **Prolactin** stimulates lactation in females, and is involved in parental behavior.
6. **Growth hormone (GH),** *somatotropin* or *somatotropic hormone* influences growth, mostly during sleep. The stomach hormone *ghrelin* also evokes GH release.

Figure 5.15 Secretions of the Anterior Pituitary (Part 1)



***Biological Psychology 5e*, Figure 5.15**

Growth Hormone



GH (STH) has a polypeptide structure, made out of 191 aminated acids.

GH is the most important hormone for normal growth to adult size.

Regulation of GH secretion

- GH is released in pulsatile fashion.
- Secretion is increased by sleep, stress, hormones related to puberty, starvation, exercise, and hypoglycemia.
- Secretion is decreased by somatostatin, somatomedins, obesity, hyperglycemia, and pregnancy.

1. Hypothalamic control - GHRH and somatostatin

   -GHRH stimulates the synthesis and secretion of GH.

   -Somatostatin inhibits secretion of GH by blocking the response of the anterior pituitary to GHRH.

2. Negative feed-back control by somatomedins

   - somatomedins are produced wheh GH acts on target tissues.

   - somatomedins inhibit the secretion of GH by acting directly on the anterior pituitary and by stimulating the secretion of somatostatin from the hypothalamus.

3. Negative feedback control by GHRH and GH

   -GHRH inhibits its own secretion from the hypothalamus.

   - GH also inhibits its own secretion by stimulating the secretion of somatostatin from the hypothalamus.

Actions of GH

- Its actions are mediated by somatomedins, liver peptides with structure similar to that of proinsulin, also called IGF (insulin like growth factor). Direct actions of GH are also described.
- Somatomedin mediated actions: protein anabolism in muscle and increase lean body mass, cellular proliferation, protein anabolism in chondrocytes and cartilage and bone growth (linear growth).
- Direct actions: lipolysis, antagonism of insulin peripheral actions (decrease glucose uptake into cells - diabetogenic), hyperglycemia, sodium and water retention, increase protein synthesis in muscle and increase lean body mass, increase production of IGF.

Growth Hormone and Aging

- Childhood and adolescence
  - bone, cartilage and muscle growth
- Adulthood
  - increase osteoblastic activity and appositional growth affecting bone thickening and remodeling
  - blood concentration decrease by age 75 to ¼ of that of adolescent
- Levels of GH
  - higher during first 2 hours of deep sleep, after high protein meals, after vigorous exercise
  - lower after high CHO meals

PRL – prolactin:

- polypeptide containing 198 aminated acids, with structure, and partly function similar to those of GH. It induces and maintains milk secretion of previously estrogen and progesterone-prepared mammary gland. Participates with estrogen in breast development. At the hypothalamic level, PRL inhibits GnRH secretion and decreases pituitary hormones. It also blocks FSH and LH gonadal actions. Inhibits ovulation by decreasing synthesis and release of GnRH; inhibits spermatogenesis (by decreasing GnRH).

- Regulation of PRL secretion is insured by PIH (dopamine). Dopamine secretion is inhibited during suckling, or nipple mechanical stimulation, via reflex neuroendocrine pathway, leading to an increase in PRL secretion. Other factors also stimulate PRL release: TRH, estrogens, serotonin, physical exercise, sleep, sexual act. Its secretion is blocked by L-Dopa and dopaminergic agonists.

ACTH – Adrenocorticotrop hormone

- 39 aminated acid-formed polypeptide. Its biological activity is given by the region 1-24. ACTH secretion has a circadian rhythm with the peak in the morning (between 6.00 and 9.00 h). ACTH stimulates the function of the cortical adrenal gland, especially glucocorticosteroid and adrenal sex hormones secretion, and less that of mineralocorticoids. Feedback control is insured by cortisol. Hypothalamic CRH stimulates its secretion.

TSH - thyroid stimulating hormone

- glycoprotein made out of two subunits (α and β). The α subunit is common to all glycoproteic hormones (TSH, FSH, LH, HCG) and possesses 96 aminated acids. The β subunit is specific to TSH, and includes 110 aminated acids. TSH controls thyroid morphogenesis, and all steps of thyroid hormones biosynthesis. Regulation of TSH secretion is made by TRH and by feed-back.

Gonadotropic hormones – LH and FSH
LH

- LH –luteinizing hormone: its α subunit is common to that of TSH and FSH, and contains 96 aminated acids, and the β subunit has 108 aminated acids. Its release is made under the influence of GnRH in a pulsatile way. LH induces androgen synthesis by the thecal cells in women. It also stimulates Leydig cells and androgen (testosterone) production in men.

- Regulation of its secretion is insured by GnRH, as well as by biorhythm and feedback. Estrogens inhibit LH in women at the beginning of the follicular phase (negative feedback). The increase of estrogen levels up to a critical preovulatory level triggers through positive feedback a raise of LH levels (preovulatory feedback). This raise of LH levels provokes the disruption of ovarian follicle and formation of the luteal body. Progesterone inhibits LH. Feedback is insured in men by testosterone. A monthly biorhythm is described in women, and an ultradian biorhythm (every 90 months) is described in both sexes.

FSH – follicular stimulating hormone

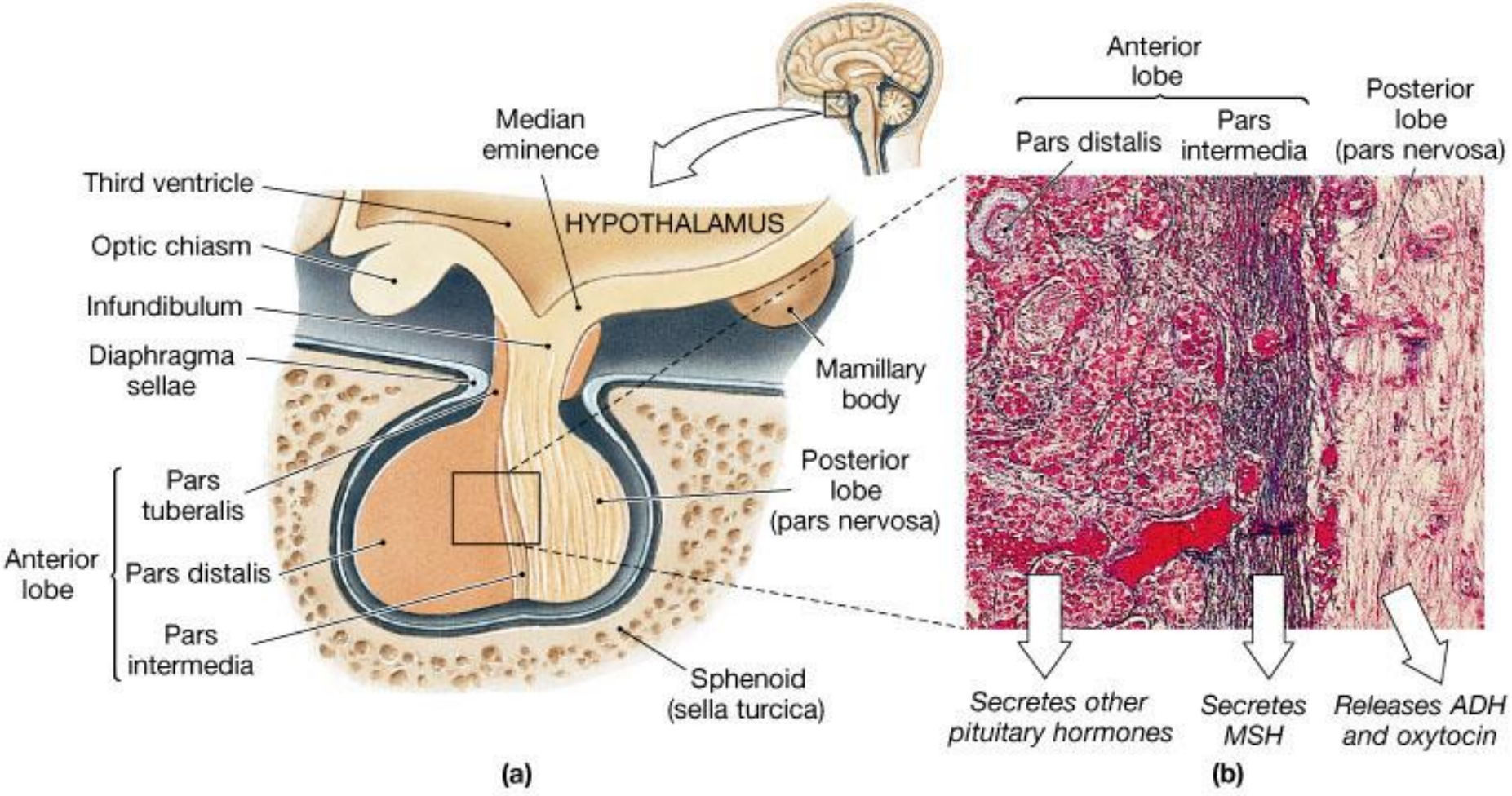
- the α subunit has 96 aa, and the β subunit has 115 aa. It is released in a pulsatile way under the influence of GnRH. It acts on follicular granulose cells (in women) and the development of LH receptors on Leydig cells (in men). FSH also increases testosterone binding protein production by Sertoli cells in men. FSH is a major spermatogenesis-regulating factor.

