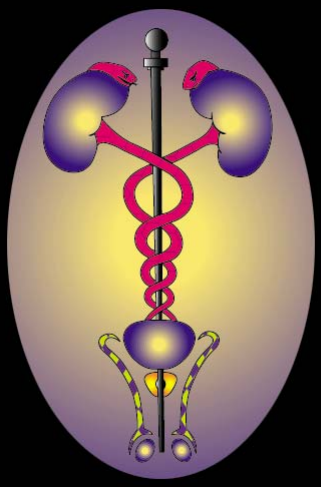
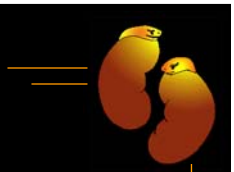


he Adrenal Glands

Thomas Jacobs, M.D.
Diane Hamele-Bena, M.D.



I. Normal adrenal gland
   A. Gross & microscopic
   B. