ENDOCRINOLOGY

ADRENAL

Kenneth Alonso, MD, FACP

Hypothalamic control of pituitary hormones

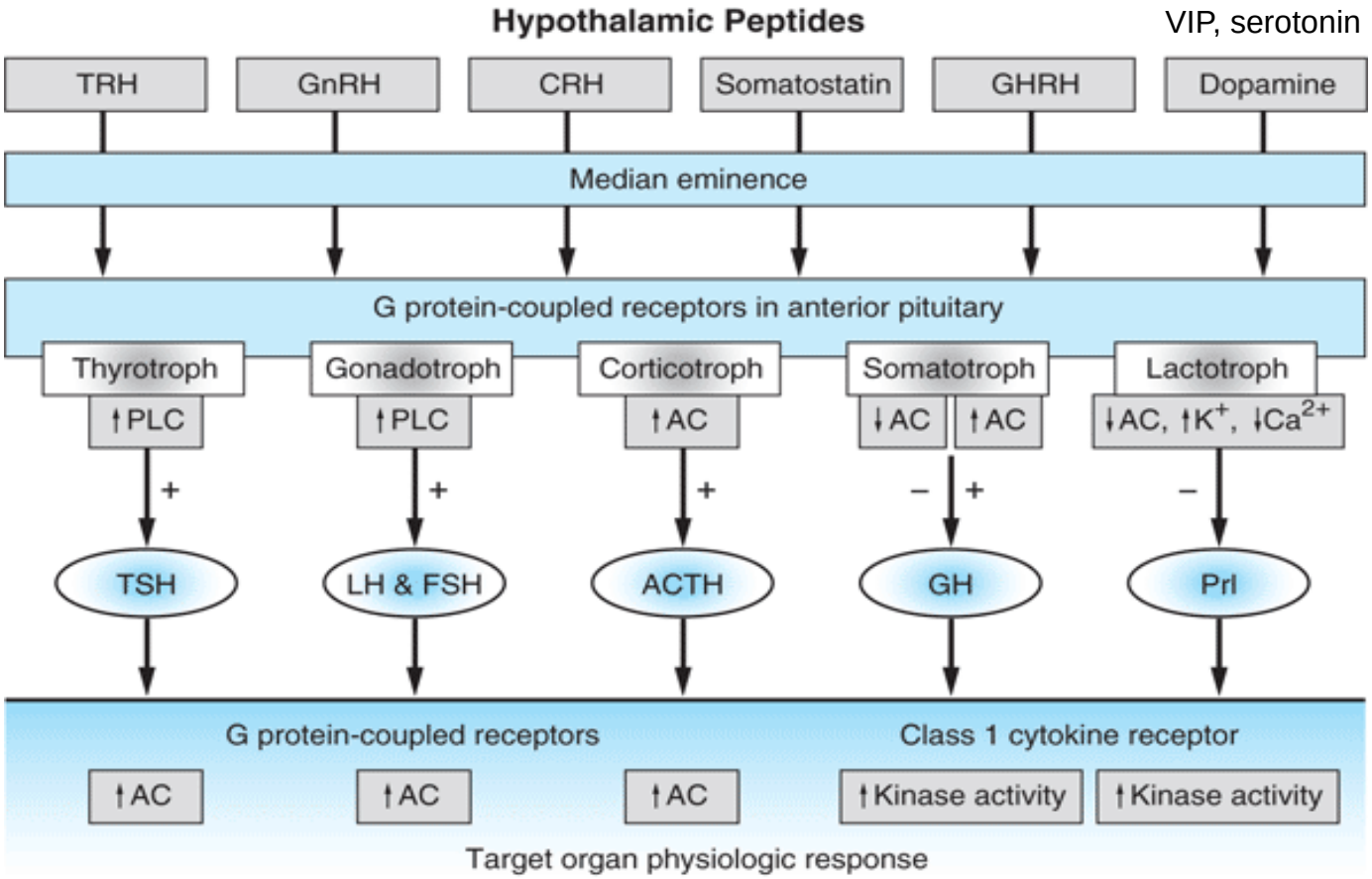

Fig. 3-3 Accessed 02/01/2010

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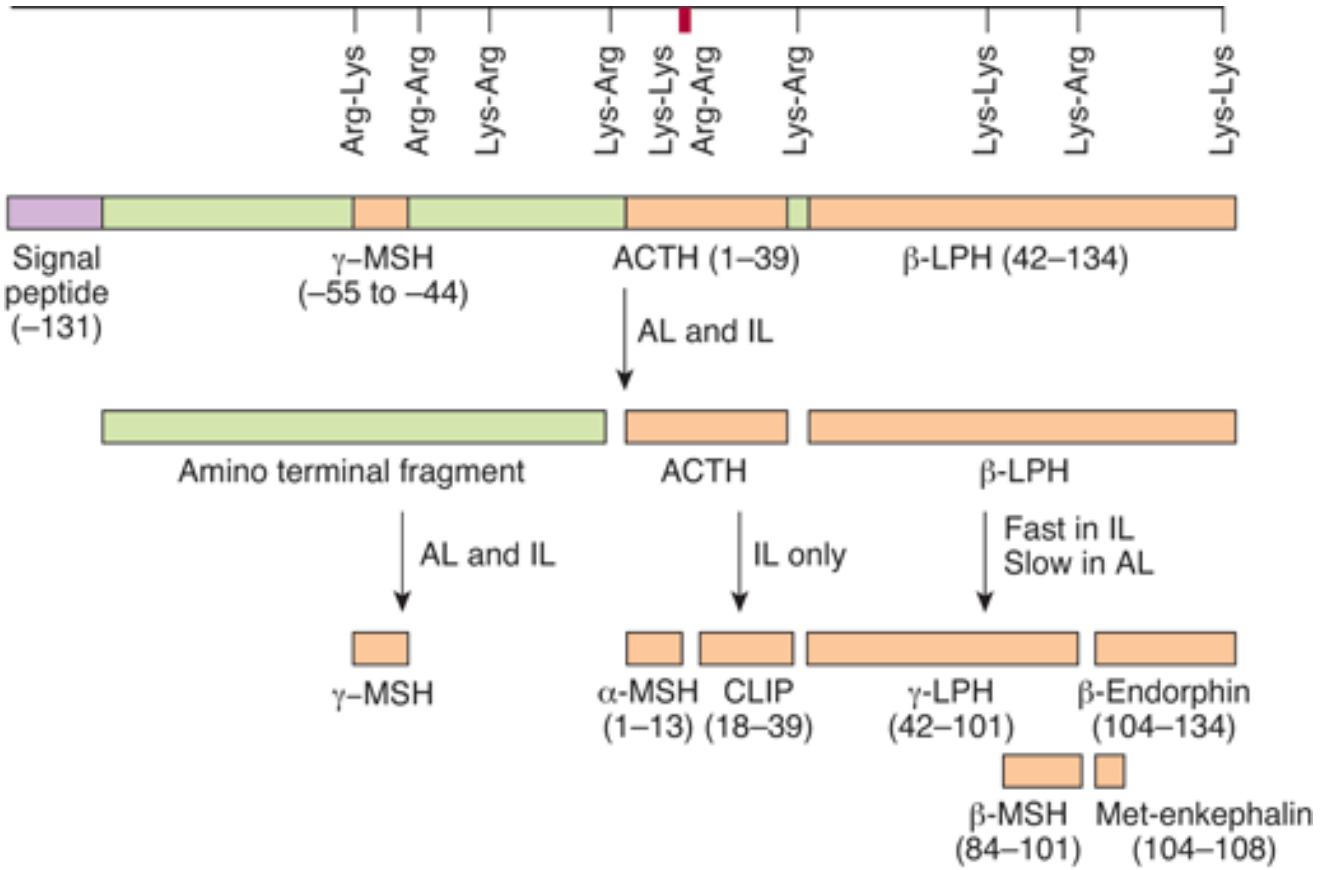
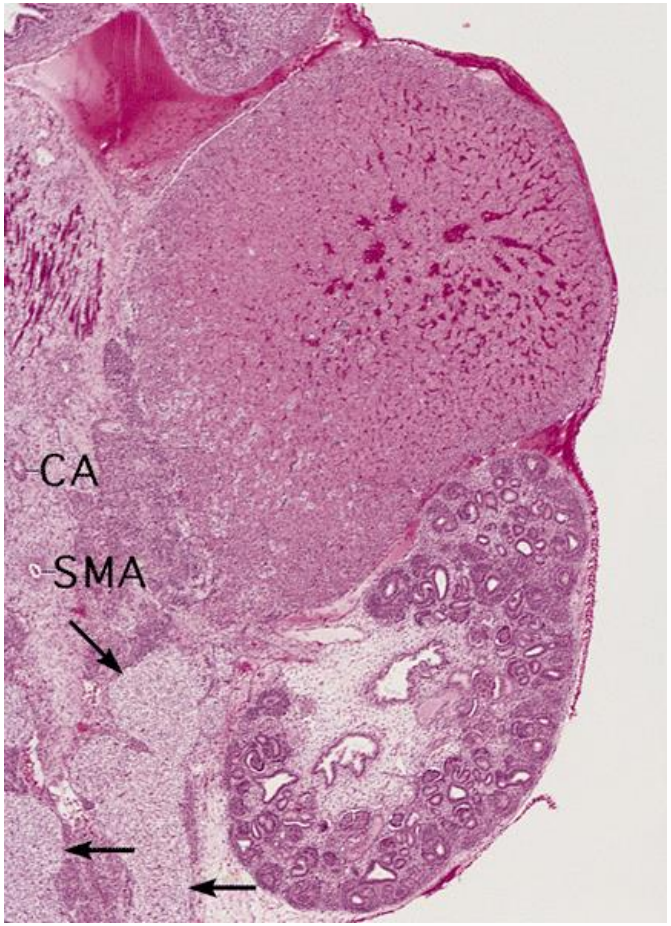


Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 24-2 Accessed 02/01/2010

Fetal adrenal

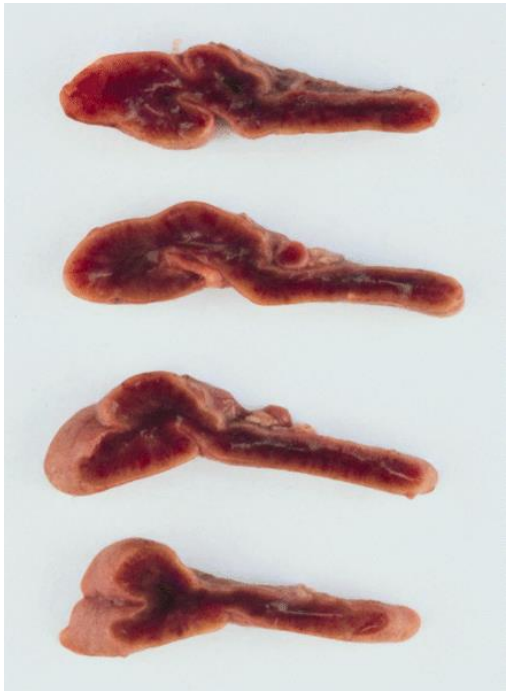


Note the close relation of developing para-aortic sympathetic plexus with medial and inferior aspects of the adrenal gland. Small pale- staining clusters of cells separate cords of provisional or fetal cortical cells in the inferomedial aspect of the gland. Note large collections of extramedullary chromaffin tissue (arrows) representing organs of Zuckerkandl. Celiac (CA) and superior mesenteric (SMA) arteries are also present. Eleven weeks gestation.

Fig. 1-3

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal gland



Figs. 1-11 and 1-15

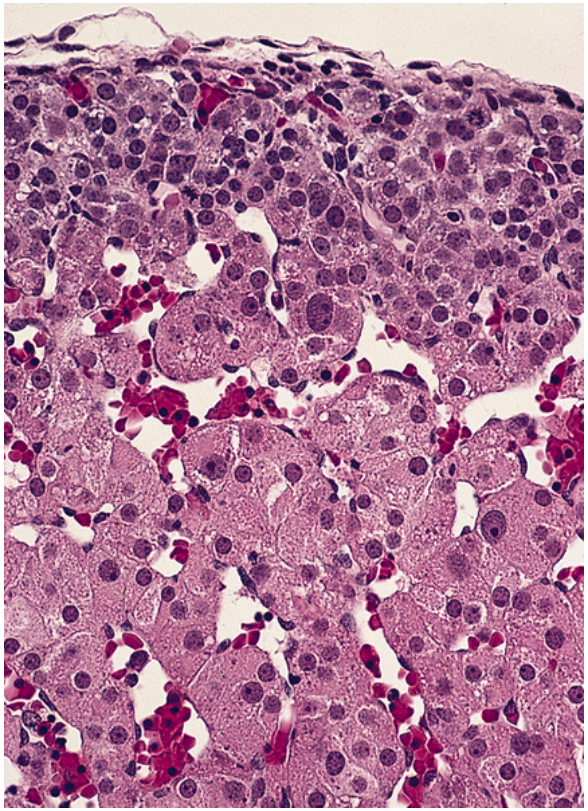
Note the dark appearance of much of the provisional or fetal cortex. (Left) Compare to the adult adrenal. (Center) The medullary compartment appears dull gray in contrast to the bright yellow cortex. Partial to complete cuffs of cortex are present around tributaries of the central adrenal vein. Note also the brown zona reticularis at the inner cortex.

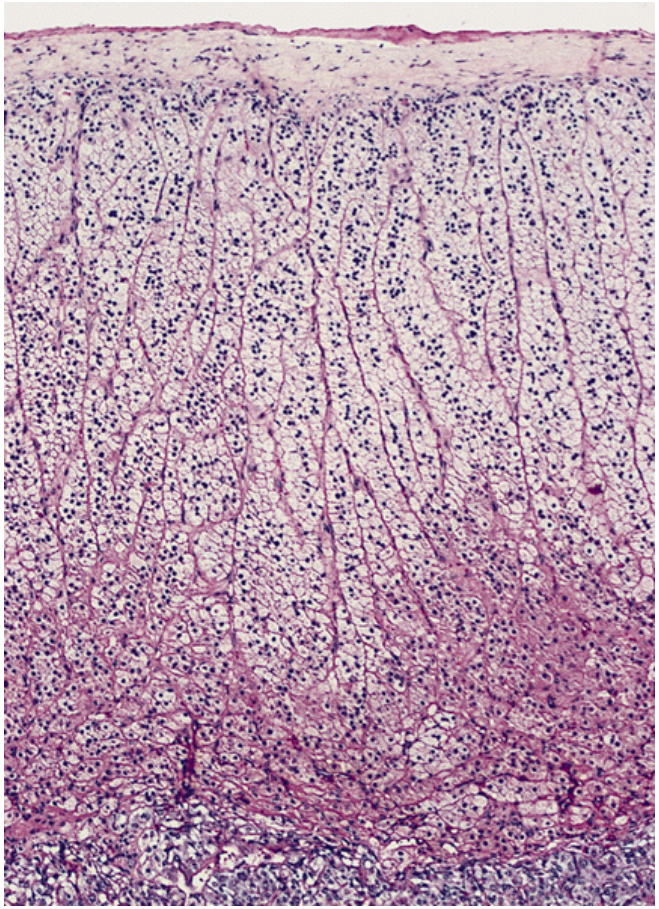
Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal

- Adrenal blood flow is centripetal: from the outer cortex to the medulla.
- Normal levels of cortisol necessary for the medulla to function.

Adrenal gland



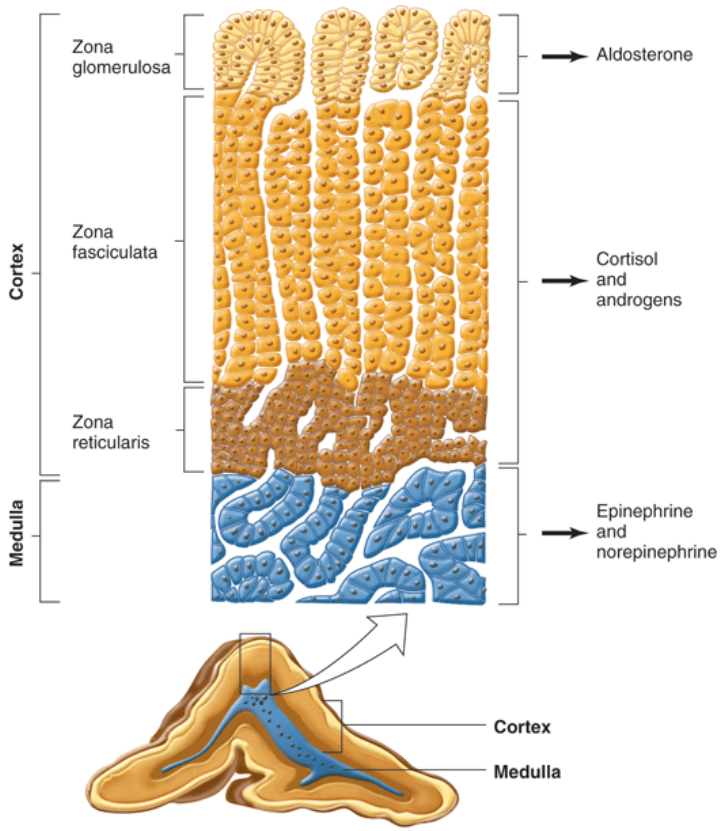


Definitive or adult cortex forms a thin rim of subcapsular cells with a high nuclear/cytoplasmic ratio. Most of the cortex is composed of provisional or fetal cortical cells. (Left) Normal adrenal cortex in an adult (Center) shows radial cords of lipid- rich cells of the zona fasciculata and an indistinct, discontinuous zona glomerulosa.

Figs. 1-17 and 1-20

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal steroid biosynthesis



(Reproduced with permission from Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology: The Mechanisms of Body Function*, 11th ed. McGraw-Hill, 2008.)

- The zona fasciculata contains abundant lipid and produces glucocorticoids (cortisol and corticosterone), and the androgens (DHEA and DHEA sulfate).
- The zona reticularis develops postnatally and is recognizable at about age 3; it also produces glucocorticoids and androgens.

KEY POINTS

- The conversion of cholesterol to pregnenolone is the quantitative, rate-limiting step of steroidogenesis and the site of acute regulation.
- Steroidogenesis follows a specific sequence with some branch points and redundancies, and each step is either irreversible or has a strong directional preference.
- Steroid formation features multiple layers of regulation, redundancy for some pathways, and multiple activities for some key enzymes.
- The two major classes of steroid biosynthetic enzymes are cytochrome P450 enzymes and the hydroxysteroid dehydrogenases/reductases.
- Of the steroidogenic cytochrome P450 enzymes, P450scc, P450c11, and P450c11AS are mitochondrial and use ferredoxin/ferredoxin reductase as electron transfer proteins; P450c17, P450c21, and P450aro reside in the endoplasmic reticulum and use P450-oxidoreductase as their electron transfer protein.
- The hydroxysteroid dehydrogenases catalyze mechanistically reversible oxidation/reduction reactions using NAD[P][H] cofactors; some enzymes strongly favor hydroxysteroid oxidation, and others strongly favor ketosteroid reduction in intact cells.
- The 17-hydroxylase and 17,20-lyase activities of P450c17 qualitatively regulate the type of steroid hormones produced in a cell.

Adrenal steroid biosynthesis

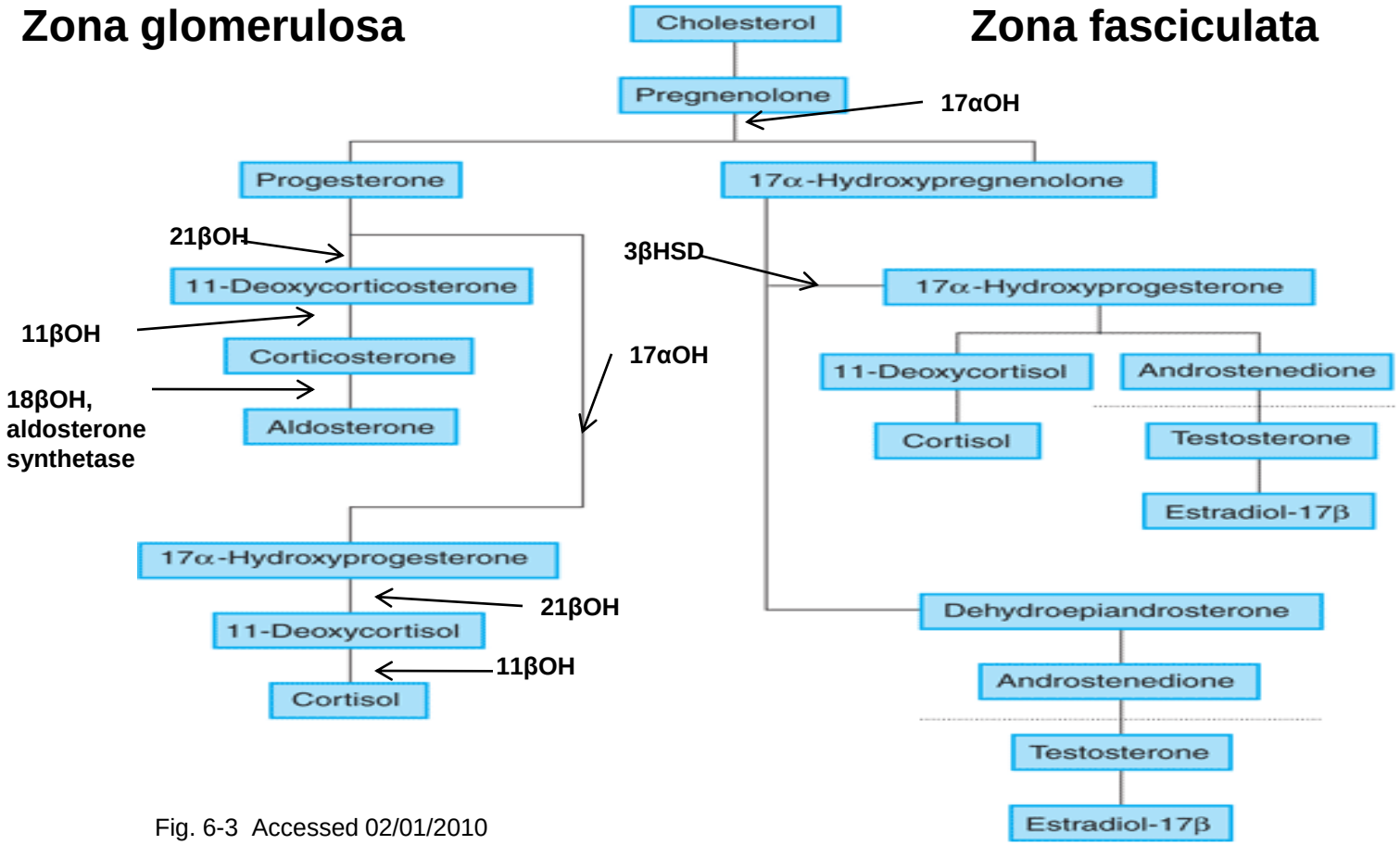


Fig. 6-3 Accessed 02/01/2010

Adrenal steroid biosynthesis

- 20% of cholesterol utilized is free within the cell. Transported to mitochondria.
- The rate limiting step in adrenal hormone synthesis is the cholesterol desmolase conversion of cholesterol to pregnenolone.
- ACTH and angiotensin II stimulate this conversion.
- ACTH regulates the hormone production of the zona fasciculata and zona reticularis.
- ACTH receptors in the plasma membrane activate adenylate cyclase with production of the second messenger, cAMP.

Adrenal steroid biosynthesis

- Glucocorticoids are principally produced in the zona fasciculata.
- Androgens are also produced in both the zona fasciculata and zona reticularis (after adrenarche).
- Mineralicorticoids are produced in the zona glomerulosa as it alone possesses aldosterone synthase activity.
- This enzyme converts deoxycorticosterone to aldosterone.

Adrenal steroid biosynthesis

- Angiotensins II and III stimulate zona glomerulosa cells by binding a plasma membrane receptor coupled to phospholipase C.
- Protein kinase C is activated and intracellular Ca^{2+} levels increase.
- Cells in the zona glomerulosa do not have 17-hydroxylase activity.
- Pregnenolone can be converted only into progesterone.

Adrenal steroid biosynthesis

- Cells of the zona glomerulosa also lack 11-hydroxylase activity.
- Deoxycorticosterone cannot be converted to corticosterone.
- But 18-hydroxylase, which possesses 11-hydroxylase activity as well, is present.
- The mineralicorticoid feedback loop is closed by K^+.
- As little as 0.1mmol change in plasma K^+ stimulates/depresses aldosterone production.
- Glucocorticoid feedback controls corticotropin releasing hormone and ACTH release.

Steroid receptor super-family

- The steroid receptor is not able to bind to DNA in the absence of the hormone.
- Steroid hormone binding to the receptor allows the complex to bind to DNA and activate gene transcription.
- While thyroid, vitamin D, and vitamin A receptors (all part of the steroid receptor super-family) are largely located in the nucleus, steroid receptors are also found in the cytoplasm.

Cortisol

- Cortisol increases gluconeogenic amino acids and glycerol in the liver for glucose conversion.
- Stimulates lypolysis and protein catabolism, leading to mobilization of fatty acids and amino acids.
- Cortisol stabilizes lysosomal membranes (limits histamine and serotonin release) as well as promotes the synthesis of lipocortin (a phospholipase A2 inhibitor)
- Blocks arachidonic acid synthesis.

Cortisol

- Cortisol inhibits the production of IL-2 and decreases production of TNF-α.
- Cortisol inhibits nitric oxide synthase and upregulates α1-adrenergic receptors on vascular smooth muscle.
- The mineralicorticoid effect of cortisol is small because of low affinity of renal mineralicorticoid type I receptors to cortisol
- BUT, increased cortisol production leads to overload of metabolizing enzymes

Cortisol

- 18-desoxycorticosterone production increases.
- Extracellular fluid volume increases.
- The change in plasma volume augments sympathetic activity.
- Renin and angiotensin production increase.
- There is a fall in kinin and prostaglandin production and release
- Catecholamine o-methyl transferase inhibited, leading to diminished degradation of catecholamines.
- Vasoconstriction results.

Aldosterone

- While ACTH promotes aldosterone synthesis and secretion, it has little effect on the rate of secretion.
- Aldosterone stimulates the synthesis of new Na^+ channels in the cells of the collecting tubules as well as opening K^+ channels.
- This leads to increased total Na^+ reabsorption with concomitant water reabsorption and K^+ secretion.

Sex hormones

- The placenta cannot synthesize cholesterol from acetate.
- Androgens are produced by the maternal and fetal adrenal glands.
- DHEA and DHEA-S are peripherally converted to testosterone and dihydrotestosterone (DHT) at adrenarche.
- Androstenedione produced by the adrenals and ovaries is peripherally convereted to estrone (E_3) by aromatase.
- At menopause, this becomes the dominant estrogen.

Glucocorticoid excess

- Central obesity with striae
- Round and plethoric facies (compare photos from different years)
- Hypertension
- Hirsutism
- Menstrual disturbance
- In children, virilization with or without salt wasting is the common presentation.
- 21 β-hydroxylase deficiency may be a late onset disease and is seen in 5-25% of women with adrenal hormone excess.

Glucocorticoid excess

Table 24-9 Clinical Features of Cushing Syndrome

Feature	Percent
Obesity or weight gain	95%*
Facial plethora	90%
Rounded face	90%
Decreased libido	90%
Thin skin	85%
Decrease in linear growth in children	70-80%
Menstrual irregularity	80%
Hypertension	75%
Hirsutism	75%
Depression/emotional liability	70%
Easy bruising	65%
Glucose intolerance	60%
Weakness	60%
Osteopenia or fracture	50%
Nephrolithiasis	50%

*100% in children.
Adapted from Newell-Price J, et al: Cushing syndrome. Lancet 367:1605-1616, 2006.

Table 24-8 Endogenous Causes of Cushing Syndrome

Cause	Relative Frequency (%)	Ratio of Females to Males
ACTH-Dependent		
Cushing disease (pituitary adenoma; rarely CRH	70	3.5:1
Ectopic corticotropin syndrome (ACTH)	10	1:1
ACTH-Independent		
Adrenal adenoma	10	4:1
Adrenal carcinoma	5	1:1
Macronodular hyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin and serotonin receptors)	<2	1:1
Primary pigmented nodular adrenal disease (*PRKARIA* and *PDE11* mutations)	<2	1:1
McCune-Albright syndrome (*GNAS* mutations)	<2	1:1

ACTH, Adrenocorticotropic hormone; GIPR, gastric inhibitory polypeptide receptor; LHR, luteinizing hormone receptor; *PRKAR1A*, protein kinase A regulatory subunit 1α; *PDE11*, phosphodiesterase 11A.

Note: These etiologies are responsible for endogenous Cushing syndrome. The most common overall cause of Cushing syndrome is exogenous glucocorticoid administration (iatrogenic Cushing syndrome).

Adapted with permission from Newell-Price J, et al: Cushing syndrome. Lancet 367:1605-1616, 2006.

Glucocorticoid excess

- Exogenous glucocorticoids in supraphysiologic doses are the most common cause of Cushing's syndrome.
- Benign adrenal adenomas are small
- 20% are functional
- Do not produce androgens or mineralocorticoids
- Fewer than 2% of adrenal masses greater than 4cm in size are adenomas
- In half of pregnant patients, the cause of the excess is an adrenal tumor.

Glucocorticoid excess

- If greater than 6cm, 92% are carcinomas
- Adrenal cortical carcinoma usually has a rapid clinical course
- May present with mass effects
- May present with virilization, and, rarely, feminization (rarely)
- 60% of adrenal carcinomas are hyperfunctional
- IGF-2 overexpressed.
- MDR-1 (p-glycoprotein pump) and ERCC-1 (excision repair) mutated.

Glucocorticoid excess

- Hyperplastic adrenal tissue over-expresses receptors for LH, ADH, gastric inhibitory peptide, and serotonin.
- This regulates ACTH production in a manner not understood.
- GNAS mutations ($G_s\alpha$ activation) in McCune-Albright syndrome affect cAMP levels
- PRKR1A mutations affect cAMP levels
- PDE11A (phosphodiesterase) mutation leads to elevated cAMP levels (failure of enzyme degradation)

Histopathology

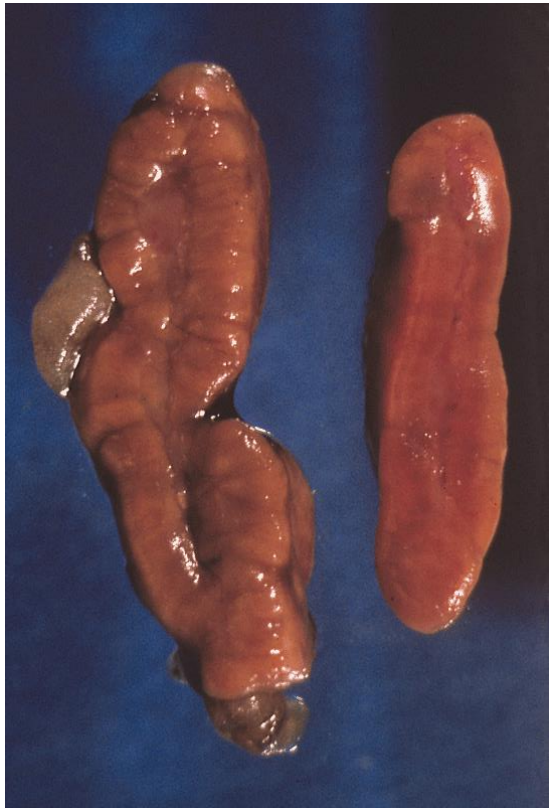
- Adrenal
- Exogenous glucocorticoid excess suppresses endogenous ACTH
- Bilateral cortical atrophy due to a lack of stimulation of the zonae fasciculata and reticularis by ACTH.
- The zona glomerulosa is of normal thickness because this portion of the cortex functions independently of ACTH

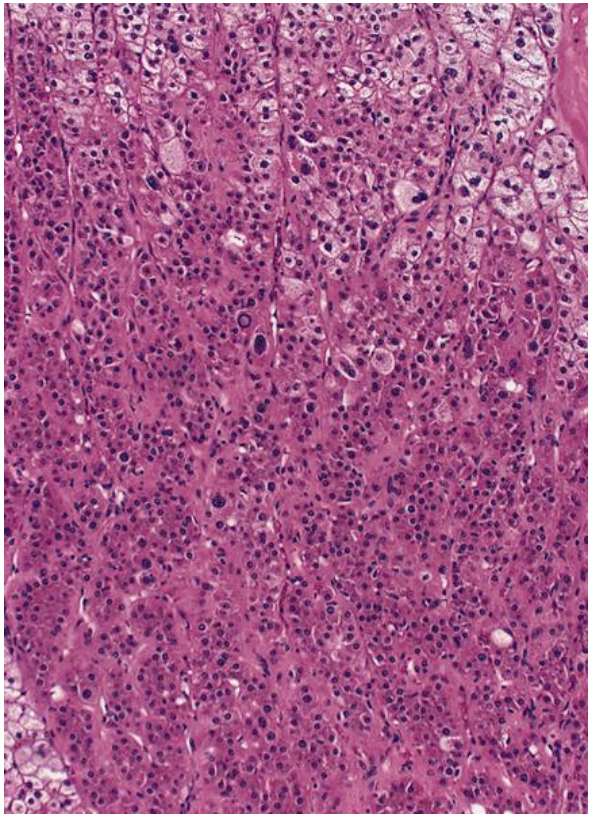
Histopathology

- Diffuse hyperplasia is found in individuals with ACTH-dependent Cushing syndrome.
- Both glands are enlarged and yellow.
- The adrenal cortex is diffusely thickened and variably nodular,
- Microscopically, the hyperplastic cortex demonstrates an expanded “lipid-poor” zona reticularis, comprising compact, eosinophilic cells, surrounded by an outer zone of vacuolated “lipid-rich” cells, resembling those seen in the zona fasciculata.
- Any nodules present are usually composed of vacuolated “lipid-rich” cells.

Figure 24-42 Diffuse hyperplasia of the adrenal contrasted with normal adrenal gland. In cross-section the adrenal cortex is yellow and thickened, and a subtle nodularity is seen (contrast with Fig. 24-46). Both adrenal glands were diffusely hyperplastic in this patient with ACTH-dependent Cushing syndrome.

Cushing’s disease





Transverse sections of a 3.5 g adrenal gland surgically resected from an 8-year-old boy with recurrent Cushing's disease. (Gross). Much of zona fasciculata is converted to cells with compact, eosinophilic cytoplasm under the trophic influence of ACTH. (Microscopic).

Figs. 3-16 and 3-17

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Histopathology

- In macronodular hyperplasia the adrenals are almost entirely replaced by prominent nodules of varying sizes, which contain an admixture of lipid-poor and lipid-rich cells.
- Micronodular change is present in intervening areas
- Micronodular hyperplasia is composed of small, darkly pigmented (brown to black) nodules, with atrophic intervening areas.

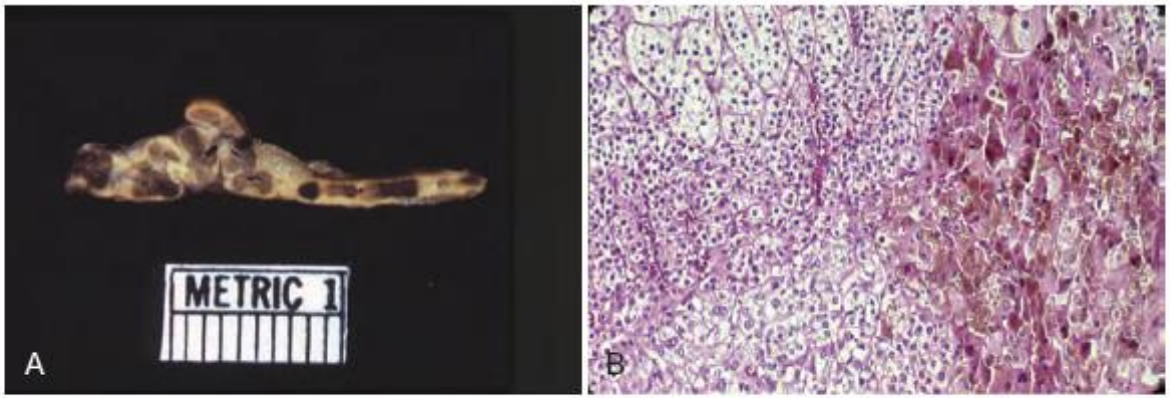
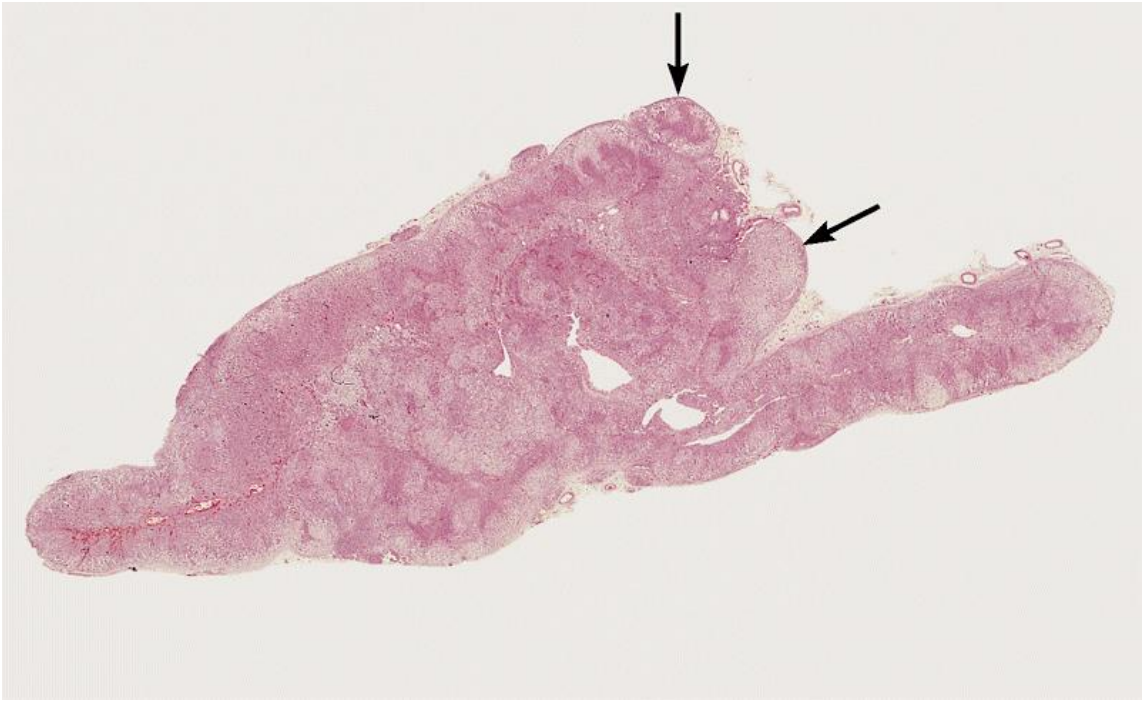


Figure 24-43 **A,** Micronodular adrenocortical hyperplasia with prominent pigmented nodules in the adrenal gland. **B,** On histologic examination the nodules are composed of cells containing lipofuscin pigment, seen in the right part of the field. (Photographs courtesy Dr. Aidan Carney, Department of Medicine, Mayo Clinic, Rochester, Minn.)

Histopathology

- Pituitary
- The most common alteration resulting from high levels of endogenous or exogenous glucocorticoids is Crooke hyaline change.
- The normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary becomes homogeneous and paler as a result of the accumulation of intermediate keratin filaments in the cytoplasm

Nodular adrenal gland



Nodular adrenal gland at autopsy of a patient with no evidence of hypercorticolism.
A dominant macronodule can simulate an adrenal cortical adenoma. Other smaller nodules were also present.

Fig. 3-2

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Histopathology

- Adrenocortical adenomas are yellow tumors surrounded by thin or well-developed capsules.
- Microscopically, they are composed of cells that are similar to those encountered in the normal zona fasciculata.
- The carcinomas associated with Cushing syndrome tend to be larger than the adenomas.
- With functioning tumors, both benign and malignant, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic

Adrenal adenoma

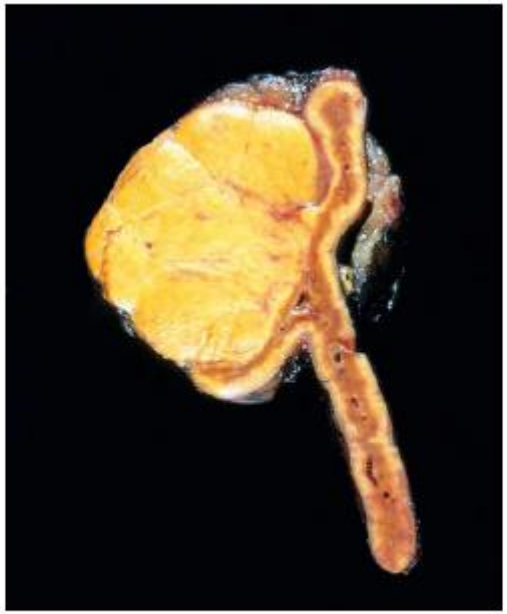


Figure 24-50 Adrenal cortical adenoma. The adenoma is distinguished from nodular hyperplasia by its solitary, circumscribed nature. The functional status of an adrenal cortical adenoma cannot be predicted from its gross or microscopic appearance.

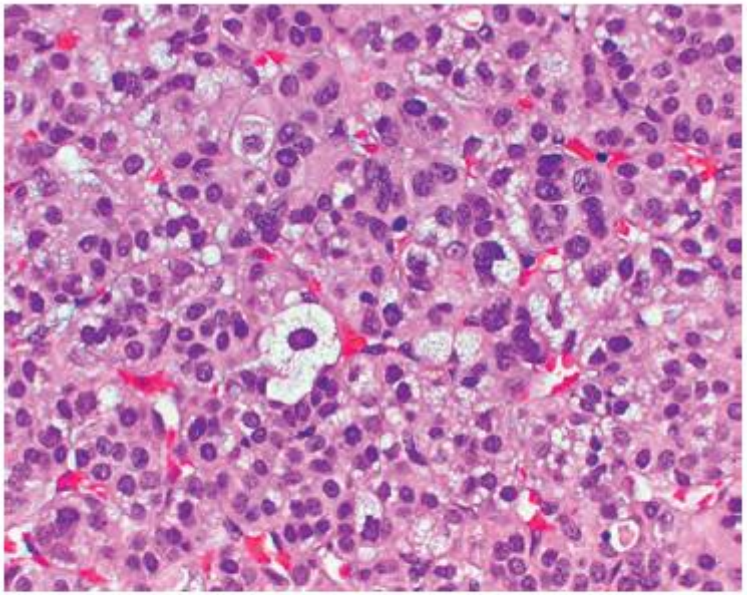
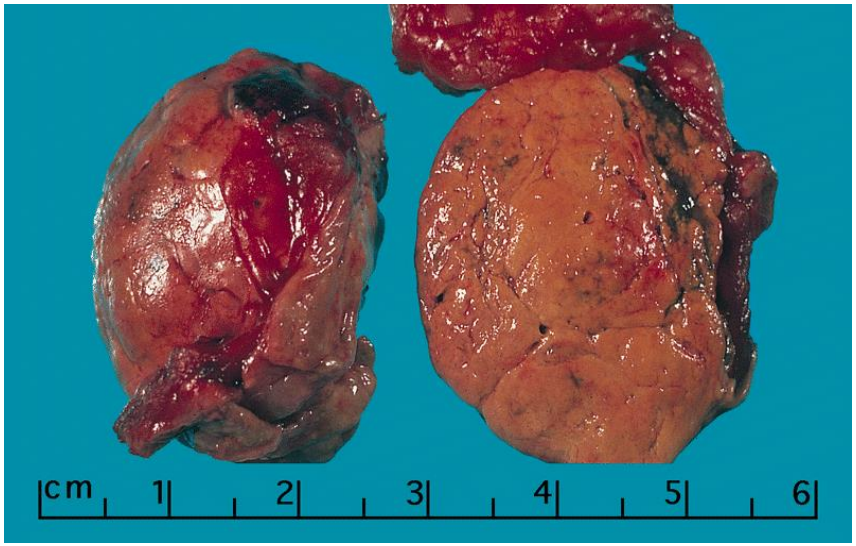
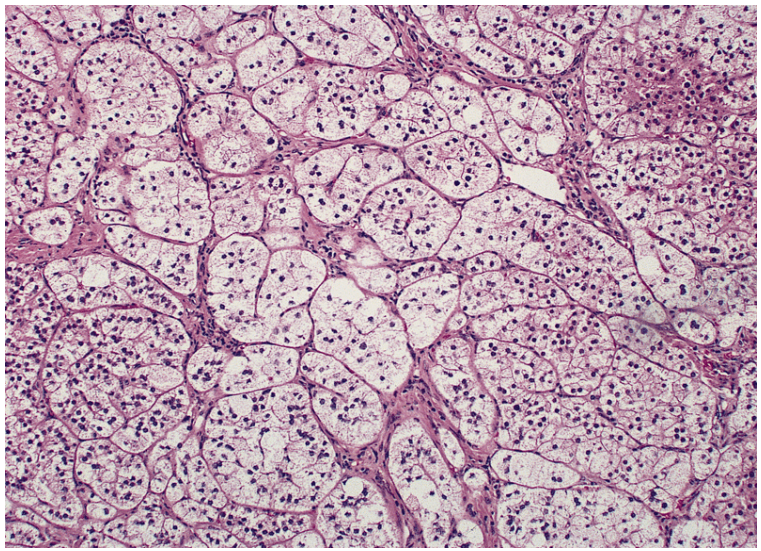


Figure 24-51 Histologic features of an adrenal cortical adenoma. The neoplastic cells are vacuolated because of the presence of intracytoplasmic lipid. There is mild nuclear pleomorphism. Mitotic activity and necrosis are not seen.

Adrenal adenoma



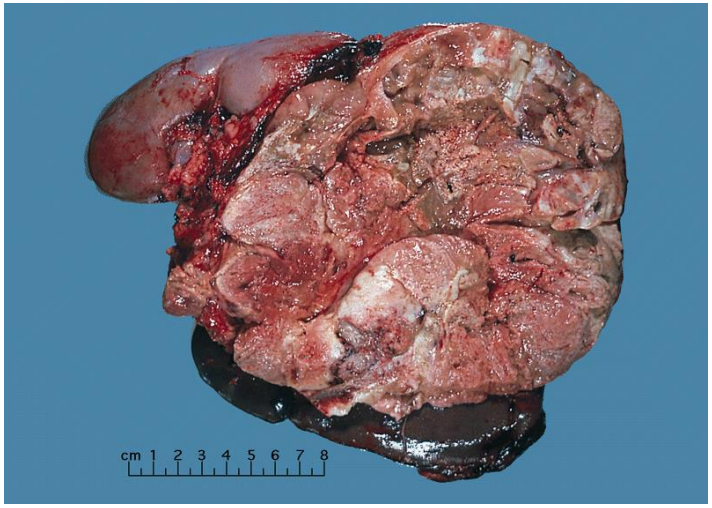


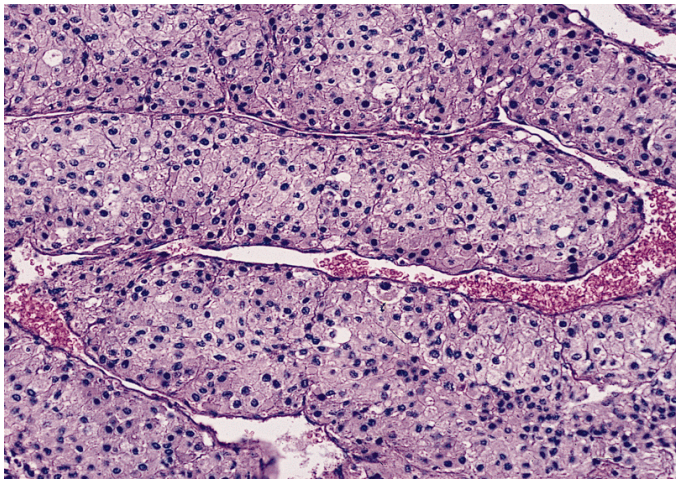
Upper:
The tumor is yellow- orange on cross section and has vague lobulations.
Lower:
The tumor cells are arranged in small clusters and short cords with pale- staining cytoplasm. Note the absence of nuclear enlargement and pleomorphism. Black nodules may contain neuromelanin.

Figs. 4-4 and 4-5

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal carcinoma





Upper:
The tumor measured invaded kidney and spleen which necessitated en bloc removal of these organs with tumor. Patient had evidence of virilization.
LowerL
Broad anastomosing trabecular pattern with intervening delicate sinusoids. Despite the lack of significant nuclear atypia, this histologic pattern may be associated with aggressive biologic behavior.

Figs. 5-6 and 5-7

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal carcinoma

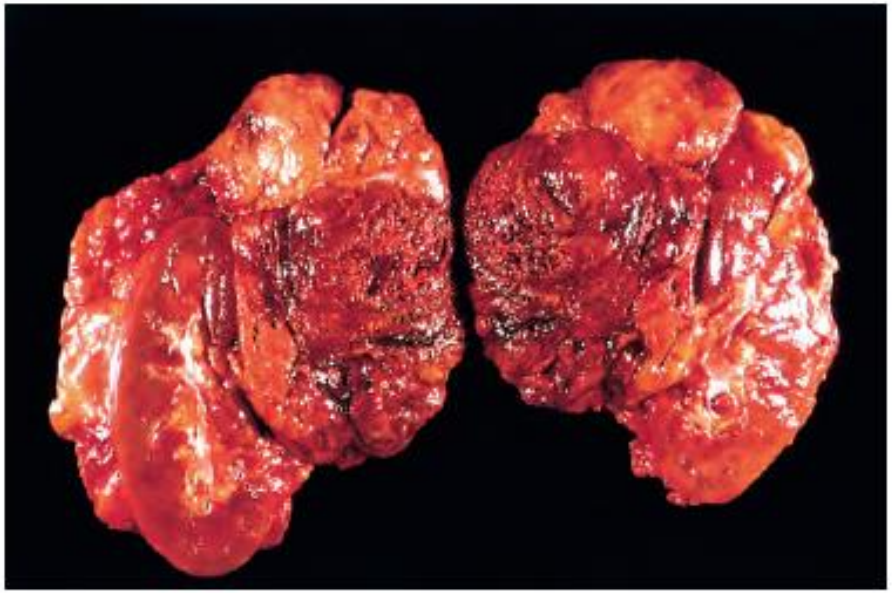


Figure 24-52 Adrenal carcinoma. The hemorrhagic and necrotic tumor dwarfs the kidney and compresses the upper pole.

Adrenal carcinoma

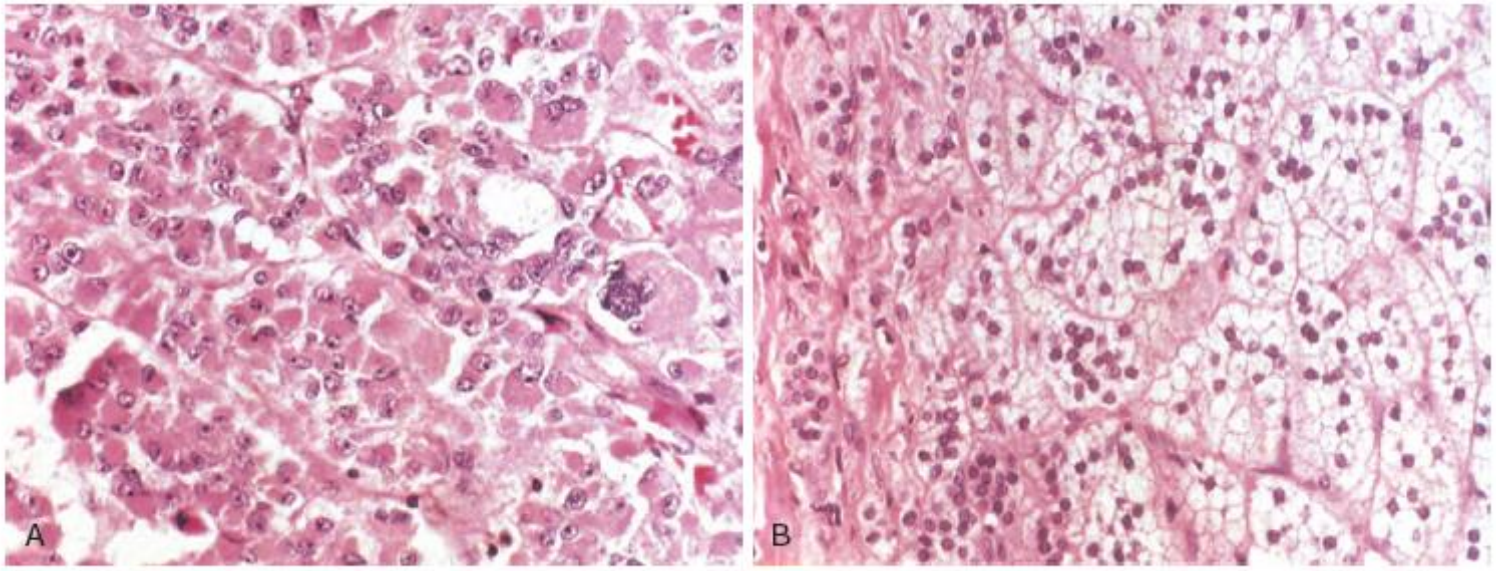


Figure 24-53 Adrenal carcinoma (**A**) revealing marked anaplasia, contrasted with normal adrenal cortical cells (**B**).

Laboratory diagnosis

- 10% of cortisol circulates unbound and is physiologically active.
- Majority is reabsorbed in renal tubules.
- A 24-hour urine free cortisol (UFC) measurement should reflect the integrated cortisol secretion
- Corrected for urine creatinine levels (reflects adequacy of collection).
- Levels may be elevated in depressed patients as well as women with polycystic ovary disease.
- Used for screening for glucocorticoid excess.
- However, a serum cortisol obtained from a sleeping patient at midnight is highly sensitive and specific for glucocorticoid excess.

Laboratory diagnosis

- Administration of 1.0mg dexamethasone followed by determination of an a.m. cortisol level the next day evaluates the hypothalamic-pituitary axis.
- If the morning cortisol is <5ug/dl, the patient does not have adrenal excess.
- Does not suppress adenomas or carcinomas
- Drugs that induce the hepatic enzymatic clearance of dexamethasone reduce plasma dexamethasone concentration (false positive)
- 50% false positive results in women taking oral contraceptives.

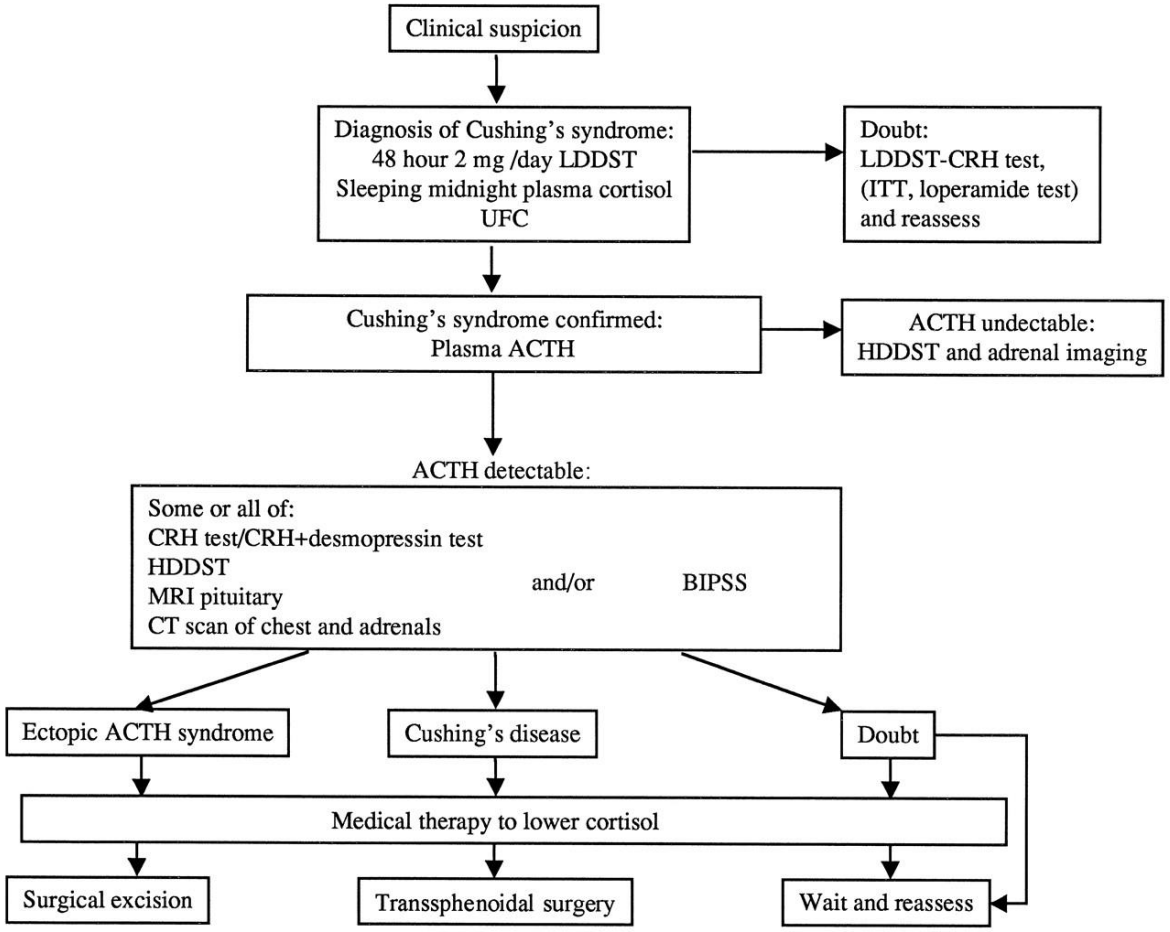
Laboratory diagnosis

- Hyperplastic adrenal tissue possesses hormone receptors and will suppress with 2mg dose dexamethasone.
- Following high dose dexamethasone administration (8mg), ACTH and cortisol levels are measured the following morning.
- ACTH not detectable, cortisol minimally affected: proceed to MRI of adrenal.
- ACTH normal or increased, cortisol not suppressed: proceed to MRI of chest.
- ACTH normal or increased, cortisol may be partially suppressed: proceed to MRI of pituitary.