Pituitary Hormones - Pars Intermedia

- Absent from adult human although present in fetus
- Reminant cells
  - produce POMC (pro-opiomelanocortin) which is processed into ACTH and endorphins
- Produces MSH in animals influencing pigmentation of skin, hair or feathers
  - not apparently present/functioning in humans

  Melanocyte stimulating hormone (MSH)
- May be secreted by the pars intermedia during fetal development, early childhood, pregnancy or certain diseases
- MSH – along with ACTH stimulates melanocytes to produce melanin

The Anatomy of the Pituitary Gland



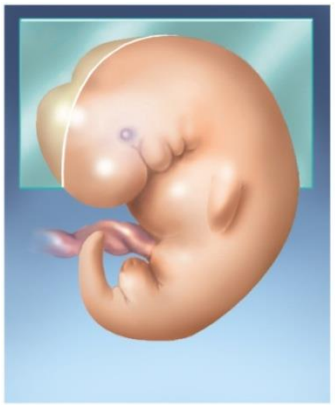
PITUITARY GLAND

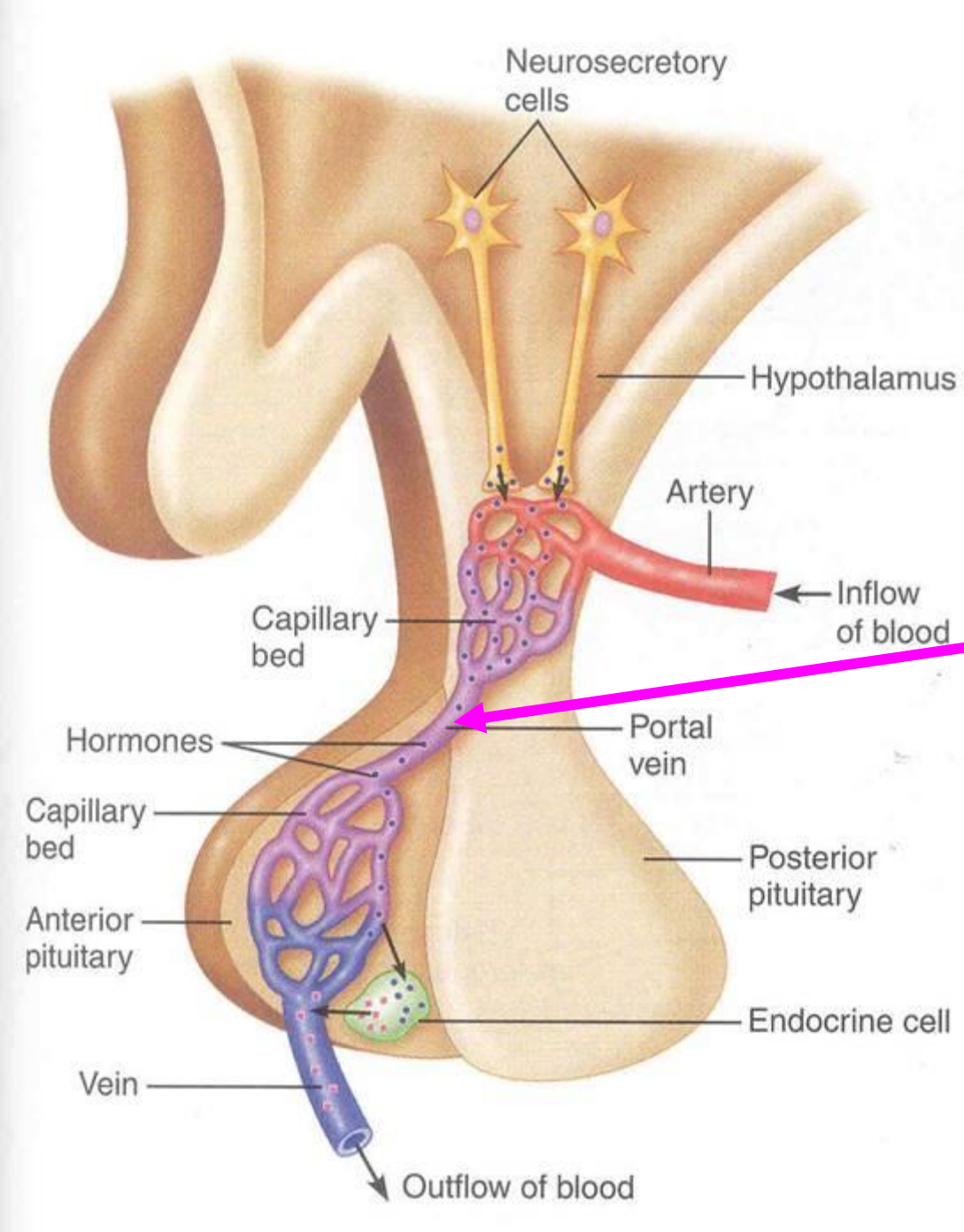
ANATOMY

- The pituitary gland is located medially, at he base of the brain, within a bony structure called sella turcica. It is connected to the hypothalamus by the pituitary stalk. Superiorly, sella turcica is separated from the brain by the diaphragma sellae, a thick reflection of dura. It is a small, pea-like gland, measuring 0,6*0,8*1,5cm. and weighs 0,5 to 0,8g. in pregnant women its weight doubles.

- The pituitary gland consists of two embryologically, structurally and functionally distinct parts. The anterior lobe or adenohypophysis is of ectodermal origin; it arises from an evagination of Rathke,s pouch and represents 75% of the gland. The posterior lobe or neurohypophysis is of diencephalic origin. Between the two lobes there is a third section, the intermediate lobe, poorly developed in human.

Embryonic Development





Note Pituitary Portal System!!

Hypothalamic-pituitary relationships

- The anterior lobe of the PG is linked to the hypothalamus by the hypothalamic-hypophysial portal system. Thus, blood from the hypothalamus that contains high concentrations of hypothalamic hormones is delivered directly to the anterior pituitary. Hypothalamic hormones [e.g.,GHRH] then stimulate or inhibit the release of anterior pituitary homones(e.g.,GH).
- The posterior lobe of the PG is derived from neural tissue. The nerve cell bodies are located in hypothalamic nuclei. Posterior pituitary hormones are synthesized in the nerve cell bodies, packaged in secretory granules, and transported down the axons to the posterior pituitary for release into the circulation.

Anatomic relationships:

- Superior: - frontal lob
- -the third ventricle
- -optic chiasm
- Anterior: -nasal fossae
- -sphenoid sinus
- Posterior: -dorsum sellae
- -basilar trunk and its branches
- Lateral: -cavernous sinuses

ADENOHYPOPHYSIS

Histology: 1. Classically, the following cells are described:

-acidophils

-basophils

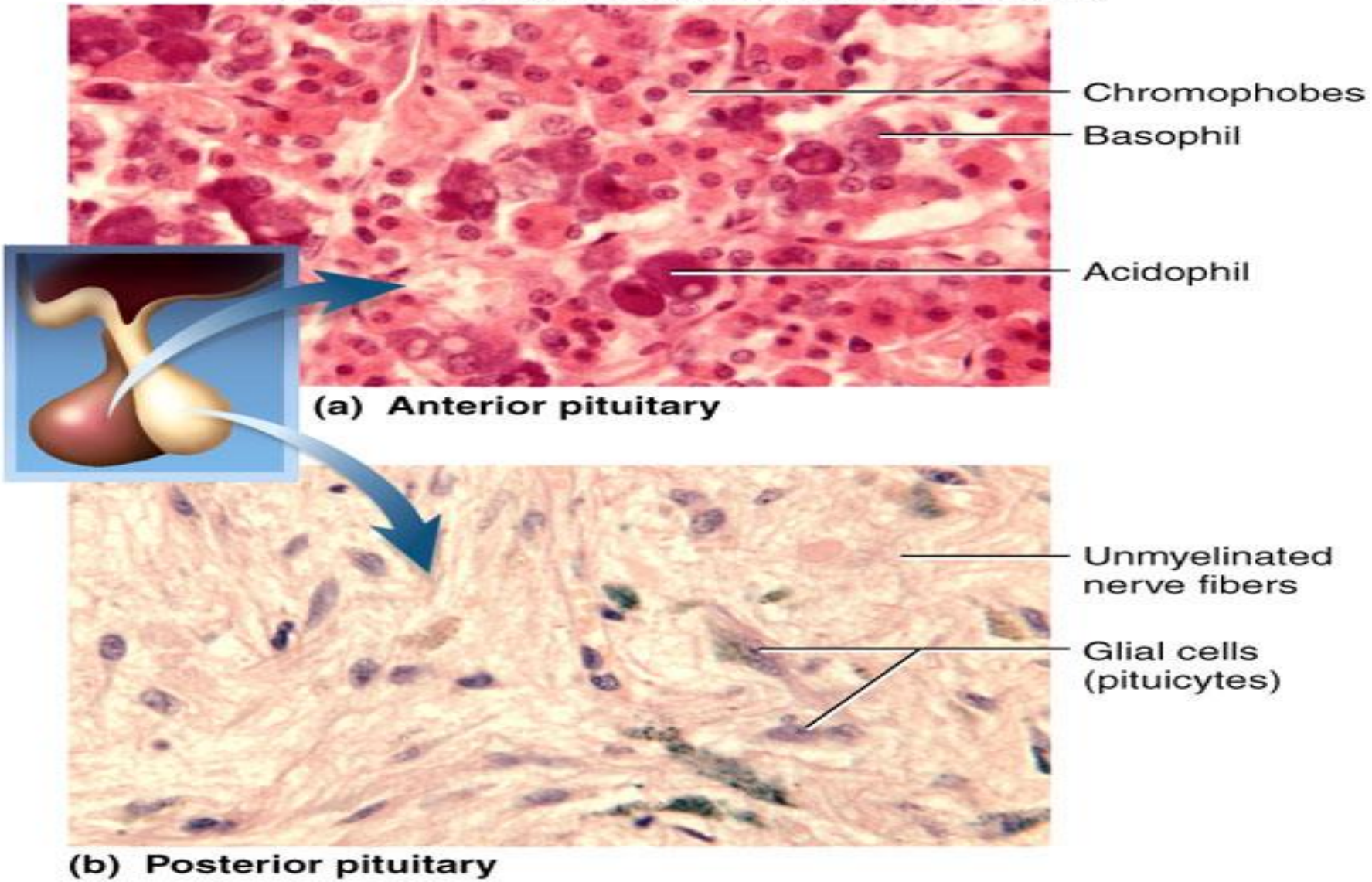
-chromophobe

2. Immunocytochemical and electron microscopic techniques classify the cells by their specific secretory products:

- somatotrophs: 50%
- lactotrophs: 10-15%
- thyreotrops: 10%
- corticotrphs: 15-20%
- gonadotrophs: 10-15%

-other cell types: chromophobes, undifferentiated primitive secretory cells or producing still unidentified hormones.

Histology of Pituitary Gland



Acromegaly

Acromegaly

- Acromegaly is a hormonal disorder that results when the pituitary gland produces excess growth hormone (GH) after puberty.
- When GH hypersecretion occurs prior to puberty and fusion of epiphyses, GIGANTISM develops, and after; puberty ACROMEGALY results.
- The name acromegaly comes from the Greek words for "extremities" and "enlargement“.

August 29th
1903

HASSAN ALI, *Egyptian Giant,*

Height 8 ft. 2 in. **Age 28 years.**

A Native of Cairo, Egypt.

What Causes Acromegaly?

- caused by prolonged overproduction of GH by the pituitary gland.
  1. Pituitary Tumors
  2. Non-pituitary Tumors

- Incidence: 20-30% of pituitary adenomas.

Acromegaly

- More than 95% of acromegaly cases are caused by a pituitary adenoma that secretes excess amounts of GH. Ectopic production of GH and GHRH by malignant tumors accounts for other causes.
- Of these tumors, up to 40% have a mutation involving the alpha subunit of the stimulatory guanosine triphosphate (GTP)–binding protein. In the presence of a mutation, persistent elevation of cyclic adenosine monophosphate (cAMP) in the somatotrophs results in excessive GH secretion.

- The pathologic effects of GH excess include acral overgrowth (ie, macrognathia; enlargement of the facial bone structure; enlarged hands and feet; visceral overgrowth, including macroglossia and enlarged heart muscle, thyroid, liver, kidney), insulin antagonism, nitrogen retention, and increased risk of colon polyps/tumors.
- **Frequency .** Acromegaly is unusual, with a new case incidence of 3-4 per million subjects per year and a mean age of 40-45 years (USA).

- Acromegaly occurs with equal frequency in males and females.
- Median age at diagnosis is 40 years in males and 45 years in females.
- Acromegaly can be an insidious disease. Symptoms might precede diagnosis by several years.

Mortality

- For individuals with acromegaly, the mortality rate is 2-3 times that of the general population. The major sequelae of acromegaly include cardiorespiratory and cerebrovascular diseases, diabetes, and neoplasia, particularly colon cancer.
- A study by Berg et al found an increased prevalence of cardiovascular risk factors in patients with acromegaly compared with controls. This study documents the importance of aggressive management as early as possible in the disease process.

- Visceral hypersomia includes heart, liver, and kidneys. Multinodular goiter is often present. With heart hypersomia comes hypertension, left ventricular hypertrophy, and, frequently, acromegalic cardiomyopathy with dysfunction and arrhythmias.
- There also appears to be a relationship between GH/SM-C excess and premalignant colon polyposis, though this is not as clear as the other effects. In studies, the polyps were generally multiple and proximal to the splenic flexure, making them less likely to be discovered during sigmoidoscopy.

Symptoms can be divided into 2 groups.

- **Symptoms due to local mass effects of the tumor**
- Symptoms depend on the size of the intracranial tumor.
- Headaches and visual field defects are the most common symptoms. Visual field defects depend on which part of the optic nerve pathway is compressed.
- The most common manifestation is a bitemporal hemianopsia due to pressure on the optic chiasm.

- Tumor damage to the pituitary stalk might cause hyperprolactinemia due to loss of inhibitory regulation of prolactin secretion by the hypothalamus.
- Damage to normal pituitary tissue can cause deficiencies of glucocorticoids, sex steroids, and thyroid hormone. Loss of end organ hormones is due to diminished anterior pituitary secretion of ACTH, LH, FSH, and TSH.

Symptoms due to excess of GH/IGF-I

- Soft tissue swelling and enlargement of extremities
- Increase in ring and/or shoe size
- Hyperhidrosis
- Coarsening of facial features
- Prognathism
- Macroglossia
- Arthritis
- Increased incidence of obstructive sleep apnea
- Increased incidence of glucose intolerance or frank diabetes mellitus, hypertension, and cardiovascular disease

Symptoms due to excess of GH/IGF-I

- Hyperphosphatemia, hypercalcuria, and hypertriglyceridemia possible
- Increased incidence of congestive heart failure, which might be due to uncontrolled hypertension or to an intrinsic form of cardiomyopathy attributable to excess GH/IGF-I
- Increased incidence of colonic polyps and adenocarcinoma of the colon

Maurice Tillet (Swedish Angel) checks head sizes with Marj.

Physical

Typical facies of acromegaly include the following:

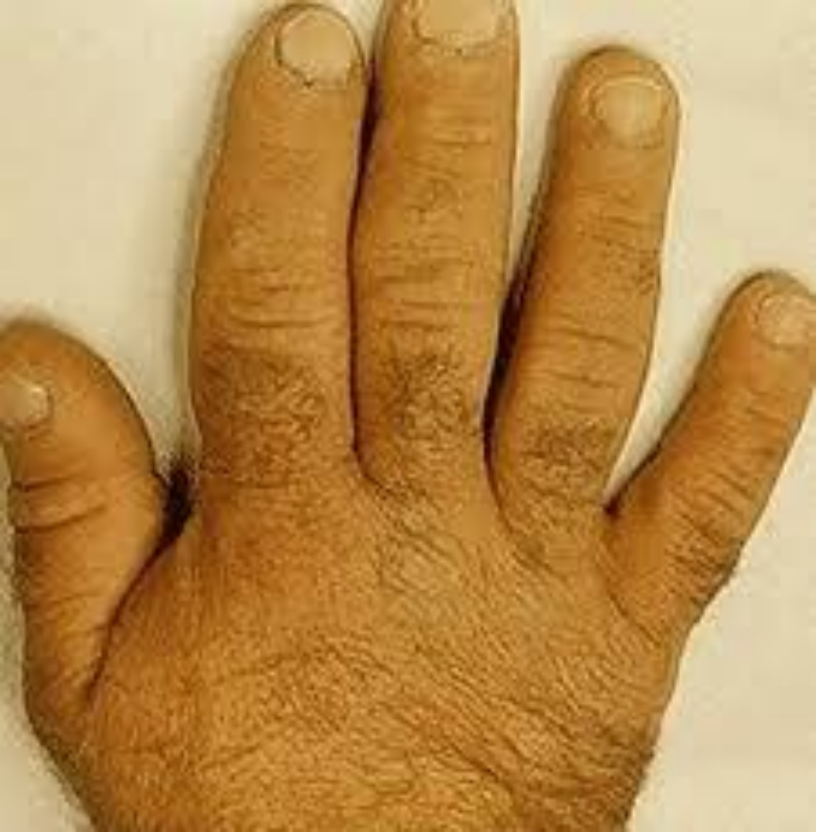
- Frontal bossing
- Thickening of the nose
- Macroglossia
- Prognathism