Endocrine Society strategy

- Screen with one of the following:
- Urine free cortisol
- 1mg dexamethasone overnight suppression (plasma cortisol measured at 8am or urinary free cortisol determined following suppression)
- 2mg dexamethasone suppression over 48 hours (plasma cortisol measured at 8am or urinary free cortisol determined following suppression)
- If the screening test is abnormal, repeat with a second screening test.
- If abnormal, CRH stimulation is performed. If abnormal CRH, proceed to imaging of the pituitary.

Figure 3. A diagnostic approach to the diagnosis and differential diagnosis of Cushing's syndrome.



Endocr Rev, Volume 19, Issue 5, 1 October 1998, Pages 647–672, https://doi.org/10.1210/edrv.19.5.0346

An efficient diagnostic strategy

- No random cortisol determinations
- 24-hour urine free cortisol.
- Cortisol and ACTH drawn at midnight, 8 am, 4 pm during the timed collection.
- If urine free cortisol is elevated, then examine cortisol and ACTH samples.
- If diurnal variation is not lost, consider depression.

An efficient diagnostic strategy

- If cortisol elevated but ACTH low, proceed to MRI of adrenal gland.
- If cortisol elevated and ACTH elevated, proceed to high dose dexamethasone suppression and CRH stimulation.
- If suppresses with dexamethasone and stimulates with CRH, proceed to MRI of pituitary.
- May have to sample inferior petrosal sinus for ACTH
- If no suppression with dexamethasone, look for ectopic source.

Alternative diagnostic strategy

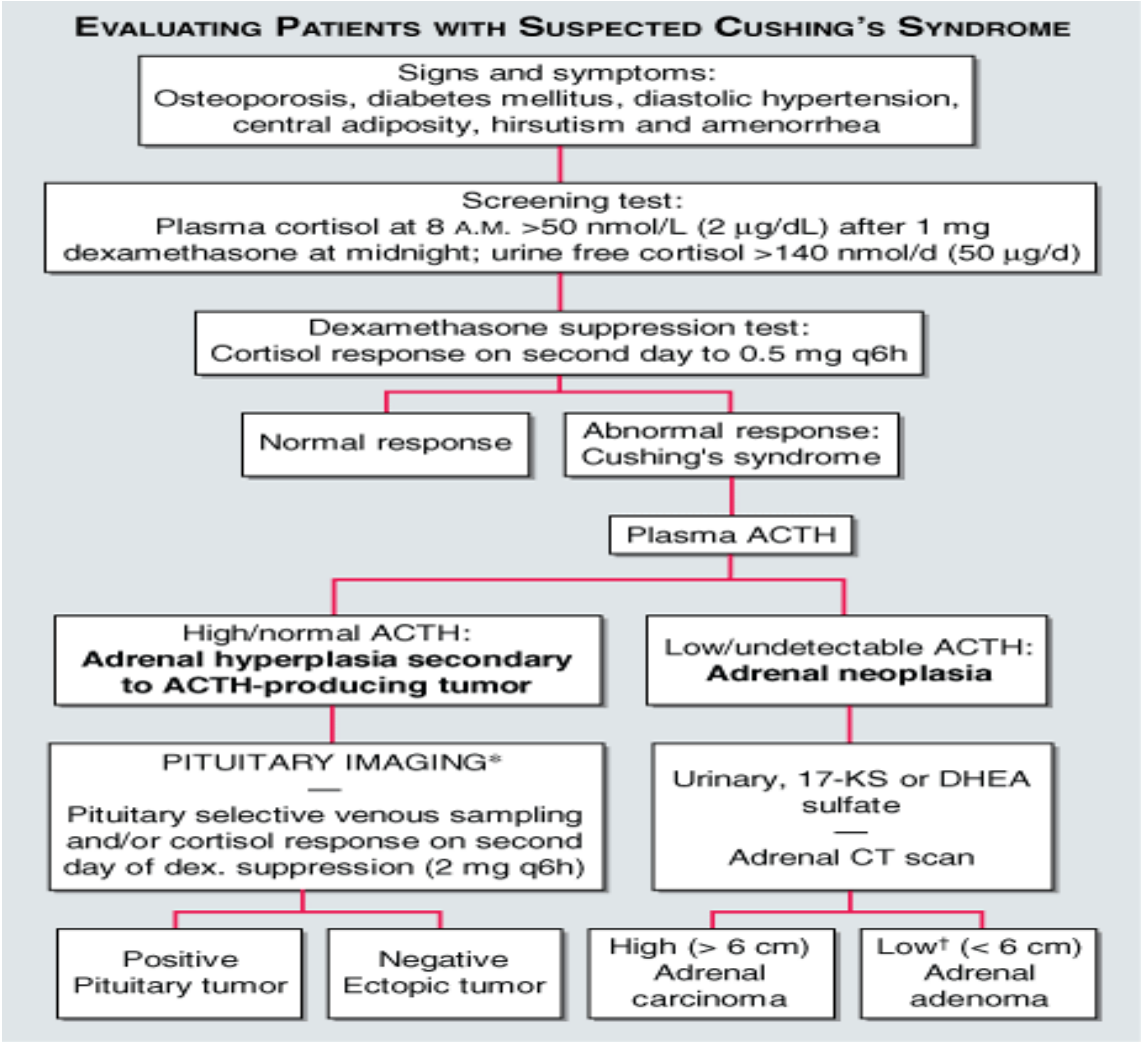


Fig. 336-7
Accessed 02/01/2010

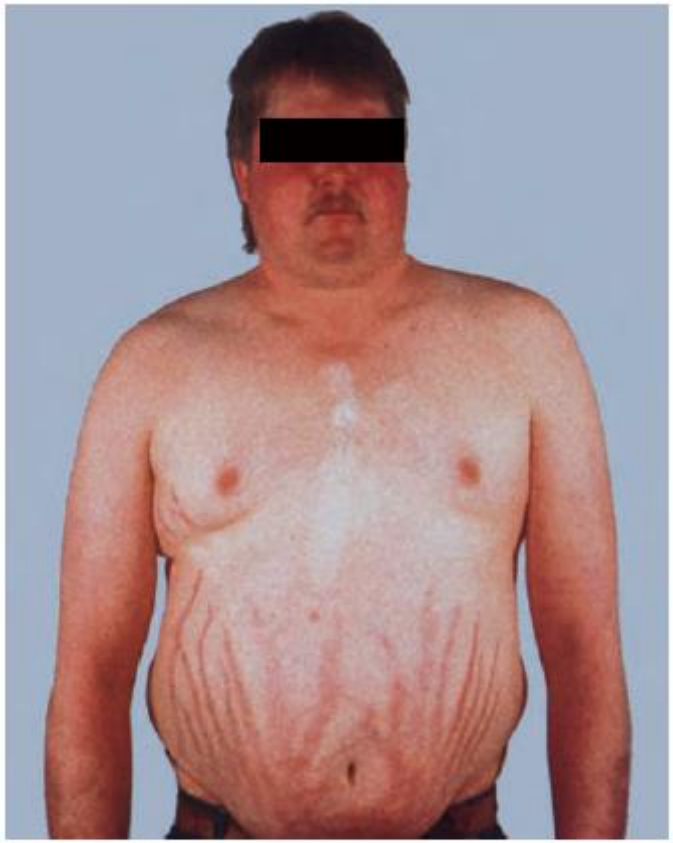
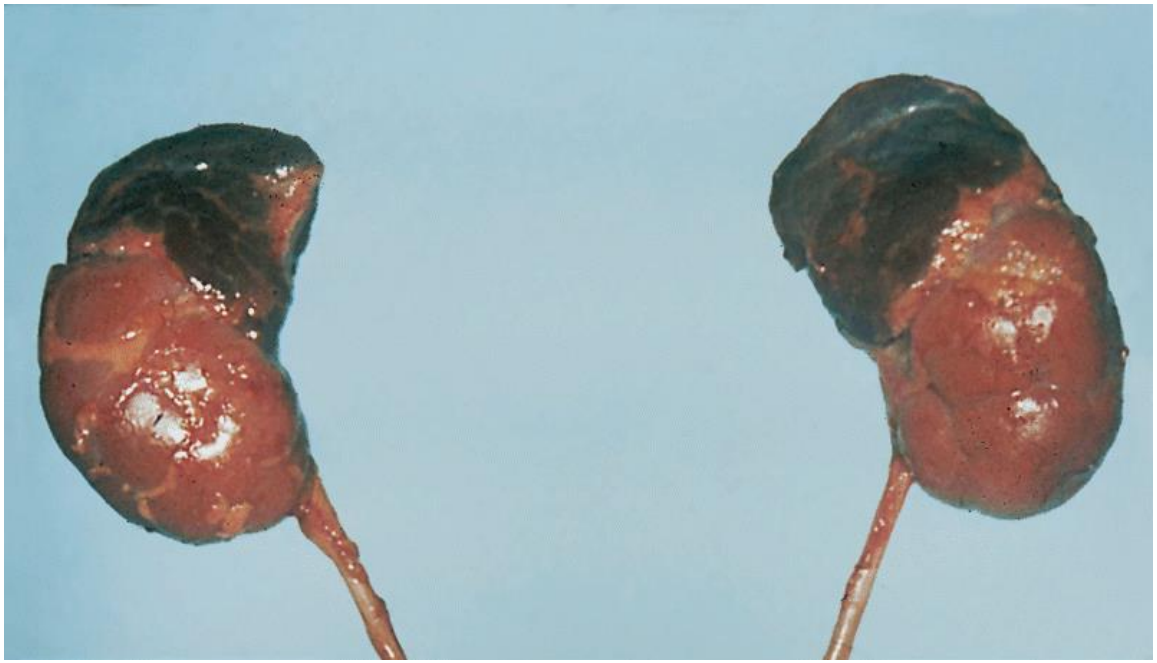


Figure 24-44 A patient with Cushing syndrome demonstrating central obesity, "moon facies," and abdominal striae. (Reproduced with permission from Lloyd RV, et al (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)

Congenital adrenal hyperplasia



Adrenal glands in congenital adrenal hyperplasia are enlarged and appear dark brown due to conversion of cortical cells into cells with compact, lipid- depleted cytoplasm. Autopsy specimen.

Fig. 2-9

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Adrenal steroid biosynthesis

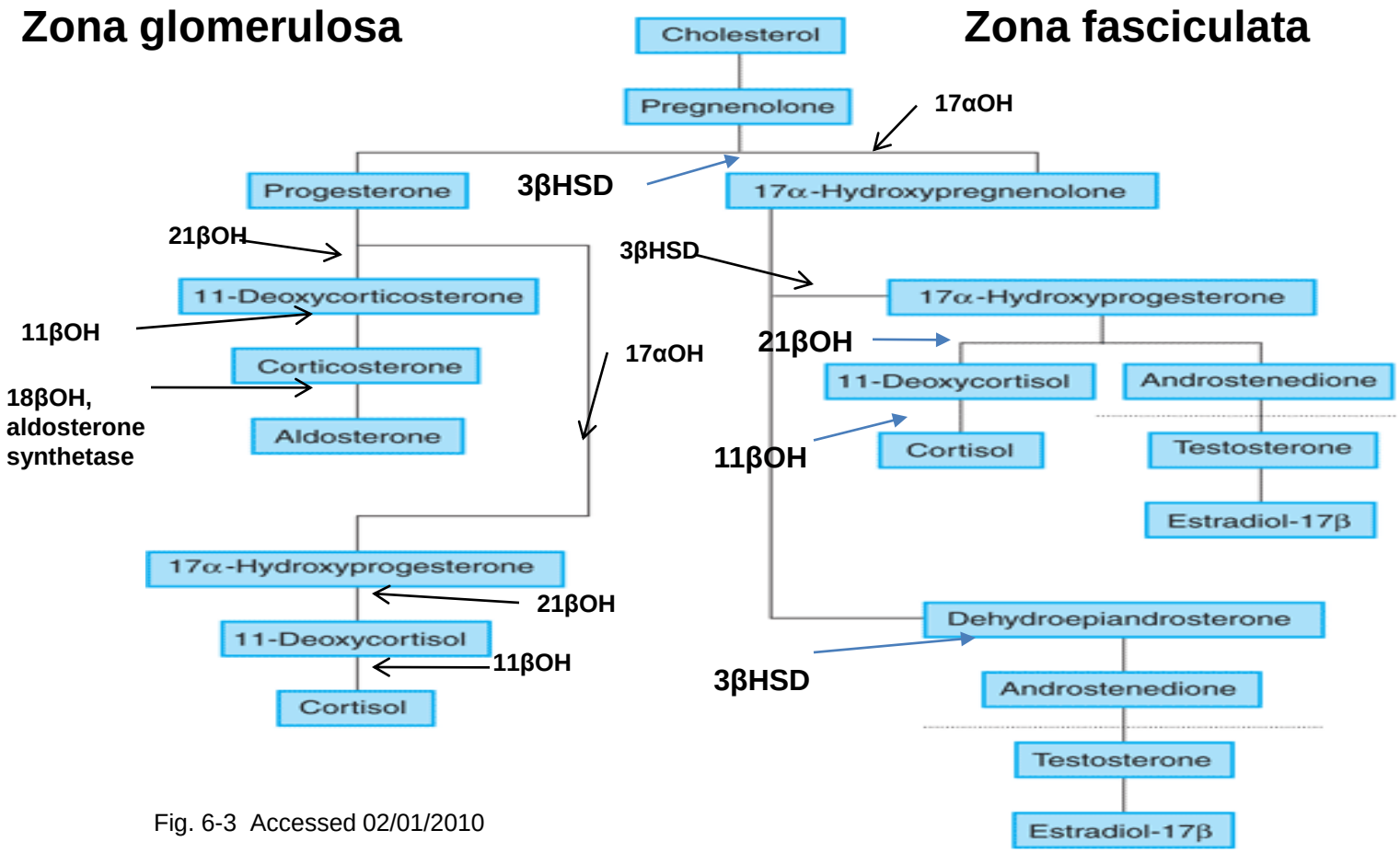


Fig. 6-3 Accessed 02/01/2010

Congenital adrenal hyperplasia

- The adrenal cortex secretes two compounds:
- Dehydroepiandrosterone (DHEA) and androstenedione
- Converted to testosterone in peripheral tissues.
- Unlike gonadal androgens, ACTH regulates adrenal androgen production.

Congenital adrenal hyperplasia

- 21β hydroxylase deficiency
- Hypotension, hyponatremia, hyperkalemia, virilization
- 90% of all cases of congenital adrenal hyperplasia
- 1 in 5 Ashkenazi are carriers
- CYP21A2 gene recombines with inactive CYP21A1 homologue at 6p21

Congenital adrenal hyperplasia

- The salt-wasting syndrome results from an inability to convert progesterone into deoxycorticosterone
- Lack of feedback inhibition
- Decreased cortisol, aldosterone
- Increased progesterone and 17OHP (and excess production of androgens)

Congenital adrenal hyperplasia

- High levels of intra-adrenal glucocorticoids are required to facilitate medullary catecholamine (epinephrine and norepinephrine) synthesis.
- In patients with severe salt-wasting 21-hydroxylase deficiency, a combination of low cortisol levels and developmental defects of the medulla (adrenomedullary dysplasia) profoundly affect catecholamine secretion
- Further predisposing these individuals to hypotension and circulatory collapse.

Congenital adrenal hyperplasia

- Simple virilizing adrenogenital syndrome without salt wasting
- Presents as genital ambiguity
- Occurs in a third of patients with 21-β hydroxylase deficiency.
- These patients generate sufficient mineralocorticoid to prevent a salt-wasting “crisis.”
- However, the lowered glucocorticoid level fails to cause feedback inhibition of ACTH secretion.
- Thus, the level of testosterone is increased, with resultant progressive virilization.

Congenital adrenal hyperplasia

- Nonclassic or late-onset adrenal virilism
- More common than classic form
- Partial deficiency in 21-β hydroxylase function, which accounts for the late onset.
- Individuals with this syndrome may be asymptomatic or have mild manifestations, such as hirsutism, acne, and menstrual irregularities.
- May be confused with polycystic ovary syndrome; no salt wasting, however.

Congenital adrenal hyperplasia

- 11β hydroxylase deficiency
- 5% of congenital adrenal hyperplasia cases
- Accelerated skeletal maturation and sexual precocity
- Hypertension
- Autosomal recessive
- CYP11B1 gene at 8q21-22
- Jews of Iranian or Moroccan ancestry
- Decreased secretion of cortisol, aldosterone
- Increased 11-desoxycorticosterone and aldosterone precursors

Congenital adrenal hyperplasia

- 17α hydroxylase deficiency
- 1% of cases of congenital adrenal hyperplasia
- Lack of pubertal development
- Primary amenorrhea in women
- Hypertension and hypokalemia
- Decreased cortisol
- Increased corticosterone, 11-desoxycorticosterone
- Autosomal recessive
- CY17A1 gene at 10q24.3
- Presents at birth

Congenital adrenal hyperplasia

- 3β hydroxysteroid dehydrogenase deficiency
- Presents at birth
- Salt wasting and non-salt wasting forms
- Micropenis and perineoscrotal hypospadias
- Decreased cortisol
- Increased pregnenolone and DHEA
- Autosomal recessive
- HSD3B2 gene at 1p13.1

Histopathology

- Adrenals are bilaterally hyperplastic,
- The adrenal cortex is thickened and nodular
- The widened cortex appears brown, because of total depletion of all lipid.
- The proliferating cells are mostly compact, eosinophilic, lipid depleted cells, intermixed with lipid-laden clear cells.
- Hyperplasia of corticotroph (ACTH-producing) cells is present in the anterior pituitary in most persons with CAH.

Aldosterone excess

- Aldosterone levels are elevated in 50% of patients with hypertension
- Primary hyperaldosteronism presents with hypertension, hypokalemia, low renin levels
- If 18OH-DOC levels elevated on standing, probably bilateral nodular hyperplasia
- 60% of cases
- If 18OH-DOC levels fall on standing, probably solitary adenoma (Conn's syndrome).
- 35% of cases
- <2cm nodules rarely produce visible enlargement
- Generally left-sided
- 67% occur in women
- Ages 30-40 years

Mineralocorticoid induced hypertension

- Increased aldosterone production leads to Na^+ retention, fluid retention, expansion of extracellular fluid volume, with resultant increased cardiac output.
- Increased aldosterone production leads to K^+ loss.
- Vasoconstriction is a result.
- Both Na^+ retention and K^+ loss contribute to hypertension.
- As a result of Na^+ retention, natriuretic hormone is released, Na^+-K^+ ATPase is inhibited.
- The rise in intracellular Na^+ leads to intracellular Ca^{2+} loss, resulting in vascular smooth muscle constriction (increased peripheral resistance).

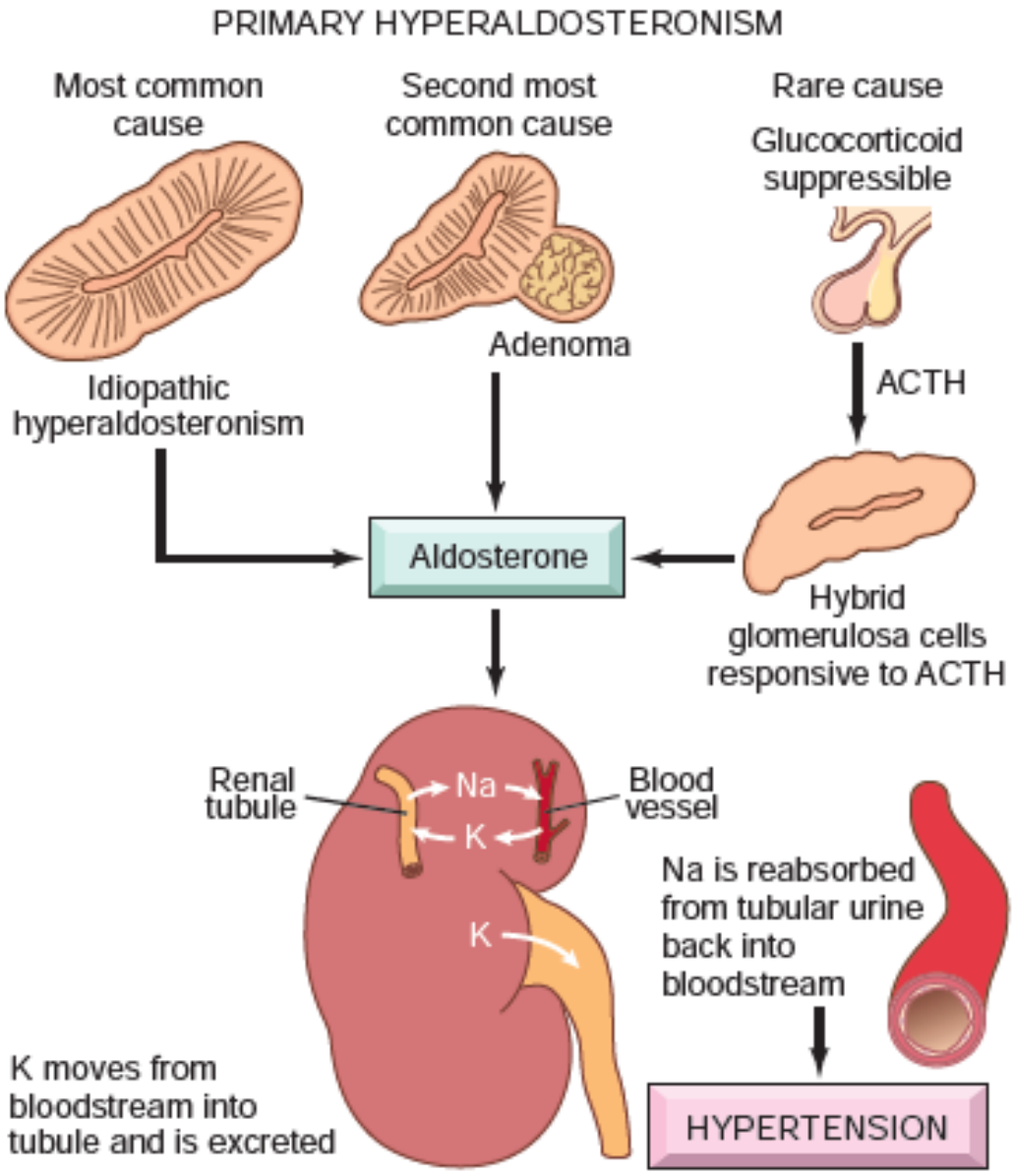


Figure 24-45 The major causes of primary hyperaldosteronism and its principal effects on the kidney.

Familial hyperaldosteronism

- Type I is glucocorticoid suppressible.
- Hypertension, of varying severity even among members of the same family
- Manifests often before the age of 20.
- Severe hypertension
- Autosomal dominant.
- CYP11B2-CYPB11B1 fusion gene at 8q24.3
- Aldosterone synthase gene fuses to ACTH responsive regulator of 11-βOH gene.
- Here aldosterone is under the influence of ACTH
- Leads to an excessive aldosterone synthase production in the zona fasciculata

Familial hyperaldosteronism

- Bilateral adrenal hyperplasia.
- Increased aldosterone levels and low plasma renin activity (tested after correction of low potassium levels)
- Elevated urinary levels of the hybrid steroids 18-oxo- and 18-hydroxycortisol.
- Type II is not glucocorticoid suppressible.
- Adrenal cortical adenoma.
- Early adult hypertension.
- Type III characterized by adrenal enlargement.
- Severe hypertension in childhood.

Histopathology

- Bilateral idiopathic hyperplasia is marked by diffuse and focal hyperplasia of cells resembling those of the normal zona glomerulosa.
- The hyperplasia is often wedge-shaped, extending from the periphery toward the center of the gland.
- KCNJ5 gene at 11q24.3
- Voltage gated potassium channel
- Mutation also noted in 40% of adenomas

Histopathology

- Nodules are buried within the gland and may not be visibly enlarged.
- The cells are lipid laden and tend to be uniform in size and shape, resembling the zona fasciculata
- Occasionally, there is modest nuclear and cellular pleomorphism
- A characteristic feature of aldosterone-producing adenomas is the presence of eosinophilic, laminated cytoplasmic inclusions (spironolactone bodies), found after treatment with the antihypertensive drug spironolactone.
- Adjacent cortex is not atrophic.

Aldosterone excess

- Bartter's syndrome (defective Na^+-K^+-Cl^- transporter) and Gitelman's syndrome (defective Na^+-Cl^-transporter) also associated with excess aldosterone.
- Secondary hyperaldosteronism
- Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
- Arterial hypovolemia and edema (congestive heart failure, cirrhosis, nephrotic syndrome)
- Pregnancy (due to estrogen-induced increases in plasma renin substrate)

Aldosterone excess

- Secondary hyperaldosteronism is associated with elevated renin levels
- Mineralocorticoid type I receptors in the kidney are sensitive to both cortisol and aldosterone.
- The kidney has 11-βOH dehydrogenase to locally convert cortisol to cortisone (low affinity).
- Permits aldosterone action.

Diagnostic strategy

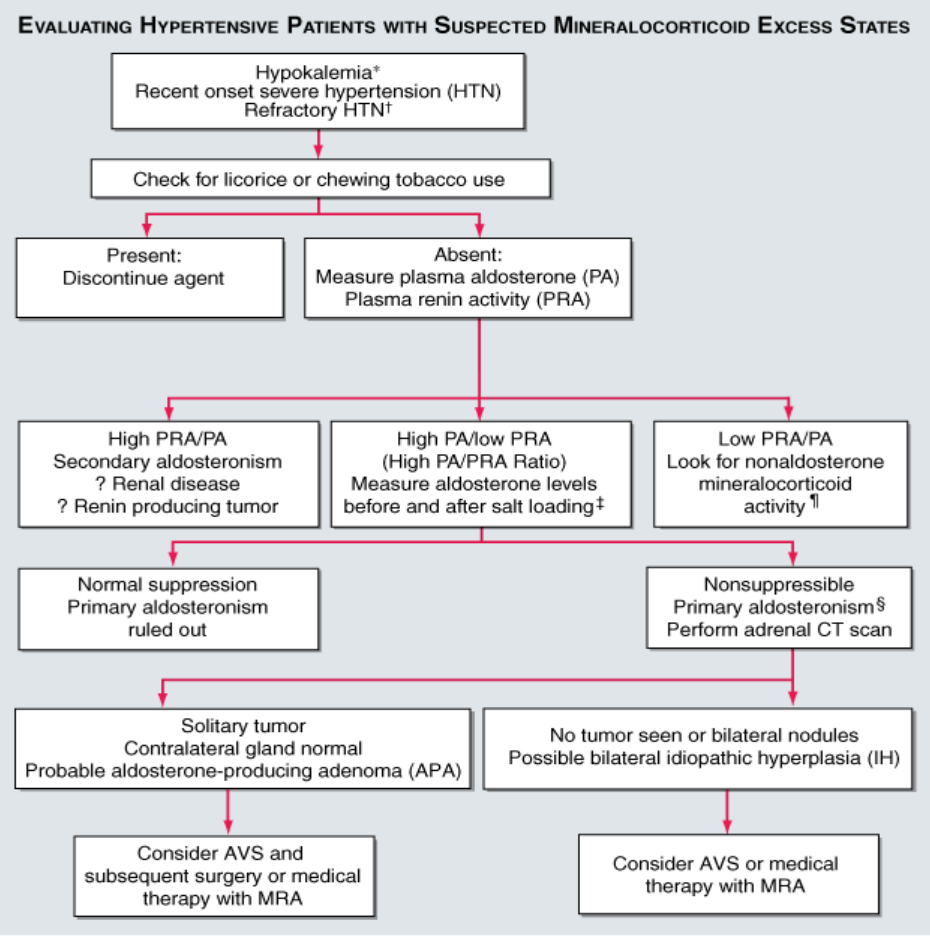


Fig. 336-10
Accessed 02/01/2010

Aldosterone tumor

- Present with hypertension, hypokalemia, low renin levels
- If 18OH-DOC levels elevated on standing, probably hyperplasia.
- 60% of cases
- If 18OH-DOC levels fall on standing, probably solitary adenoma (Conn's syndrome).
- 35% of cases
- Occasionally bilateral nodular hyperplasia
- 80% of nodules are neoplastic
- <2cm nodules rarely produce visible enlargement
- Generally left-sided
- 67% occur in women, ages 30-40 years

Aldosterone producing tumor

- May see spironolactone bodies in the nodule (eosinophilic)
- Secondary hyperaldosteronism is associated with elevated renin levels
- Mineralocorticoid type I receptors in the kidney are sensitive to both cortisol and aldosterone.
- The kidney has 11-βOH dehydrogenase to locally convert cortisol to cortisone (low affinity).
- Permits aldosterone action.

Table 24-10 Adrenocortical Insufficiency

Primary Insufficiency
Loss of Cortical Cells
Congenital adrenal *hypo*plasia
X-linked adrenal hypoplasia (*DAX1* gene on Xp21)
"Miniature"-type adrenal hypoplasia (unknown cause)
Adrenoleukodystrophy (*ALD* gene on Xq28)
Autoimmune adrenal insufficiency
Autoimmune polyendocrinopathy syndrome type 1 (*AIRE1* gene on 21q22)
Autoimmune polyendocrinopathy syndrome type 2 (polygenic)
Isolated autoimmune adrenalitis (polygenic)
Infection
Acquired immune deficiency syndrome
Tuberculosis
Fungi
Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome*)
Amyloidosis, sarcoidosis, hemochromatosis
Metastatic carcinoma
Metabolic Failure in Hormone Production
Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virilization)
Drug- and steroid-induced inhibition of ACTH or cortical cell function
Secondary Insufficiency
Hypothalamic Pituitary Disease
Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)
Hypothalamic Pituitary Suppression
Long-term steroid administration
Steroid-producing neoplasms

ACTH, Adrenocorticotropic hormone.

Acute adrenal hormone insufficiency

- Crisis in a patient with chronic adrenal disease related to any form of stress resulting in a need to enhance steroid production.
- Rapid withdrawal of exogenous steroids in a patient whose adrenal does not respond to ACTH
- Massive adrenal hemorrhage
- DIC
- Post prolonged and traumatic delivery (newborn)
- Anticoagulant use
- Disseminated bacterial infection (Waterhouse-Friderichsen syndrome)

Waterhouse-Friderichsen syndrome

- Onset of fever, petechiae, shock, and DIC
- Late in disease, petechiae coalesce into purpuric plaques
- Acute adrenal insufficiency develops
- 80%, Neisseria meningitides infection
- May be seen with Streptococcus pneumoniae infection post-splenectomy
- May be seen in antiphospholipid syndrome.

Waterhouse-Friderichsen syndrome

- Direct bacterial seeding of small vessels in the adrenal probable precipitating event
- DIC as well as endothelial damage as other possible causes
- Histopathology
- Bilateral adrenal hemorrhage beginning in the medulla near venous sinusoids, with suffusion into cortex.

Waterhouse-Friderichsen syndrome

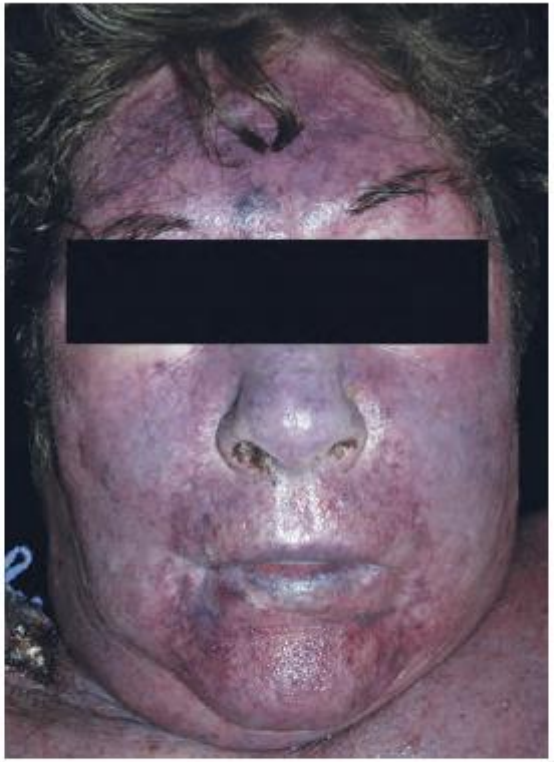


Figure 24-47 Diffuse purpuric rash in a patient with Waterhouse-Friderichsen syndrome. (Reproduced with permission from C. Vincentelli et al, Am J Emerg Med, 27:751, 2009).

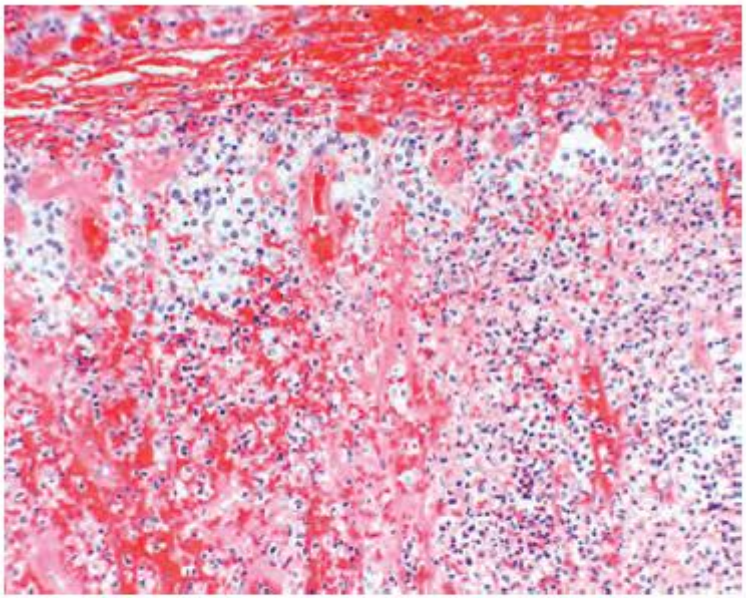
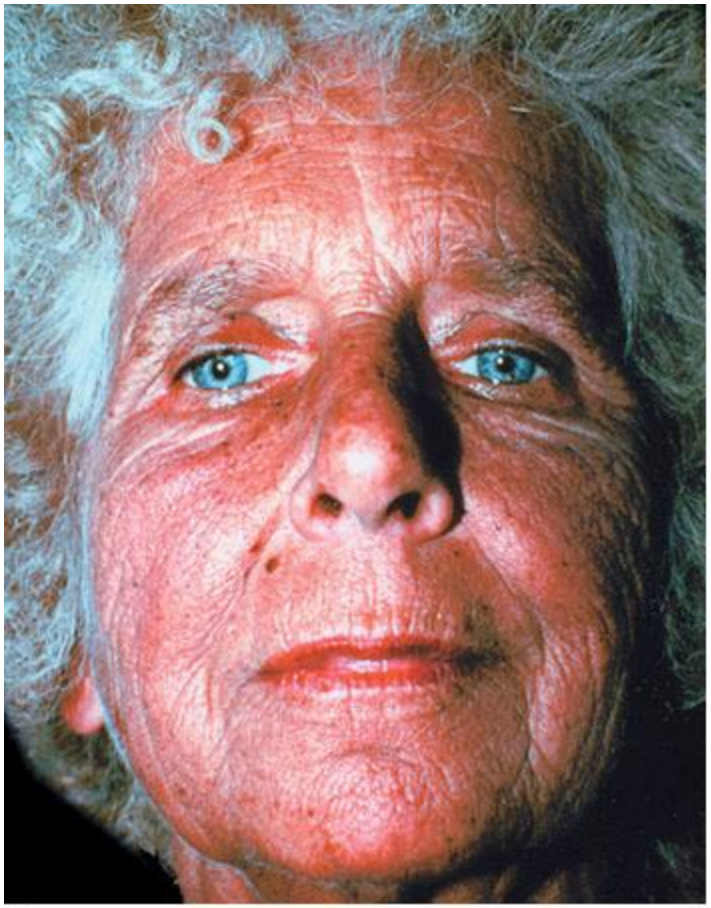


Figure 24-48 Waterhouse-Friderichsen syndrome. At autopsy, the adrenals were grossly hemorrhagic and shrunken; microscopically, little residual cortical architecture is discernible.