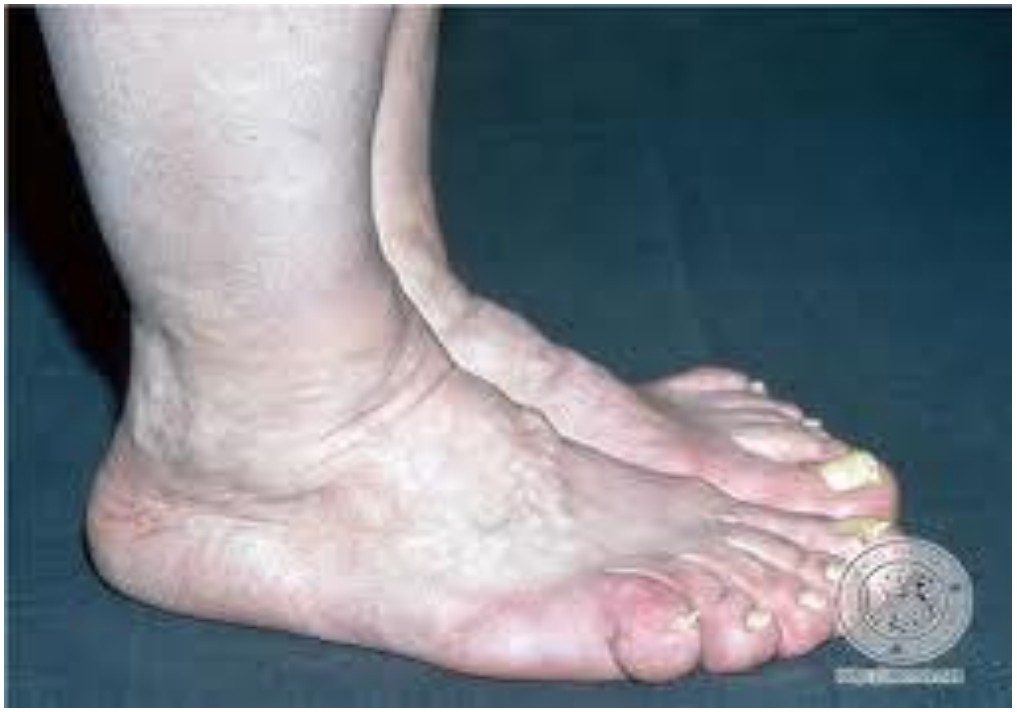
Women can have mild hirsutism.

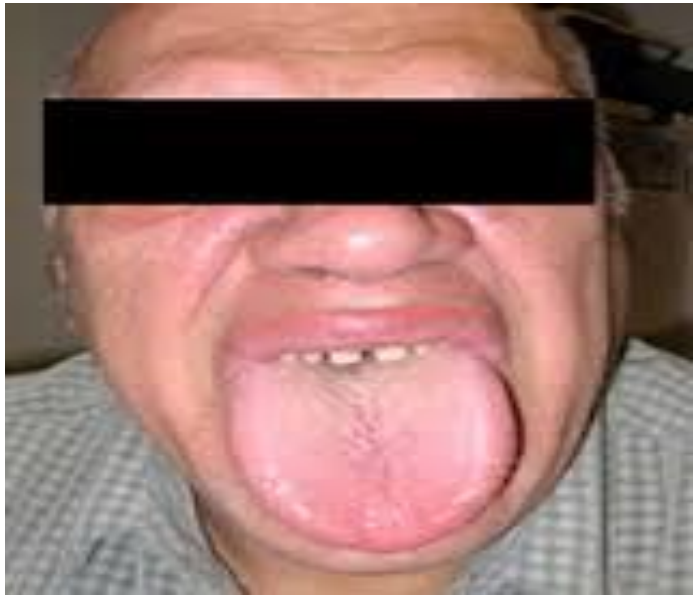
The thyroid gland might be enlarged and typically manifests as multinodular goiter.

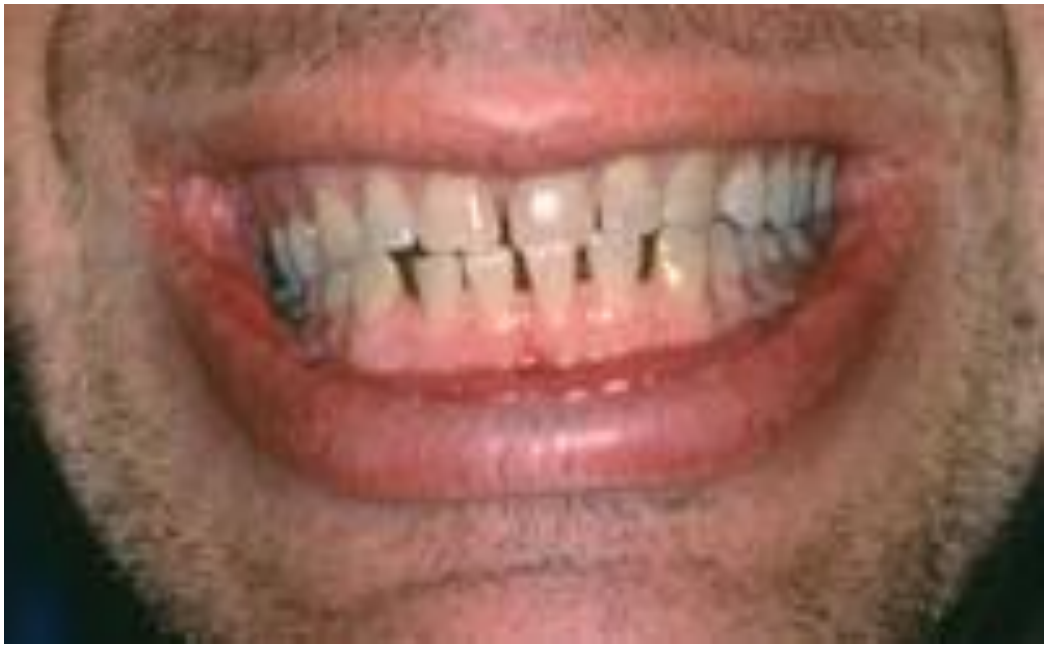
Enlarged extremities with sausage-shaped fingers are signs of acromegaly.

Skin is oily and has skin tags. Skin tags are possible markers for colonic polyps.









Causes (1)

- Acromegaly can be either GHRH independent or GHRH dependent. Both forms cause identical clinical syndromes.
- Most cases are GHRH independent. Elevated GH concentration suppresses GHRH production by the hypothalamus. More than 95% of the GHRH-independent cases are due to a GH-secreting pituitary tumor. The pituitary adenoma might be a macroadenoma (>1 cm) or a microadenoma (< 1 cm).

- Macroadenomas account for 80% of tumors; microadenomas account for the remaining 20%. Histopathologically, tumors include acidophil adenomas, densely granulated GH adenomas, sparsely granulated GH adenomas, somatomammotropic adenomas, and plurihormonal adenomas.

Causes (2)

- In rare cases, GHRH-independent acromegaly may result from an ectopic pituitary tumor or ectopic production of GH by other tumors (eg, cancers of the pancreas or lung).
- In GHRH-dependent cases, GHRH stimulates the somatotrophs of the anterior pituitary, leading to hyperplasia and increased GH secretion. GHRH-dependent acromegaly can be caused by eutopic production of GHRH by a hypothalamic tumor or by ectopic production of GHRH by tumors such as those of the pancreas, kidneys, or lungs.

Laboratory Studies

- Random GH measurements are often not diagnostic because of the episodic secretion of GH, its short half-life, and the overlap between GH concentration in acromegalic patients and healthy subjects.
- Because GH secretion is inhibited by glucose, measurement of glucose nonsuppressibility might be useful. Two baseline GH levels are obtained prior to ingestion of 75 or 100 g of oral glucose, and additional GH measurements are made at 30, 60, 90, and 120 minutes following the oral glucose load.

- Patients with active acromegaly are unable to suppress GH concentration below 2 ng/mL after a 75-g oral glucose load. With newer assays for GH using the immunoradiometric assay (IRMA), a criterion of less than 1 mcg/L is used following oral glucose ingestion.
- A paradoxical rise in GH concentration is observed in 15-20% of patients with acromegaly following oral glucose ingestion.

- Because IGF-I has a long half-life, its measurement is useful to gauge integrated GH secretion, to screen for acromegaly, and to monitor the efficacy of therapy. IGF-I concentrations vary with age.
- Starvation, obesity, and diabetes mellitus decrease IGF-I concentration. Pregnancy increases IGF-I concentration.

- Measurement of IGF-binding protein-3 (IGFBP-3), the main binding protein for circulating IGF, is increased in acromegaly and might be useful in the diagnosis of acromegaly. Measurement may also be helpful in following the activity of the disease during treatment.
- GHRH concentration can be obtained if clinically indicated. Levels of less than 300 pg/mL usually indicate an ectopic source of GHRH. In pituitary disease (GHRH independent), GHRH concentration is within reference ranges or suppressed.

- Because up to 20% of GH-secreting pituitary adenomas cosecrete prolactin, the prolactin level may also be elevated. However, as indicated above, a rise in prolactin can be due to stalk compression as well as co-secretion from a pituitary adenoma.
- Pituitary adenomas can be associated with deficiencies of other pituitary hormones. Consider evaluation of the adrenal, thyroid, and gonadal axes.

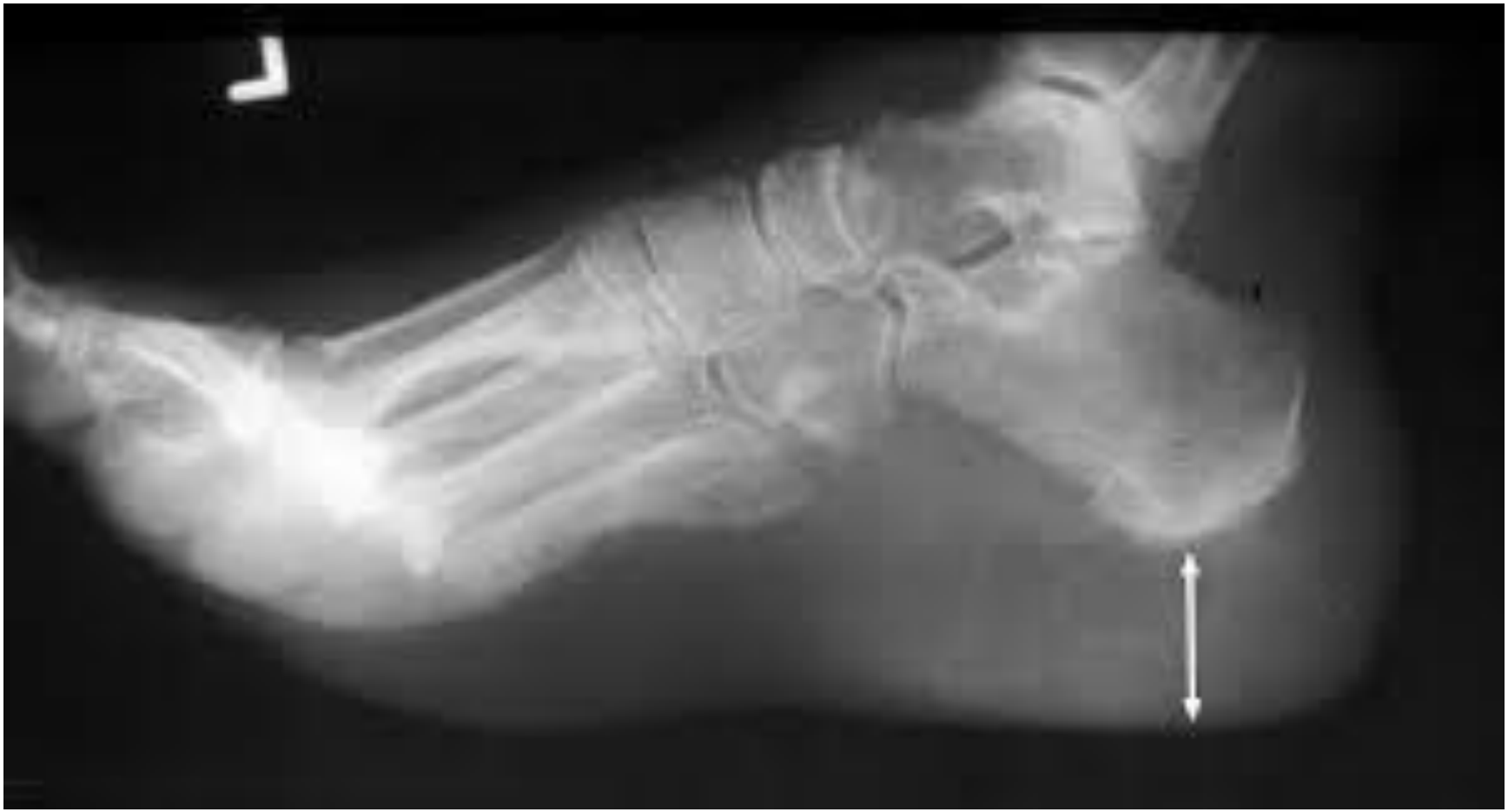
Imaging Studies

- Because of the relatively high incidence of nonfunctioning, incidentally discovered pituitary adenomas, obtain imaging studies only after a firm biochemical diagnosis of acromegaly.
- Because GH-secreting pituitary adenoma is the most common cause, perform imaging of the sella turcica first. MRI is more sensitive than CT scan. MRI provides detailed information about surrounding structures such as the optic chiasm and cavernous sinuses.

- If the MRI findings of the sella are negative, appropriate studies to localize tumors causing ectopic secretion of GH or GHRH can be obtained.
- CT scan of the abdomen/pelvis evaluates for pancreatic, adrenal, or ovarian tumors secreting GH/GHRH. Chest CT scanning evaluates for bronchogenic carcinoma secreting GH/GHRH.

Radiologic:

- Skull x-ray including sella turcica:
- periosteal thickening, thickened cranial vault, increased antero-posterior skull diameter
- enlargement of frontal, maxillary and sphenoid sinuses
- enlargement of anterior and posterior clinoid processes
- in hands and feet - enlargement of articular space
- enlargement of soft tissues
- in the spine - dorsal kyphosis
- enlarged vertebral bodies
- osteoporosis, osteophytosis
- sella turcica: ballooned, double contour, destroyed



Medical Care

- The goal of treatment is amelioration of symptoms caused by the local effects of the tumor, excess GH/IGF-I production, or both.
- Because elevated GH/IGF-I concentration is associated with increased mortality rates, try to decrease/normalize their concentration. Most experts define cure, or adequate control, as a glucose-suppressed GH concentration of less than 2 ng/mL by radioimmunoassay (RIA) (1 mcg/L by IRMA) and normalization of the serum IGF-I concentration.

Medical Care

- No single modality of treatment consistently achieves the above levels. A multimodality approach usually requires surgery as the first line of treatment, followed by medical therapy for residual disease. Radiation treatment is generally reserved for refractory cases.
- Somatostatin and dopamine analogues and GH receptor antagonists are the mainstays of medical treatment and are generally used after failure of primary surgery to induce complete remission.

- **Bromocriptine** is a dopamine agonist with limited effectiveness in the treatment of acromegaly. It can reduce the circulating GH level to less than 5 ng/mL in only 20% of patients and can normalize the IGF-I concentration in 10% of patients. Shrinkage in tumor size is also observed in fewer than 20% of patients. **Cabergoline**, another dopamine agonist, fares somewhat better with response rates of 46%.
- A meta-analysis found that cabergoline used as single-agent therapy in patients with acromegaly normalized IGF-I levels in one third of patients.

- Tumors that cosecrete prolactin have a better response rate to dopamine agonists.
- **Somatostatin** is a natural inhibitor of GH secretion. Because of its very short half-life, long-acting analogues have been developed. The long-acting analogue can be administered once per month but is extremely expensive .
- **Octreotide** is the most extensively studied and used somatostatin analogue. Treatment with octreotide reduces GH concentration to less than 5 ng/mL in 65% of patients and to less than 2 ng/mL in 40% of patients; it normalizes concentration IGF-I in 60% of patients. Tumor shrinkage is observed in 20-50% of patients.

- **Pegvisomant**, a GH receptor antagonist normalizes IGF-I levels in 90-100% of patients. As expected from its mechanism of action, GH levels increase during treatment and no decrease in tumor size is seen. A minority of patients may experience an increase in tumor size; whether this is due to natural history of the disease or an effect of treatment is unclear. Periodic imaging studies are advised in patients on this medication.

- Radiation treatment takes to reduce/normalize GH/IGF-I levels. About 60% of patients have a GH concentration of less than 5 ng/mL 10 years after radiotherapy. A similar percentage of patients develop panhypopituitarism as a result of treatment. Because of the disappointing results and adverse effects, radiotherapy is used as an adjuvant for large invasive tumors and when surgery is contraindicated. Some studies suggest that radiation is associated with the development of secondary tumors.

Surgical Care

- Even though surgery might not cure a significant number of patients, it is employed as first-line therapy. Patients with residual disease can then be offered adjuvant treatment.

- Transsphenoidal hypophysectomy has the dual advantage of rapidly improving symptoms caused by mass effect of the tumor and significantly reducing or normalizing GH/IGF-I concentrations. Remission depends on the initial size of the tumor, the GH level, and the skill of the neurosurgeon

- A remission rate of 80-85% can be expected for microadenomas and 50-65% for macroadenomas.
- The postoperative GH concentration may predict remission rates.
- After transsphenoidal surgery, somatostatin analogues are generally the first line of treatment, followed by GH receptor antagonist or dopamine agonists.