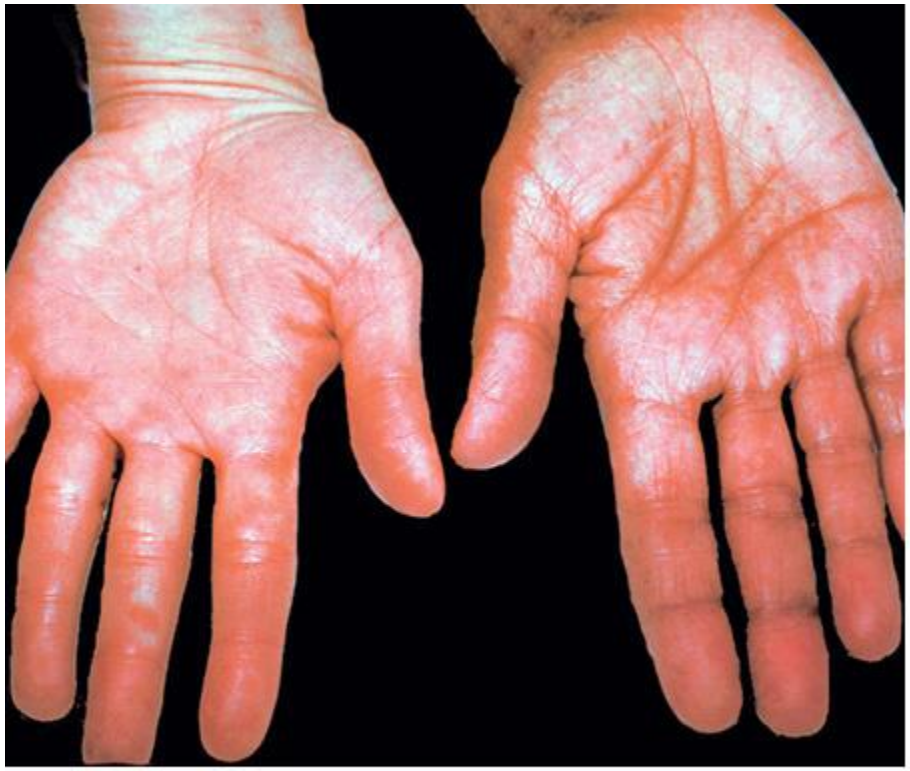
Chronic adrenal hormone insufficiency

- Weakness with undue fatigue are early presenting symptoms.
- Anorexia, skin pigmentation at pressure points, and weight loss are also seen.
- Pigmentation secondary to elevated levels of POMC
- Low Sodium, elevated Potassium, and Hypoglycemia are found.
- No response to ACTH.
- 90% of adrenal cortical tissue lost before symptomatic
- In patients with hypothalamic or pituitary disease, no pigmentation is noted
- Respond to ACTH

Hypoadrenalism



A



B

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:
Fitzpatrick's Dermatology in General Medicine, 7th Edition: http://www.accessmedicine.com

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Fig. 152-16 Accessed 02/01/2010

Laboratory diagnosis

- If cortisol <18 ug/dl at 30 or 60 minutes after ACTH administration and baseline ACTH is elevated, proceed to MRI of the adrenal.
- Check for tuberculosis.
- If, however, baseline ACTH is low, proceed to MRI of the pituitary and measure other pituitary hormones.
- If the patient has been on long-term steroid therapy but produces cortisol (>18ug/dl) after ACTH administration, it is safe to stop steroid therapy.

Chronic adrenal hormone insuficiency

- Autoimmune disease as cause in 80% of patients
- Addison's disease is most frequent
- Antibodies to 21-β hydroxylase, 17-α hydroxylase, as well as CYP450 enzymes

Chronic adrenal hormone insuficiency

- Autoimmune polyendocrine syndrome (APS) Type I
- Muco-cutaneous candidiasis and hypoparathyroidism
- AIRE mutation (21q22) leads to loss of self-tolerance by T-cells in thymus.
- Antibodies to T_{H17} cytokines IL-17, Il-22
- Predispose to fungal infections
- Prevalent among Finns and Jews of Iranian ancestry.

Chronic adrenal hormone insuficiency

- APS Type II
- Associated with pernicious anemia, insulin dependent diabetes mellitus, and hypothyroidism.
- More common than APS Type I.
- Women twice likely than men to be affected.
- 20-40 years of age.
- Linked to HLA-DR3 (DQ2,DQ*, DRBi*0404 genotype).

Chronic adrenal hormone insuficiency

- Tuberculosis, Histoplasma, Coccidioces infections as other causes in patients with active disease
- Must be considered with Mycoplasma and Kaposi's sarcoma as cause of asthenia in AIDS.
- Occasionally seen with metastatic disease
- Congenital adrenal hypoplasia
- Mutation in NROB1 gene at Xp21.2 (DAX1 protein)
- Failure in maturation of adrenals and gonads
- Adrenal hormone insufficiency, delayed puberty
- Adrenoleukodystrophy
- Mutation in ABCD1 gene at Xp28 (ALDP protein)
- Unable to metabolize very long chain fatty acids

Histopathology

- Primary autoimmune adrenalitis
- Characterized by irregularly shrunken glands
- The cortex contains only scattered residual cortical cells in a collapsed network of connective tissue.
- A variable lymphoid infiltrate is present in the cortex and may extend into the adjacent medulla
- The medulla is otherwise preserved
- Tuberculosis, fungal infections
- Granulomas prominent

Adrenal medulla

- Neural crest derivation
- Chromaffin cells (brown-black after exposure to Potassium Dichromate fixative of Zenker) are of sympathetic innervation
- Norepinephrine functions as local neurotransmitter (sympathetic postganglionic neurons) with little hormone circulating
- In contrast, epinephrine enters into circulation
- May produce other bioactive amines

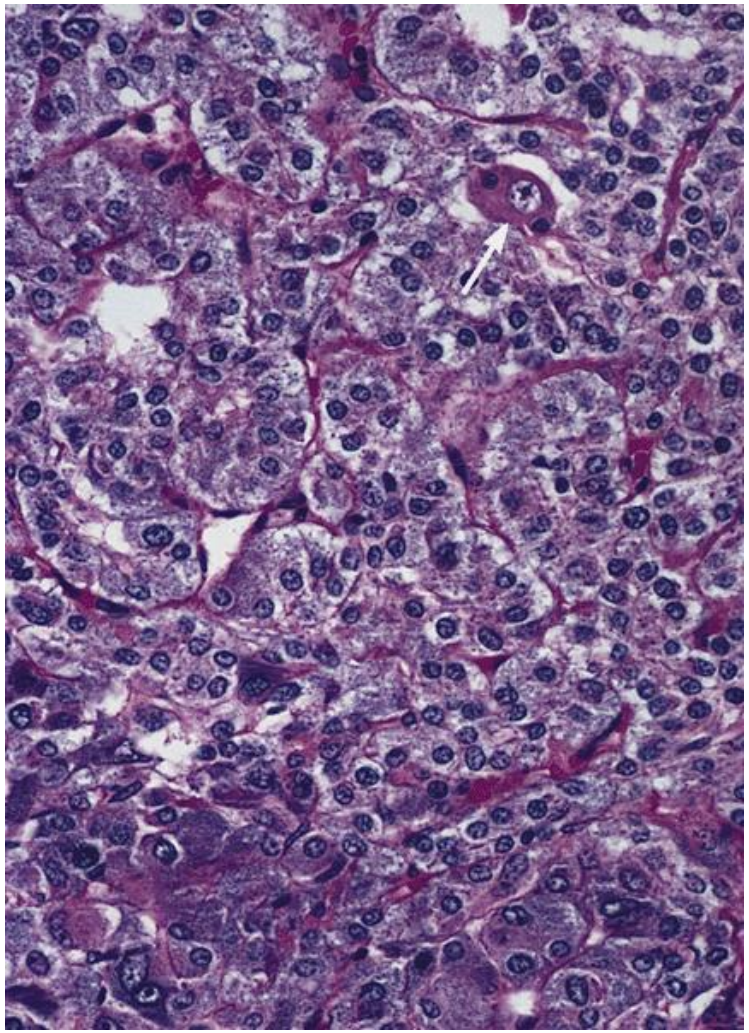
Paraganglion system

- Neuroendocrine cells similar to chromaffin cells
- Together with the adrenal medulla,
- There are three groups based on their anatomic distribution:
- (1) Branchiomeric and (2) Intravagal
- The branchiomeric and intravagal paraganglia associated with the parasympathetic system are located close to the major arteries and cranial nerves of the head and neck and include the carotid bodies
- Intravagal ganglia found along course of vagus nerve

Paraganglion system

- (3) Aorticosympathetic
- Found in association with segmental ganglia of the sympathetic system
- Distributed mainly alongside of the abdominal aorta.
- The organs of Zuckerkandl, close to the aortic bifurcation, belong to this group.
- Bladder

Adrenal medulla



Chromaffin cells contain a myriad of pinpoint cytoplasmic granules. A mature ganglion cell is also apparent (arrow).

Fig. 1-29L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Pheochromocytoma

- 90% occur below the diaphragm
- 10% extra-adrenal chromaffin negative (paraganglioma)
- 10% associated with MEN syndromes (RET mutation)
- 10% arise in childhood
- 10% not associated with hypertension.
- Of those with hypertension, two-thirds show paroxysmal rise with tachycardia, hyperglycemia, and a sense of apprehension.

Pheochromocytoma

- 10% bilateral
- If VHL mutation, multifocal, peak age in fourth decade
- If NF1 mutation, multifocal, peak age in fifth decade.
- If familial, 70% usually involved with succinic dehydrogenase, or SDHB,SDHC, SDHD mutations
- SDHD AF2 encodes folic acid; SDH mutations, promote stabilization of HIF-1α.

Pheochromocytoma

- SDHC and SDHD associated with head and neck locations;
- SDHB associated with bilateral lesions, extra-adrenal locations, and are frequently malignant. Renal cell carcinoma and gastrointestinal stromal tumors found in 35-70% of those harboring this mutation.
- SDH, VHL mutated tumors are pseudo-hypoxic.
- RET, NF1 mutated tumors have abnormal RAS/RAF/ERK activity.

Pheochromocytoma

- 10% malignant (if extra adrenal, 20-40%)
- Only diagnosed if metastases present
- As many as 25% of individuals with pheochromocytoma and paraganglioma harbor a germline mutation
- Usually appear at a young age

Table 24-11 Familial Syndromes Associated with Pheochromocytoma and Extra-adrenal Paragangliomas

Syndrome	Gene	Associated Lesion	Other Features
Multiple endocrine neoplasia, type 2A (MEN-2A)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Parathyroid hyperplasia
Multiple endocrine neoplasia, type 2B (MEN-2B)	*RET*	Pheochromocytoma	Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous GNs
Neurofibromatosis, type 1 (NF1)	*NF1*	Pheochromocytoma	Neurofibromatosis Café-au-lait spots Optic nerve glioma
Von Hippel-Lindau (VHL)	*VHL*	Pheochromocytoma, paraganglioma *(uncommon)*	Renal cell carcinoma Hemangioblastoma Pancreatic endocrine neoplasm
Familial paraganglioma 1	*SDHD*	Pheochromocytoma, paraganglioma	
Familial paraganglioma 3	*SDHC*	Paraganglioma	
Familial paraganglioma 4	*SDHB*	Pheochromocytoma, paraganglioma	

GN, Ganglioneuroma; *NF1*, neurofibromin; *SDHB*, succinate dehydrogenase complex, subunit B; *SDHC*, succinate dehydrogenase complex, subunit C; *SDHD*, succinate dehydrogenase complex, subunit D.

Adapted with permission from Elder EE, et al: Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 89:193-201, 2005.

Pheochromocytoma

- 24 hour urine total catecholamines, vanilmandelic acid, and metanephrines. (Metanephrines most specific.)
- If NF1 mutation, plasma epinephrine often elevated.
- If VHL mutation, plasma norepinephrine alone often elevated.
- If SDH mutations, plasma dopamine often elevated.
- Clonidine suppression test if values somewhat elevated as pheochromocytoma will not suppress with clonidine.

Pheochromocytoma

- Both CT and MRI are equally sensitive imaging alternatives.
- Bone scan for detecting bone metastases.
- PET scan if known metastases.
- ^{131}I-MIBG (structurally similar to norepinephrine) is concentrated in adrenergic tissues; highly sensitive and specific for malignant tissues.

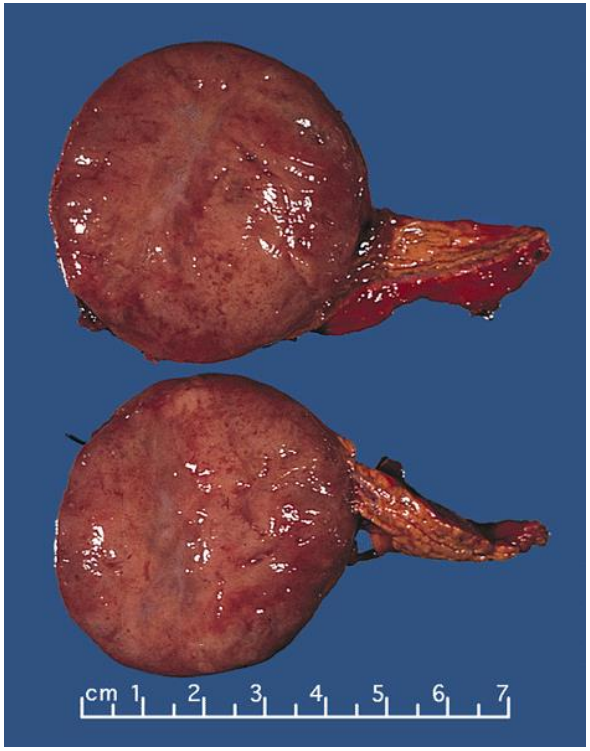
Pheochromocytoma

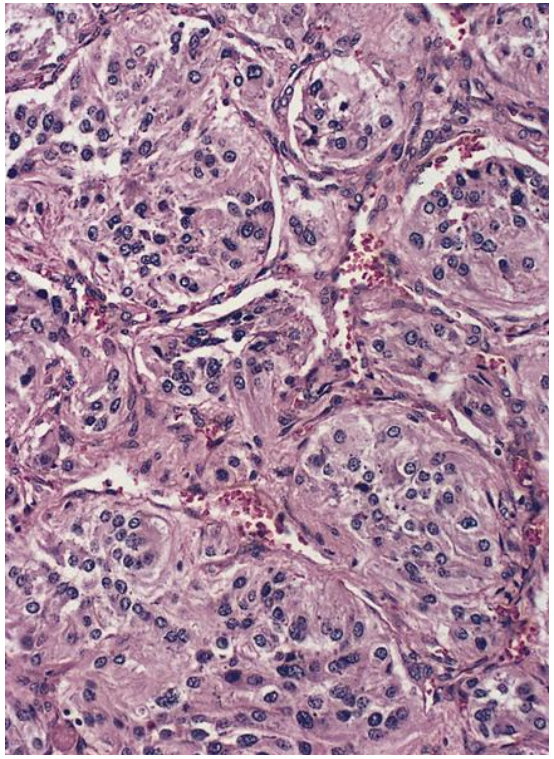
- 90% with symptomatic hypertension
- Largely resistant to 3 drug therapy
- Malignant hypertension
- 67% will have paroxysmal hypertension and tachycardia, sweating, palpitations, abdominal pain
- May be precipitated by activity that increases intra-abdominal pressure
- Orthostatic hypotension
- Precipitate myocardial infarction (in the absence of coronary disease) or aortic dissection
- Catecholamine cardiomyopathy (myocardial necrosis and ventricular arrhythmia)

Histopathology

- Richly vascularized fibrous trabeculae within the tumor produce a lobular pattern.
- In many tumors, remnants of the adrenal gland can be seen, stretched over the surface or attached at one pole.
- On section, the cut surfaces of smaller pheochromocytomas are yellow-tan. Larger lesions tend to be hemorrhagic, necrotic, and cystic and typically efface the adrenal gland.
- Polygonal or spindle cells with stippled nuclei in nests and balls (zellballen) with little supporting sustenacular reticulin.
- Chromaffin positive.

Pheochromocytoma





Left:
The pheochromocytoma is well-circumscribed with a bulging pale- gray surface. Attached adrenal remnant is also present.
Right:
Alveolar or nesting arrangement of tumor cells is shown.

Figs. 10-4L and 10-11

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

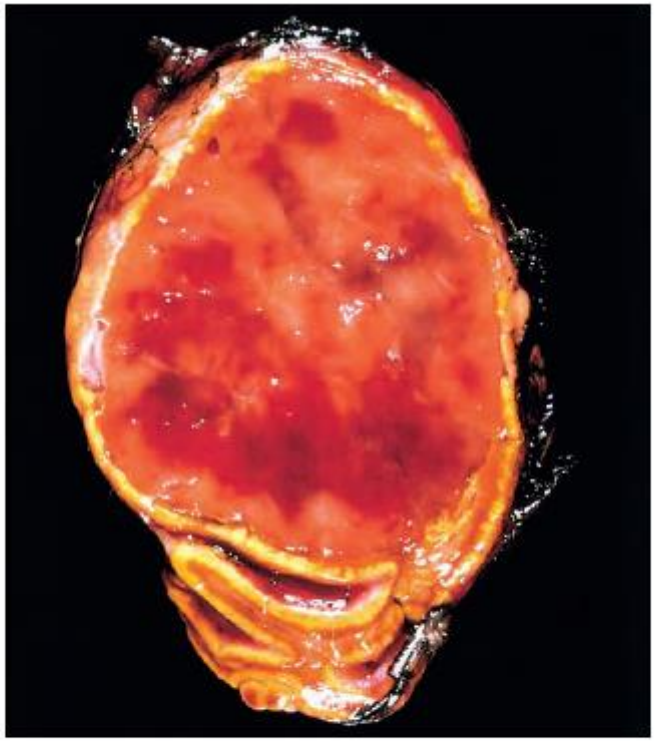


Figure 24-54 Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma-shaped residual adrenal is seen below. (Courtesy Dr. Jerrold R. Turner, Department of Pathology, University of Chicago Hospitals, Chicago, Ill.)

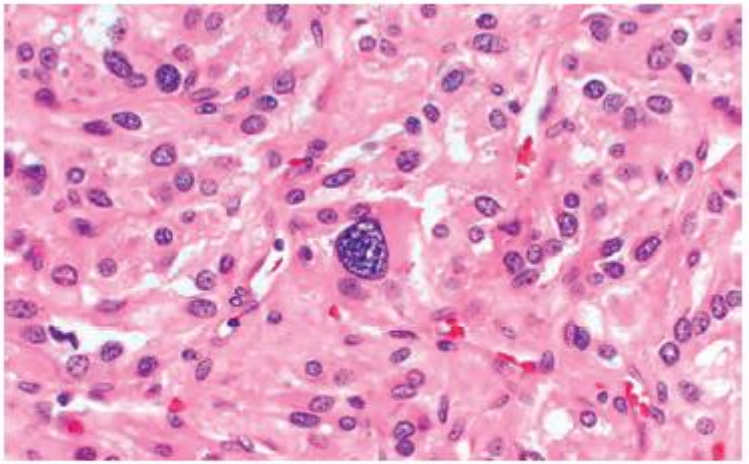


Figure 24-55 Pheochromocytoma demonstrating characteristic nests of cells ("zellballen") with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytomas that are biologically benign. (Courtesy Dr. Jerrold R. Turner, Department of Pathology, University of Chicago Hospitals, Chicago, Ill.)

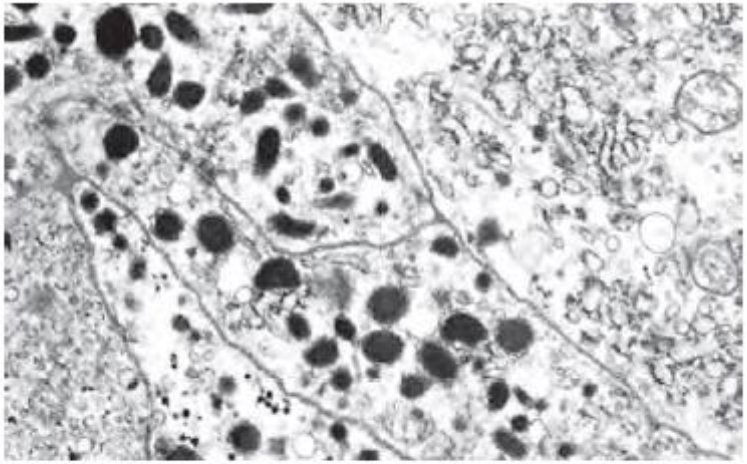


Figure 24-56 Electron micrograph of pheochromocytoma. This tumor contains membrane-bound secretory granules in which catecholamines are stored (30,000×).