Gigantism

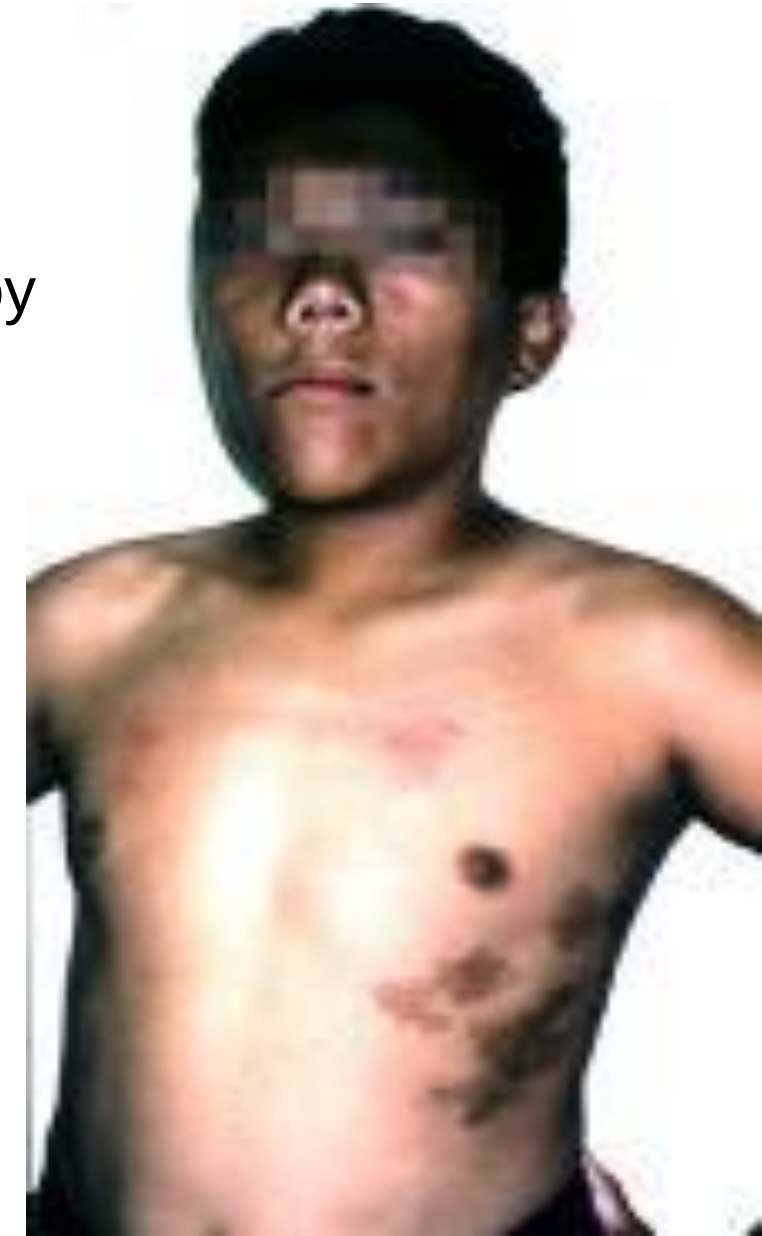
refers to abnormally high linear growth due to excessive action of insulin-like growth factor-I (IGF-I) while the epiphyseal growth plates are open during childhood. Gigantism is a nonspecific term that refers to any standing height more than 2 standard deviations above the mean for the person's sex, age, and Tanner stage. These disorders are placed along a spectrum of IGF-I hypersecretion, wherein the developmental stage when such excess originates determine the principal manifestations. The onset of IGF-I hypersecretion in childhood or late adolescence results in tall stature.

The most remarkable example of a person with gigantism was Robert Wadlow, called the Alton giant, who stood
8 feet 11 inches tall
at the time of his death in his mid-20s

Causes

- of excess IGF-I action may be divided into 3 categories: (1) those originating from primary GH excess released from the pituitary; (2) those caused by increased GH-releasing hormone (GHRH) secretion or hypothalamic dysregulation; and (3) hypothetically, those related to the excessive production of IGF-binding protein, which prolongs the half-life of circulating IGF-I.
- most people with giantism have GH-secreting pituitary adenomas or hyperplasia. Although gigantism is typically an isolated disorder, rare cases occur as a feature of other conditions, such as multiple endocrine neoplasia (MEN) type I, McCune-Albright syndrome (MAS), neurofibromatosis, tuberous sclerosis, or Carney complex.
- Approximately 20% of patients with gigantism have MAS (the triad of precocious puberty, café au lait spots, fibrous dysplasia) and may have either pituitary hyperplasia or adenomas.

Photograph shows a 12-year-old boy with McCune-Albright syndrome. His growth-hormone excess manifestedas tall stature, coarse facial features, and macrocephaly.



Gigantism may begin at any age before epiphyseal fusion.

- Longitudinal acceleration of linear growth secondary to IGF-I excess is the cardinal clinical feature of gigantism.
- Tumor mass may cause headaches, visual changes due to optic nerve compression, and hypopituitarism.
- A common finding from pituitary GH excess is hyperprolactinemia, which manifests in childhood because mammosomatotrophs are the most common type of GH-secreting cells involved in childhood gigantism.

Physical

- All growth parameters are affected, although not necessarily symmetrically. Physical manifestations include the following:
- Tall stature
- Mild-to-moderate obesity (common)
- Macrocephaly (may precede linear growth)
- Soft-tissue hypertrophy
- Exaggerated growth of the hands and feet with thick fingers and toes
- Coarse facial features
- Frontal bossing

- Prognathism
- Hyperhidrosis
- Peripheral neuropathies (eg, carpel tunnel syndrome)
- Cardiovascular disease (eg, cardiac hypertrophy, hypertension, left ventricular hypertrophy) if IGF-I excess is prolonged
- Benign tumors, including uterine myomas, prostatic hypertrophy, colon polyps, and skin tags, which are frequently
- Frequently associated endocrinopathies (eg, hypogonadism, diabetes and/or impaired glucose tolerance, hyperprolactinemia)

- *Hormonal:-* GH
- static: elevated values, associated attenuation of the underlying 24-h rhythm
- dynamic: GHRH or TRH stimulation test empty the pituitary GH reserve
- - other determinations: - PRL is normal or elevated
- elevated somatomedines
- elevated urine OH-proline during progression

Radiologic:

- Skull x-ray including sella turcica:
- periosteal thickening, thickened cranial vault, increased antero-posterior skull diameter
- enlargement of frontal, maxillary and sphenoid sinuses
- enlargement of anterior and posterior clinoid processes
- in hands and feet - enlargement of articular space
- enlargement of soft tissues
- in the spine - dorsal kyphosis
- enlarged vertebral bodies
- osteoporosis, osteophytosis
- sella turcica: ballooned, double contour, destroyed

Hyperprolactinemia

- Hyperprolactinemia is a condition of elevated serum prolactin.
- Prolactin is a 198-amino acid protein (23-kD) produced in the lactotroph cells of the anterior pituitary gland.
- The primary function is to enhance breast development during pregnancy and to induce lactation. However, prolactin also binds to specific receptors in the gonads, lymphoid cells, and liver.

The primary action of prolactin is to stimulate breast epithelial cell proliferation thereby inducing and maintaining milk production. Estrogen stimulates the proliferation of pituitary lactotroph cells, resulting in an increased quantity of these cells in premenopausal women, especially during pregnancy. During lactation and breastfeeding, ovulation may be suppressed due to the suppression of gonadotropins by prolactin but may return before menstruation resumes. Therefore, this cannot be considered a reliable form of birth control.

Secretion regulation

- Dopamine has the dominant influence over prolactin secretion. Secretion of prolactin is under tonic inhibitory control by dopamine, which acts via D2-type receptors located on lactotrophs. Prolactin production can be stimulated by the hypothalamic peptides, thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP), along with epidermal growth factor and dopamine receptor agonists. Thus, primary hypothyroidism (a high TRH state) can cause hyperprolactinemia. VIP increases prolactin in response to suckling, probably because of its action on receptors that increase adenosine 3',5'-cyclic phosphate (cAMP).

Secretion regulation

- Secretion is pulsatile; it increases with sleep, stress, pregnancy, and chest wall stimulation or trauma, and therefore must be drawn after fasting. Normal fasting values are generally less than 25-30 ng/mL, depending on the individual laboratory but can also vary for numerous reasons. Normal levels are also generally higher in women.