Pheochromocytoma treatment

- α-blockade (phenexybenzamine) followed by β-blockade before surgery.
- Surgical resection required. Laparoscopic approach acceptable if no obvious tumor invasion or metastases on imaging studies.
- Preservation of one-third of adrenal cortex permits normal adrenal function.
- Cyclophosphamide, vincristine, dacarbazine chemotherapy associated with biochemical response (79%) and reduction in measurable disease (59%) with median response duration of 20 months.

Treatment

- α-blockade (phenexybenzamine) followed by β-blockade before surgery.
- Surgical resection required.
- Laparoscopic approach acceptable if no obvious tumor invasion or metastases on imaging studies.
- Cyclophosphamide, vincristine, dacarbazine chemotherapy associated with biochemical response (79%) and reduction in measurable disease (59%) with median response duration of 20 months.

Multiple endocrine neoplasia

- MEN 1
- Werner Syndrome
- 80-95% of patients present with primary hyperparathyroidism by age 40
- Multiple gastrinomas, VIPomas, and insulinomas in pancreas
- Duodenal gastrinoma principal site of gastrin tumor
- Prolactinoma
- Cushing's syndrome
- MEN1 mutation. Menin complexes with and blocks transcriptional activation of JunD
- Loss of p16 and p27 cell cycle regulators

Multiple endocrine neoplasia

- MEN 2A (Sipple Syndrome)
- 95% of cases
- Germline gain of function mutation of RET gene at 10q11.2
- 95% occur in cysteine-rich domain of exon 10
- Codon 634 point mutation most common
- Binds to glial derived neurotropic factor (GDNF)
- Promotes receptor dimerization (recapitulates ligand binding)
- Medullary Thyroid Carcinoma, 100%
- Pheochromocytoma, 40-50%
- Parathyroid Hyperplasia, 10-20%

Multiple endocrine neoplasia

- MEN 2A variant
- Familial Medullary Thyroid Carcinoma
- Present at older age and have more indolent course
- Germline gain of function mutation of RET gene at 10q11.2
- 85% occur in cysteine-rich domain of exon 10
- Codon 634 point mutation most common
- Binds to glial derived neurotropic factor (GDNF)
- Promotes receptor dimerization (recapitulates ligand binding)

Multiple endocrine neoplasia

- MEN 2B Medullary Thyroid Carcinoma
- Point mutation of RET gene at codon 918 of TK 2
- Domain activates receptor TK function and also causes it to phosporoylate C-SRC and C-ABL
- Pheochromocytoma
- Mucosal ganglioneuromas
- Marfanoid habitus
- More aggressive than are 2A tumors
- Present earlier in life than does 2A

Neuroblastoma

- 7-10% all pediatric neoplasms
- 50% diagnosed in infancy
- 40% arise in adrenal medulla
- 25%, Para vertebral region of abdomen
- 15%, posterior mediastinum
- Disialoganglioside (GD2) expressed.
- ALK germline mutation (at 2p23.2-23.1) associated with familial predisposition.
- Affects tyrosine kinase receptors

Histopathology

- In situ neuroblastomas are reported to occur 40 times more frequently than clinically overt tumors.
- The great majority of these silent lesions spontaneously regress, leaving only a focus of fibrosis or calcification in the adult.
- Neuroblastoma is often sharply demarcated by a fibrous pseudo-capsule, but others are far more infiltrative and invade surrounding structures, including the kidneys, renal vein, and vena cava, and envelop the aorta.
- When cut, they are gray-tan. Focal calcification may be noted. Larger tumors may have areas of necrosis and hemorrhage.

Histopathology

- Composed of small, primitive-appearing cells with dark nuclei, scant cytoplasm, and poorly defined cell borders growing in solid sheets.
- Mitotic activity, nuclear breakdown (“karyorrhexis”), and pleomorphism may be prominent.
- The background often demonstrates a faintly eosinophilic fibrillary material (neuropil) that corresponds to neuritic processes of the primitive neuroblasts.
- Homer-Wright rosettes can be found in which the tumor cells are concentrically arranged about a central space filled with neuropil.

Histopathology

- Larger cells having more abundant cytoplasm, large vesicular nuclei, and a prominent nucleolus, representing ganglion cells in various stages of maturation, may be found in tumors admixed with primitive neuroblasts (ganglioneuroblastoma).
- More mature lesions are ganglioneuromas.
- Maturation of neuroblasts into ganglion cells is usually accompanied by the appearance of Schwann cells.

Histopathology

- The presence of a so-called schwannian stroma composed of organized fascicles of neuritic processes, mature Schwann cells, and fibroblasts is a histologic prerequisite for the designation of ganglioneuroblastoma and ganglioneuroma
- Ganglion cells in and of themselves do not fulfill the criteria for maturation.

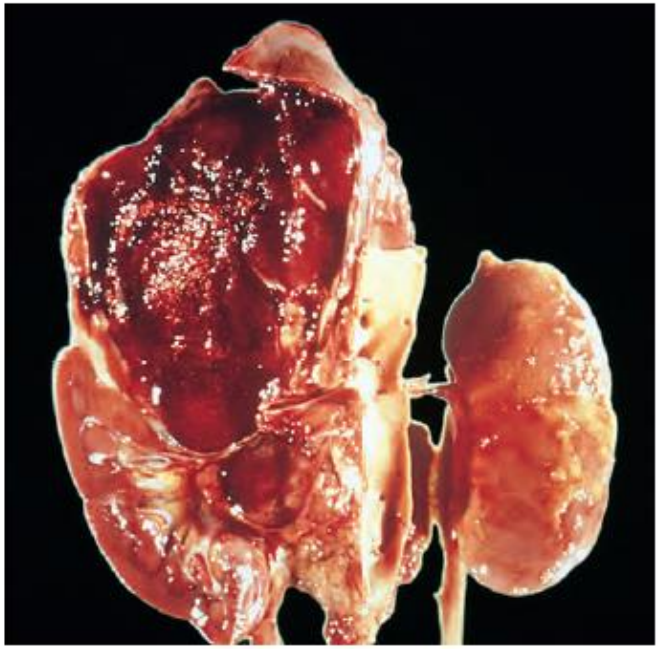


Figure 10-24 Adrenal neuroblastoma in a 6-month-old child. The hemorrhagic, partially encapsulated tumor has displaced the opened left kidney and is impinging on the aorta and left renal artery. (Courtesy Dr. Arthur Weinberg, University of Texas Southwestern Medical School, Dallas, Texas.)

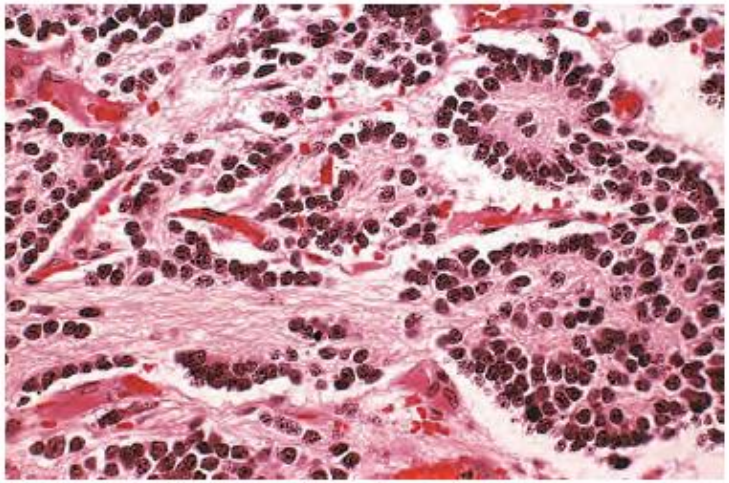


Figure 10-25 Adrenal neuroblastoma. This tumor is composed of small cells embedded in a finely fibrillar matrix.

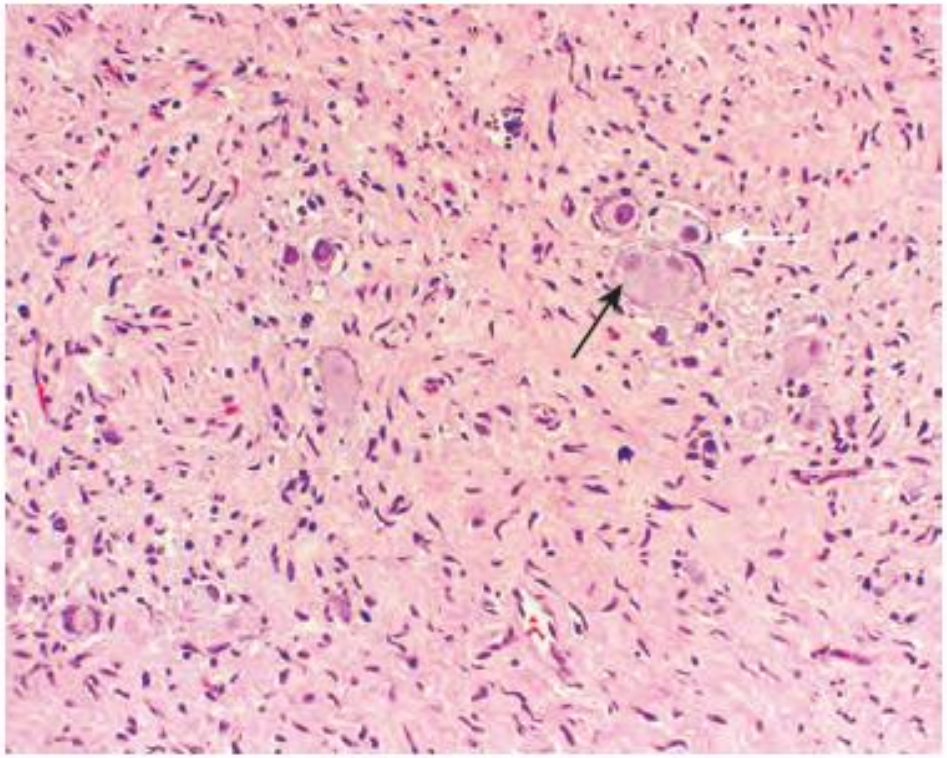


Figure 10-26 Ganglioneuromas, arising from spontaneous or therapy-induced maturation of neuroblastomas, are characterized by clusters of large cells with vesicular nuclei and abundant eosinophilic cytoplasm, representing neoplastic ganglion cells *(arrow)*. Spindle-shaped Schwann cells are present in the background stroma.

Staging

- Stage I is confined to the area of origin (usually, adrenal) with uninvolved nodes.
- Stage II is unilateral with positive ipsilateral node.
- Stage III involves tumor infiltrating across midline OR unilateral tumor with contralateral node involvement OR midline tumor with bilateral node involvement.
- Stage IV is disseminated
- IVS dissemination is limited to liver, skin, or marrow.

Table 10-8 Prognostic Factors in Neuroblastomas

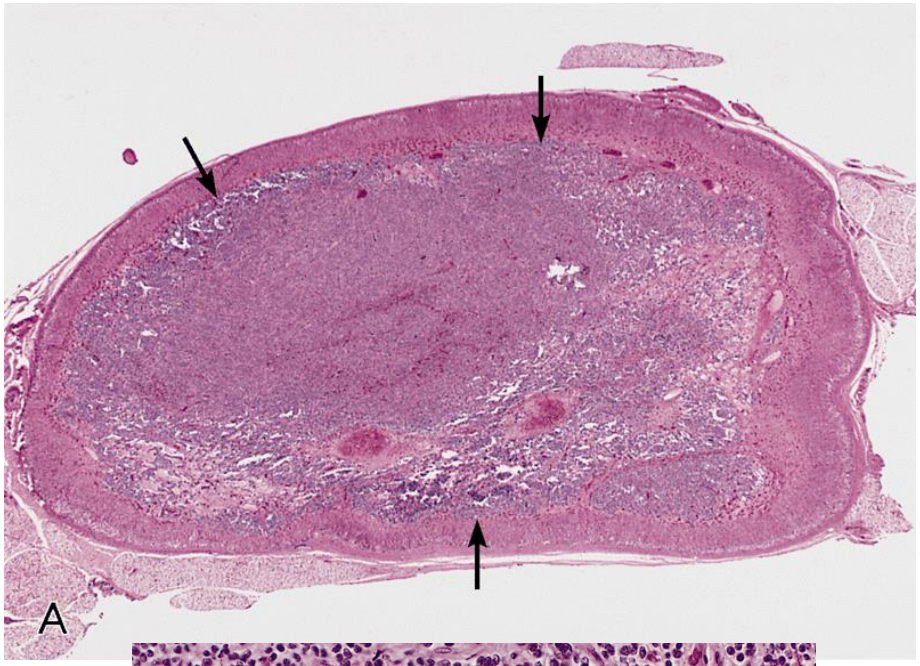
Variable	Favorable	Unfavorable
Stage*	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age*	<18 months	>18 months
Histology*		
Evidence of schwannian stroma and gangliocytic differentiation†	Present	Absent
Mitosis-karyorrhexis index‡	<200/5000 cells	>200/5000 cells
DNA ploidy*	Hyperdiploid (whole chromosomal gains)	Near-diploid (Segmental chromosomal losses; chromothripsis)
*MYCN**	Not amplified	Amplified
Chromosome 1p loss	Absent	Present
Chromosome 11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
Mutations of neuritogenesis genes	Absent	Present

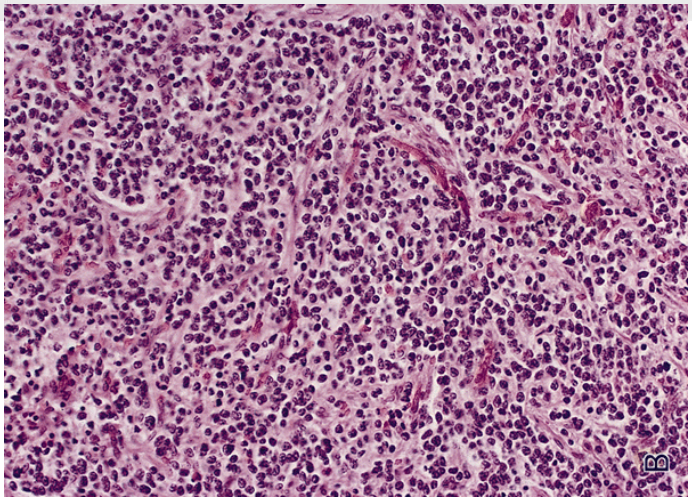
*Corresponds to the most commonly used parameters in clinical practice for assessment of prognosis and risk stratification.
†It is not only the presence but also the amount of schwannian stroma that confers the designation of a favorable histology. At least *50% or more schwannian stroma* is required before a neoplasm can be classified as ganglioneuroblastoma or ganglioneuroma.
‡Mitotic karyorrhexis index (MKI) is defined as the number of mitotic or karyorrhectic cells per 5000 tumor cells in random foci.

Prognostic factors

- Low LDH and age younger than 18 months if no MYC amplification are favorable prognostic factors as is tumor differentiation and presence of tyrosine kinase receptor B.
- Tyrokine kinase receptor A presence is associated with poor prognosis.
- PTRP gene mutation at 9p24.1-p23 unfavorable
- Loss of neurite maturation
- 90% produce catecholamines.
- Vanillmandelic and homovanillic acid elevated in urine.
- Hypertension is not common, however.

Neuroblastoma



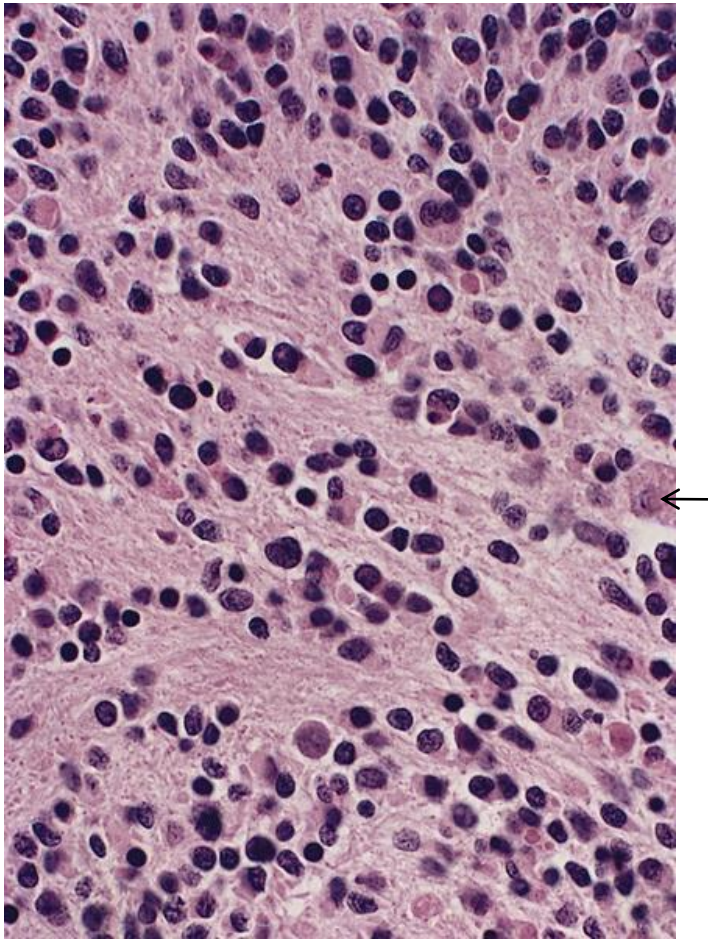


Incidental in situ neuroblastoma
Upper:
The junction with residual adult or definitive cortex is indicated by arrows.
Lower:
Primitive cells are identified.

Figs. 23-7A and 23-7B

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Ganglioneuroblastoma

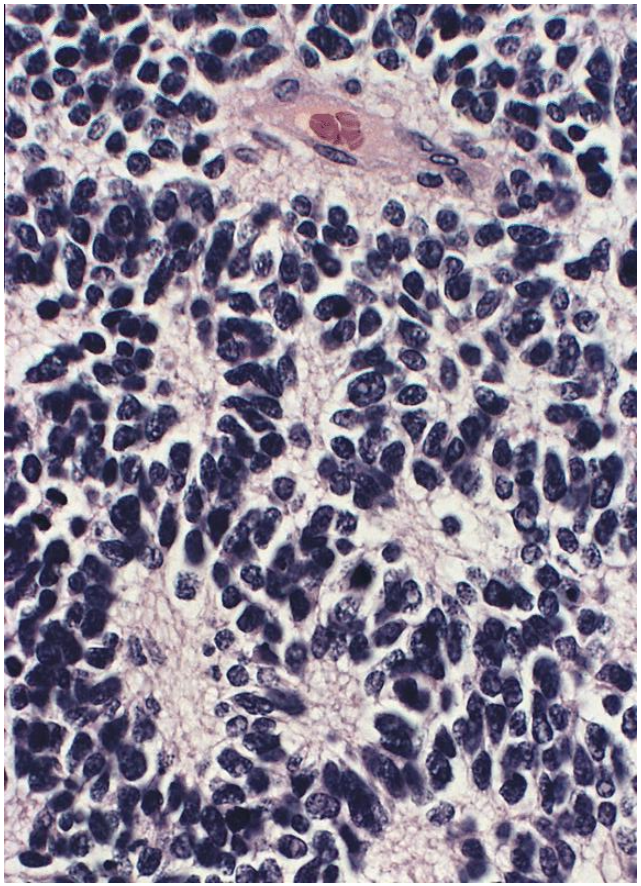


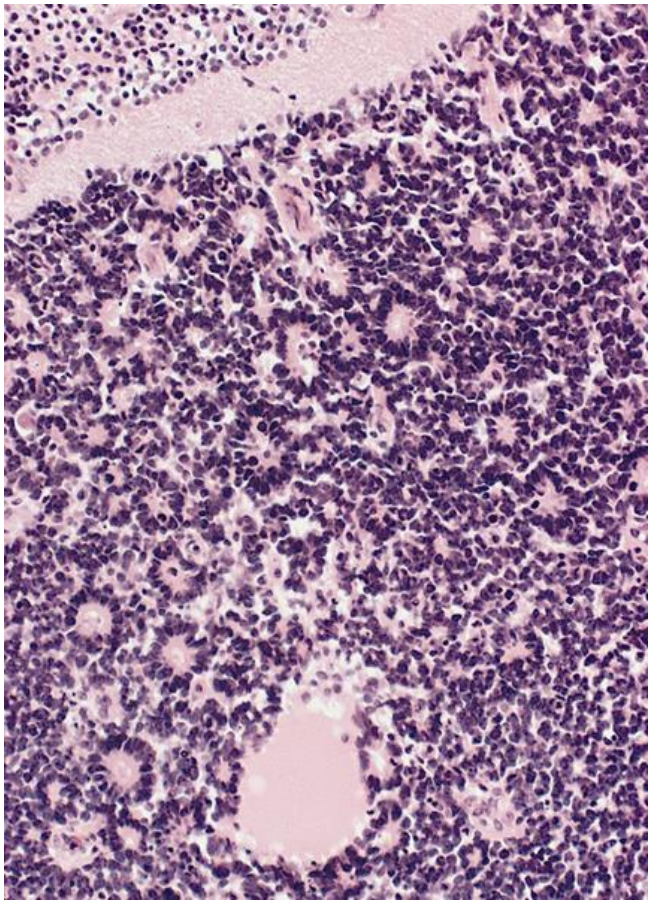
Tumor cells of neuroblastoma are separated by pale pink fibrillar material representing neuritic cell processes. The tumor was largely undifferentiated, with some cells showing early ganglion cell differentiation (arrow added).

Fig. 23-19L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Rosettes



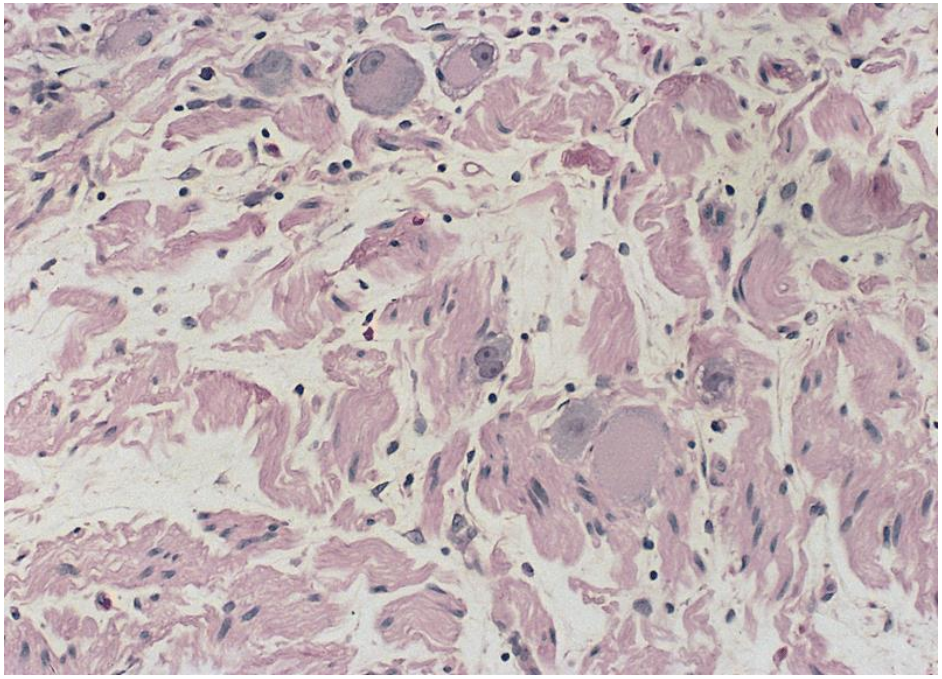


Homer-Wright rosettes in neuroblastoma (Left). Flexner-Wintersteiner rosettes in retinoblastoma. (Right)

Figs. 23-22 and 23-23L

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Ganglioneuroma



This ganglioneuroma is composed of abundant Schwann cells with admixed mature ganglion cells. Some mature ganglion cells were associated with cells resembling satellite cells.

Fig. 23-63

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

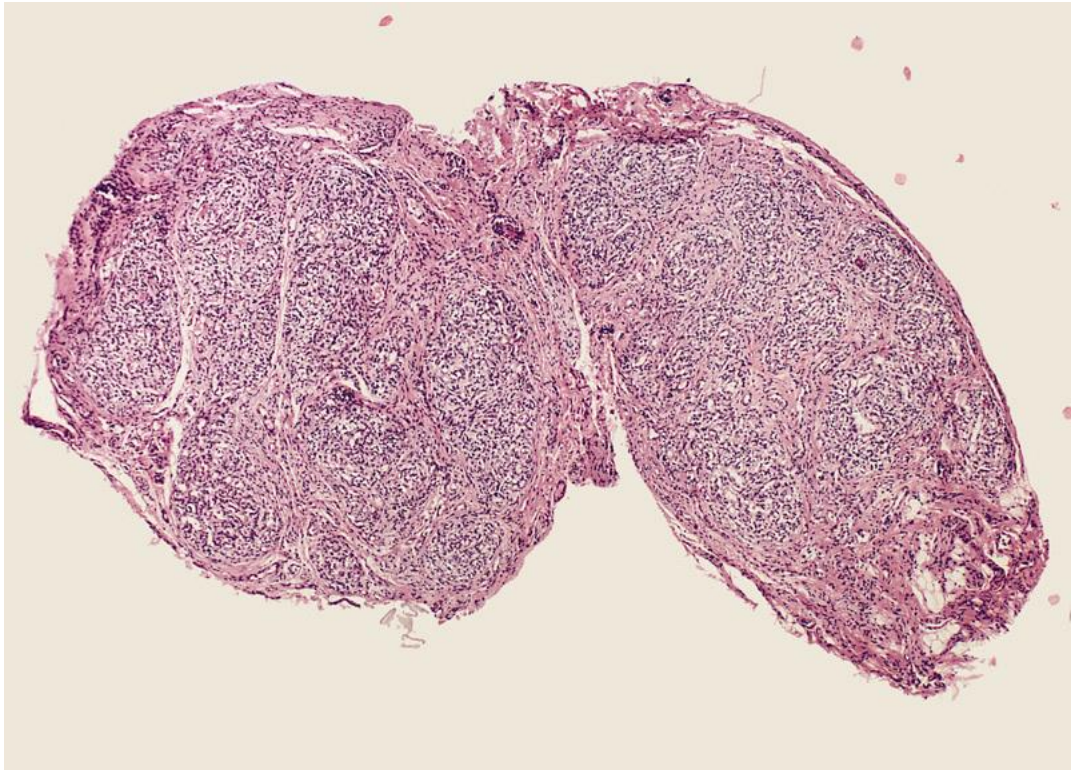
Pathologic criteria for neuroblastoma

- Neuron specific enolase positive
- Catecholamine granules on electron microscopy.
- Mature elements associated with better outcomes.

Pathologic criteria for peripheral neuroectodermal tumor (PNET)

- Brown tumor appearance.
- Polygonal chief cells enveloped in fibrous tissue and sustenacular elongated cells.
- Clear or granular cytoplasm.
- Neurosecretory granules on electron microscopy.
- Neuron specific enolase positive.

Carotid body tumor



Both carotid bodies are from a 38-year-old patient. Note the ovoid shape with multiple lobules. These carotid bodies are well-circumscribed but not truly encapsulated. (X25, Hematoxylin and eosin stain).

Fig. 15-4

Lack, EE., “Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia.” Atlas of Tumor Pathology, Third Series, Fascicle 19. Armed Forces Institute of Pathology, Washington, D.C. 1997.

Pineal

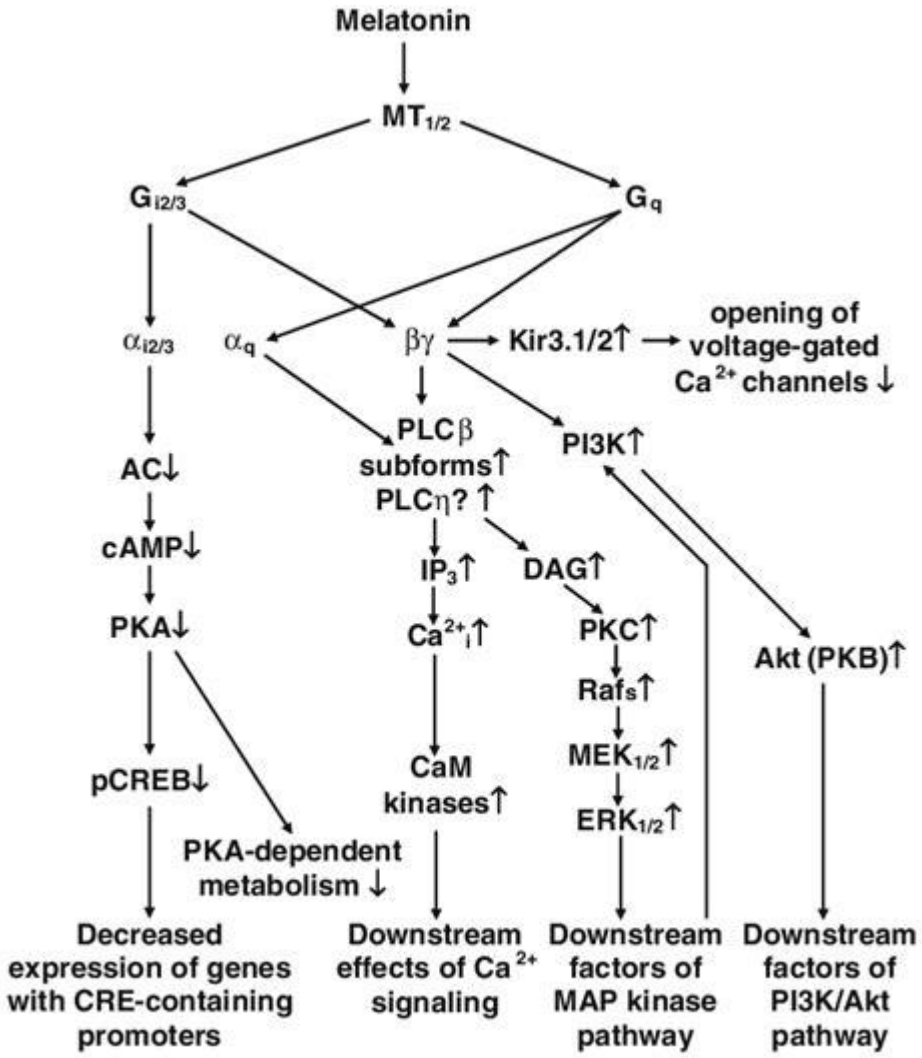
- Light exposure to the retina is first relayed to the suprachiasmatic nucleus of the hypothalamus
- Fibers from the hypothalamus descend to the spinal cord and ultimately project to the superior cervical ganglia, from which post-ganglionic neurons ascend back to the pineal gland.
- The gland is situated below the posterior edge of the corpus callosum, suspended from the roof of the third ventricle over the superior colliculi.
- Lobulated, with cords and clusters of large cells (pinealocytes) as well as astrocytes.

Pineal

- Produces melatonin from serotonin
- Diurnal secretion with elevated levels at night.
- Duration of activity related to duration of night.
- Suprachiasmatic nucleus not active.
- Norepinephrine release from superior cervical ganglion to pineal during darkness activates suprachiasmatic nucleus.
- Dopamine release modulates norepinephrine release
- Active prior to waking.

Melatonin

- Melatonin binds to calmodulin
- Inhibits LH, FSH
- Inhibits estrogen receptor
- Melatonin as releasing factor for arginine vasotocin from ependymal cells of the pineal recess.
- Arginine vasotocin activates serotonin neurotransmission, inducing sleep.
- Serotonin needed as well to maintain circadian sleep cycle.



https://www.researchgate.net/profile/Seithikurippu_R_Pandi-Perumal/publication/228081983/figure/fig2/AS:601650007920662@1520455948367/Overview-of-major-signaling-pathways-of-the-melatonin-membrane-receptors-MT-1-and-MT-2.png

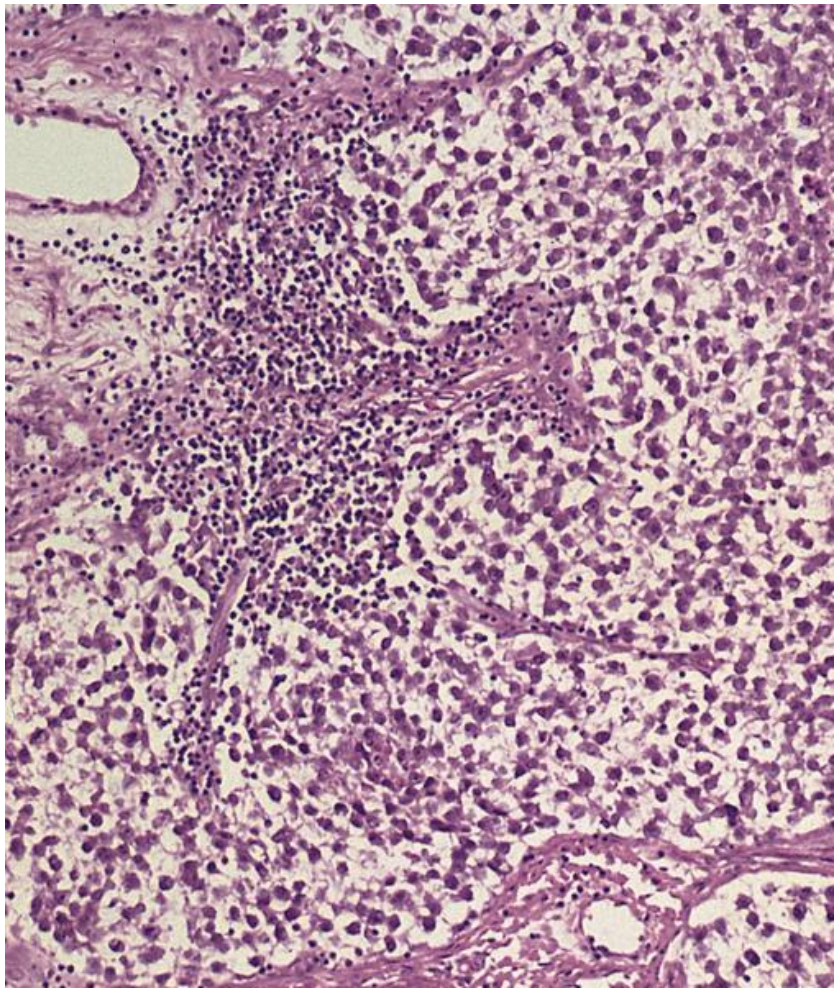
Pineal

- Dysgerminoma most common tumor.
- May cause precocious puberty, particularly in boys.
- Mass effect.
- Surgical excision difficult.
- Radiosensitive.
- Often positive for placental alkaline phosphatase, C-KIT, and OCT4.

Pineal

- Pineocytomas resemble paragangliomas
- Benign
- No secretory function.
- Pineoblastomas resemble medullobastoma or neuroblastoma
- Mitoses common
- Positive for synaptophysin but negative for glial fibrillary acidic protein.

Dysgerminoma



The tumor is composed of uniform cells resembling primordial germ cells in diffuse, insular, trabecular, and cord-like patterns. Rarely, the tumor cells line irregular or rounded gland-like spaces or form solid tubular structures.

Fig. 13-4

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Radiologic diagnosis

- Adrenal masses less than 2cm in size are benign.
- Fewer than 2% of adrenal masses greater than 4cm in size are adenomas
- If greater than 6cm, 92% are carcinomas.
- Pheochromocytoma is a dense, cystic mass.
- However, a small indeterminate (MRI) mass warrants screening for pheochromocytoma (plasma metanephrines) as well as adenoma.
- In patients with known cancer, 50% of masses are metastases.
- Fine needle aspiration best confirmatory method.

Cushing syndrome treatment

- Trans sphenoidal removal of a pituitary microadenoma (80% remission rate) has few complications.
- Unilateral micoadrenalectomy is appropriate for treating an adrenal adenoma in patients with confirmed autonomous glucocorticoid hyper-secretion even if not full overt Cushing syndrome.
- Bilateral adrenalectomy is necessary for ACTH-dependent Cushing's syndrome not treatable by pituitary surgery or removal of the ectopic ACTH source and for the rare case of bilateral adrenal adenomas.

Cushing syndrome treatment

- Patients with pituitary-dependent Cushing's syndrome treated with bilateral adrenalectomy should be carefully monitored for enlargement of an ACTH-secreting adenoma (Nelson's syndrome) and for the return of Cushing's syndrome from ACTH stimulation of adrenal rest tissue.

Cushing disease treatment

- En-bloc resection of adrenal (with the carcinoma) and kidney.
- Left adrenal vein drains into left renal vein.
- Mitotane leads to hormonal improvement in 75% of patients but does not affect overall survival.
- The addition of streptozocin may improve results.
- Etomidate inhibits 11β-hydorxylase and cholesterol side chain cleavage; may limit hormone production.
- 23% 5 year survival.

Cushing disease treatment

- Corticosteroid replacement is indicated in the intraoperative and postoperative period.
- Recovery from the hypothalamic pituitary axis suppression by pituitary or adrenal adenoma may take 12 months following surgery.
- Corticosteroid coverage for stressful periods, including pregnancy, is needed.
- Following bilateral adrenalectomy, lifelong replacement with corticosteroid and mineralocorticoid is required.
- Screen for MEN 1.

Neuroblastoma treatment

- Surgical resection, particularly for low risk tumors
- Stage I plus hyderdiploidy but without N-myc amplification.
- Radiation therapy reserved for unresectable, unresponsive tumors.
- Infants <2 months old require aggressive therapy.
- 94% 11 year survival if hyperdiploid (52% if diploid).
- Neonates with localized disease and infants 2-18 months old have 90% survival rates if no N-myc amplification.
- Neonates with Stage IVS disease have 75% survival rates. If not bulky, observe.
- Children >18 months old have 50% survival rates.

Neuroblastoma treatment

- Chemotherapy with cyclophosphamide and doxorubicin or etoposide and carboplatin following surgery for Stage II or III disease 3 year survial >96% unless N-myc amplification (survival 10%).
- Stage IV patients diagnosed after first birthday or stages IIB, III, IVS at any age are treated with cyclophosphamide, cisplatin, doxorubicin, etoposide, and vincristine with radiotherapy to sites of residual disease, and consolidated with myeloablative therapy using (cyclophosphamide), etoposide, and cisplatin followed by stem cell rescue.

Neuroblastoma treatment

- High risk patients benefit from intense dosing regimen of busulfan and melphalan as compared to carboplatin, etoposide, melphalan.
- Total body radiation may be employed as the myeloablative regimen.
- Retinoids to treat residual high risk disease.
- ACTH treatment for opsoclonus/myoclonus symptoms.
- Coagulopathy may be a problem with bulky IVS disease.