Frequency

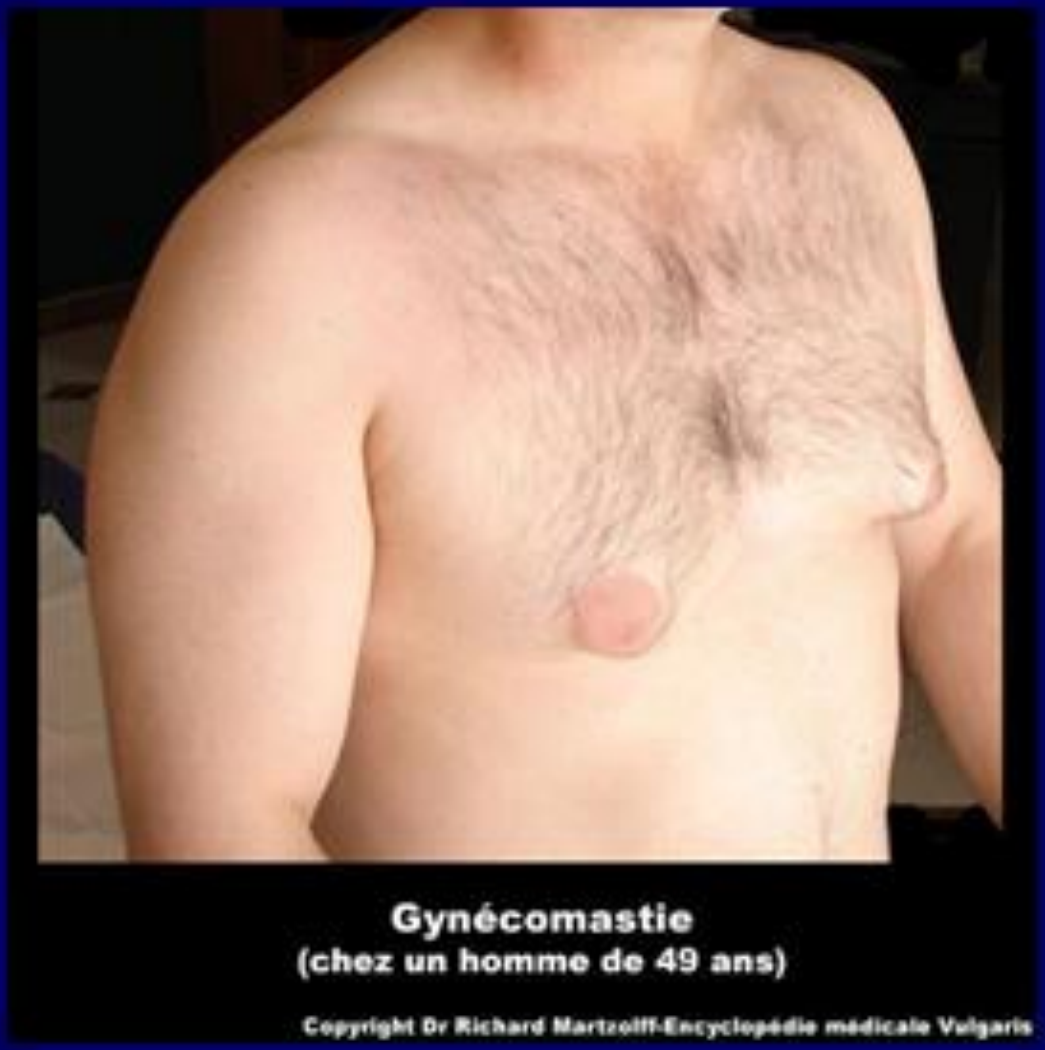
- This condition occurs in less than 1% of the general population and in 10-40% of patients presenting with secondary amenorrhea. Approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Of these patients, approximately 30% have prolactin-secreting tumors.

CLINICAL PICTURE

- Clinical presentation in women is more obvious and occurs earlier than in men. They typically present with oligomenorrhea, amenorrhea, galactorrhea, or infertility, which generally results from prolactin suppression of gonadotropin-releasing hormone (GnRH). Galactorrhea is due to the direct physiologic effect of prolactin on breast epithelial cells.

CLINICAL PICTURE

- Men typically present with complaints of sexual dysfunction, visual problems, or headache and are subsequently diagnosed with hyperprolactinemia in the evaluation process. Prolactin suppresses GnRH, causing a decrease in luteinizing hormone and follicle-stimulating hormone, ultimately leading to decreased serum testosterone levels and hypogonadism. Prolactinoma in men also may cause neurological symptoms, particularly visual-field defects.
- In both sexes, the presence of a pituitary tumor may cause visual-field defects or headache. Most patients with a prolactinoma (the most common type of pituitary adenoma) are women.



Gynécomastie
(chez un homme de 49 ans)

Causes

- The diagnosis of hyperprolactinemia should be included in the differential for female patients presenting with oligomenorrhea, amenorrhea, galactorrhea, or infertility or for male patients presenting with sexual dysfunction. The condition is discovered in the course of evaluating the patient's problem. Once discovered, hyperprolactinemia has a broad differential that includes many normal physiologic conditions.
- Pregnancy should always be excluded unless the patient is postmenopausal or has had a hysterectomy. In addition, hyperprolactinemia is a normal finding in the postpartum period.

- Other common conditions to exclude include a nonfasting sample, excessive exercise, a history of chest wall surgery or trauma, renal failure, and cirrhosis. Postictal patients also develop hyperprolactinemia within 1-2 hours after a seizure. These conditions usually produce a prolactin level of less than 50 ng/mL.
- Hypothyroidism, an easily treated disorder, also may produce a similar prolactin level.
- Detailed drug history should be obtained because many common medications cause hyperprolactinemia, usually with prolactin levels of less than 100 ng/mL.

Drugs that may cause the condition include the following:

- Dopamine-receptor antagonists (eg, phenothiazines, butyrophenones, thioxanthenes, risperidone, metoclopramide, sulpiride, pimozide)
- Dopamine-depleting agents (eg, methyldopa, reserpine)
- Others (eg, isoniazid, danazol, tricyclic antidepressants, monoamine antihypertensives, verapamil, estrogens, antiandrogens, cyproheptadine, opiates, H2-blockers [cimetidine], cocaine)

- If no obvious cause is identified or if a tumor is suspected, MRI should be performed. Although no single test can help determine the etiology of hyperprolactinemia, a prolactinoma is likely if the prolactin level is greater than 250 ng/mL and less likely if the level is less than 100 ng/mL. Medications can cause significant elevation of prolactin. A prolactin level of 500 ng/mL or greater is diagnostic of a macroprolactinoma.

- Prolactin-secreting adenomas are divided into 2 groups: (1) microadenomas (more common in premenopausal women), which are smaller than 10 mm and

  (2) macroadenomas (more common in men and postmenopausal women), which are 10 mm or larger.
- If the prolactin level is greater than 100 ng/mL or less than 250 ng/mL, the evaluating physician must decide whether a radiographic study is indicated. In many cases, with the availability of MRI scanners, imaging is performed earlier and at lower prolactin levels to rule out a non–prolactin-producing tumor.

Laboratory Studies

- Generally, hyperprolactinemia is discovered in the course of evaluating a patient's presenting complaint, for instance amenorrhea, galactorrhea, or erectile dysfunction. Occasionally, several fasting measurements of prolactin must be obtained.
- Current thyroid-stimulating hormone assays are very sensitive for detecting hypothyroid conditions.
- Measuring blood urea nitrogen and creatinine is important for detecting renal failure.
- History of alcohol abuse and abdominal examination may give clues for cirrhosis as a possible etiology.

Laboratory Studies

- Pregnancy testing is required unless the patient is postmenopausal or has had a hysterectomy.
- Patients with macroadenoma should be evaluated for possible hypopituitarism. Male patients should have testosterone levels checked.
- Many patients with acromegaly have prolactin co-secreted with growth hormone. Anyone thought to have acromegaly should be evaluated with an insulin-like growth factor-1 (IGF-1) level measurement and a glucose tolerance test for nonsuppressible growth hormone levels if needed.

Imaging Studies

Although modern high-speed helical CT scanners produce very detailed images, MRI is the imaging study of choice. MRI can detect adenomas that are as small as 3-5 mm.

- **Other Tests**

These would be determined by any identified cause, (eg, visual-field testing especially if a pituitary macroadenoma is found or if optic nerve involvement is noted on imaging studies).

Medical Care

- Direct treatment is geared toward resolving hyperprolactinemic symptoms or reducing tumor size. Patients on medications that cause hyperprolactinemia should have them withdrawn if possible. Patients with hypothyroidism should be given thyroid hormone replacement therapy.
- In cases of pharmacologic-induced hyperprolactinemia, an evaluation of the risk-benefit of the causative agent is imperative. Stopping the drug is ideal but may not be feasible. A good example is a patient with schizophrenia in whom a single antipsychotic agent is the cause, but in whom that drug is keeping the patient's psychoses under control. The cautious addition of a dopamine agonist may be considered.

- Radiation treatment is another option. However, the risk of hypopituitarism makes this a poor choice. It may be necessary for rapidly growing tumors, but its benefits in routine treatment have not been shown to outweigh the risks.

Medication

- The dopamine agonist, bromocriptine mesylate, is often the initial drug of choice and may require high doses to achieve clinical improvement and shrinkage of prolactinomas. It can lower the prolactin level in 70-100% of patients.
- Agents other than bromocriptine have been used (eg, cabergoline, quinagolide). Cabergoline, in particular, is more effective and causes fewer adverse effects than bromocriptine. However, it is much more expensive.
- Pergolide, a drug previously used for the treatment of hyperprolactinemia was withdrawn from the US market 2007, because of heart valve damage resulting in cardiac valve regurgitation. It is important not to stop pergolide abruptly.

- Response to therapy should be monitored by checking fasting serum prolactin levels and checking tumor size with MRI. Most women (approximately 90%) regain cyclic menstruation and achieve resolution of galactorrhea. Testosterone levels in men increase but may remain below normal.
- Therapy should be continued for approximately 12-24 months (depending on the degree of symptoms or tumor size) and then withdrawn if prolactin levels have returned to the normal range. After withdrawal, approximately one sixth of patients maintain normal prolactin levels.

Surgical Care

- General indications for pituitary surgery include patient drug intolerance, tumors resistant to medical therapy, patients who have persistent visual-field defects in spite of medical treatment, and patients with large cystic or hemorrhagic tumors. In patients with symptomatic prolactinomas who are either not responding to high doses of dopamine agonists or cannot tolerate the high doses necessary, transspenoidal surgery has been suggested as the best treatment.
- <u>Complications</u>

Potential complications of hyperprolactinemia are primarily related to tumor size and the physiologic effects of the condition. These include blindness, hemorrhage, osteoporosis, and infertility.

DIABETES INSIPIDUS

Definition

- Diabetes insipidus (DI) is defined as the passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg).
- Excessive urination and extreme thirst as a result of inadequate output of the pituitary hormone ADH or the lack of the normal response by the kidney to ADH

- There are two major types of diabetes insipidus -- central and nephrogenic.
- Central (neurogenic, pituitary, or neurohypophyseal) diabetes insipidus is a lack of ADH production and is due to damage to the pituitary gland or hypothalamus where ADH is produced.
- Nephrogenic diabetes insipidus can be due to diseases of the kidney (such as polycystic kidney disease), certain drugs (such as lithium), and can also occur an inherited disorder, characterized by decreased ability to concentrate urine because of resistance to ADH action in the kidney.

CAUSES

- The most common causes of central DI (CDI), accounting for the vast majority of cases, are idiopathic DI, primary or secondary tumors or infiltrative diseases (such as Langerhans cell histiocytosis), neurosurgery, and trauma.

Idiopathic CDI

- Approximately 30 to 50 percent of cases of CDI are idiopathic, being associated with destruction of the hormone-secreting cells in the hypothalamic nuclei. It has been suggested that an autoimmune process is involved in many, if not most, patients. Insight into the mechanism of autoimmunity in some individuals was provided the presence of cytoplasmic antibodies directed against vasopressin cells (Ab-positive) in patients with endocrine autoimmune diseases but initially without CDI.

- This autoimmune process is characterized by lymphocytic inflammation of the pituitary stalk and posterior pituitary that resolves after destruction of the target neurons. MRI early in the course often reveals thickening or enlargement of these structures.
- Thickening of the pituitary stalk is a nonspecific finding, since some patients with this finding later develop a germinoma or histiocytosis. In children, progressive thickening of the stalk as determined by serial MRIs is strongly suggestive of a germinoma.

- Anterior pituitary hormone deficiency, with decreased release of growth hormone, thyroid stimulating hormone, and ACTH, also may be present or develop in patients with idiopathic CDI.

Tumor-associated DI

- Primary intracranial tumors causing DI include craniopharyngiomas, germinomas, and pineal tumors, among others. The appearance of other hypothalamic manifestations may be delayed for as long as 10 years in these cases.
- Craniopharyngioma is a benign tumor that arises from squamous cell nests in the primitive Rathke pouch. It is the most frequent pediatric intracranial neoplasm, accounting for nearly 54% of cases. Central DI insipidus and multiple pituitary hormone deficiencies are common manifestations in childhood craniopharyngiomas. Surgery is the preferred treatment.

Postoperative DI

- The frequency with which DI develops after neurosurgery varies with the surgery's scope. Not all cases of postoperative DI are permanent. only 8.7% of DI cases persisted for more than 3 months after transsphenoidal pituitary adenoma surgery.
- Postoperative polyuria does not necessarily indicate DI. The most common causes of postoperative polyuria are excretion of excess fluid administered during surgery and an osmotic diuresis resulting from treatment for cerebral edema.

Hereditary central DI

- Approximately 10% of central DI cases are familial. Most of these cases show autosomal dominant inheritance and result from a defect in the *AVP-NP2* gene on chromosome 20p13. The defect results in the production of mutant prohormone that is toxic to the neuron and eventually destroys it.
- There are also autosomal recessive forms of DI, which result from defects in the *AVP-NP2* (AVP neurophysin) gene, as well as in the *WFS1* gene. Mutations in *WFS1* lead to Wolfram syndrome, which is also known by the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness).
- Another recessive form of central DI results from the production of biologically inactive AVP. In addition, an X-linked form of neurohypophyseal DI exists. A specific genetic defect has not been identified.

Other causes of central DI include the following:

- Cancer - Eg, metastatic lung cancer, lymphoma, leukemia
- Hypoxic encephalopathy
- Granulomatous disease - Eg, histiocytosis X, sarcoidosis, tuberculosis, Wegener granulomatosis
- Anorexia nervosa
- Vascular lesions - Eg, arteriovenous malformations, aneurysms, Sheehan syndrome, sickle cell disease, aortocoronary bypass

Nephrogenic diabetes insipidus

In adults, nephrogenic DI most often develops as a result of lithium toxicity or hypercalcemia.

Other causes of acquired nephrogenic DI include the following:

- Hypokalemia
- Renal disease - Eg, from sickle cell disease, amyloidosis
- Pregnancy (transient)

In addition to lithium, other drugs that can reduce urinary concentrating ability include the following:

- Amphotericin B
- Cidofovir
- Demeclocycline
- Didanosine
- Foscarnet
- Ofloxacin

Prognosis

- The prognosis for patients with DI is generally excellent, depending on the underlying illness. In nephrogenic DI caused by medication, stopping the medication may help to restore normal renal function; after many years of lithium use, however, permanent nephrogenic DI may occur.
- DI-related mortality is rare in adults as long as water is available. Severe dehydration, hypernatremia, fever, cardiovascular collapse, and death can ensue in children and elderly people, as well as in persons with complicating illnesses.

- In both central and nephrogenic diabetes insipidus, patients excrete extraordinarily large volumes of very dilute urine. They feel thirsty and drink very large amounts of water to compensate for the water they lose in the urine.
- Polyuria, polydipsia, and nocturia are the predominant manifestations of DI. The daily urine volume is relatively constant for each patient but is highly variable between patients, ranging from 3-20 L.
- The main danger with diabetes insipidus comes when fluid intake does not keep pace with urine output, resulting in dehydration and high blood sodium.

CLINICAL MANIFESTATIONS

- The serum sodium concentration in untreated central DI is often in the high normal range, which is required to provide the ongoing stimulation of thirst to replace the urinary water losses. Moderate to severe hypernatremia can develop when thirst is impaired or cannot be expressed.

- Patients with central DI may develop decreased bone mineral density at the lumbar spine and femoral neck. It is unclear how the deficiency of ADH results in bone loss, particularly since treatment fails to prevent bone disease. However, since ADH acts upon both V1 and V2 receptors and desmopressin principally upon V2 receptors, one possible mechanism is that activation of V1 receptors stimulates bone formation.

Physical Examination

- The physical examination findings vary with the severity and chronicity of DI. The examination findings may be entirely normal. Hydronephrosis, with pelvic fullness, flank pain or tenderness, or pain radiating to the testicle or genital area, may be present. Bladder enlargement occurs in some patients. Unless the thirst mechanism is impaired or access to fluid is restricted, dehydration is not seen. Aside from an enlarged bladder, no specific signs of DI exist.

In a patient whose clinical presentation suggests DI, laboratory tests must be performed to confirm the diagnosis. A 24-hour urine collection for determination of urine volume is required. In addition, should be measured the following:

- Serum electrolytes and glucose
- Urinary specific gravity
- Simultaneous plasma and urinary osmolality
- Plasma antidiuretic hormone (ADH) level

Water deprivation testing may be useful in situations in which the diagnosis is uncertain.

- A urinary specific gravity of 1.005 or less and a urinary osmolality of less than 200 mOsm/kg are the hallmark of DI. Random plasma osmolality generally is greater than 287 mOsm/kg.
- Suspect primary polydipsia when large volumes of very dilute urine occur with plasma osmolality in the low-normal range. Polyuria and elevated plasma osmolality despite a relatively high basal level of ADH suggests nephrogenic DI.

Water Deprivation Testing

- The water deprivation test (ie, the Miller-Moses test), a semiquantitative test to ensure adequate dehydration and maximal stimulation of ADH for diagnosis, is typically performed in patients with more chronic forms of DI.

- All water intake is withheld, and urinary osmolality and body weight are measured hourly. When 2 sequential urinary osmolalities vary by less than 300 mOsm/kg or when the weight decreases by more than 3%, 5 U of aqueous ADH or desmopressin are administered subcutaneously. A final urine specimen is obtained 60 minutes later for osmolality measurement.

Magnetic Resonance Imaging

- Cranial magnetic resonance imaging (MRI) can be used to exclude pituitary cysts, hypoplasia, and destruction secondary to mass lesions.

Treatment

- In patients with central DI, desmopressin is the drug of choice. A synthetic analogue of antidiuretic hormone (ADH), desmopressin is available in subcutaneous, IV, intranasal, and oral preparations. Generally, it can be administered 2-3 times per day. Patients may require hospitalization to establish fluid needs. Frequent electrolyte monitoring is recommended during the initial phase of treatment.
- Alternatives to desmopressin as pharmacologic therapy for DI include synthetic vasopressin and the nonhormonal agents chlorpropamide, carbamazepine, clofibrate, thiazides, and nonsteroidal anti-inflammatory drugs (NSAIDs). Because of side effects, carbamazepine is rarely used, being employed only when all other measures prove unsatisfactory. NSAIDs (eg, indomethacin) may be used in nephrogenic DI, but only when no better options exist.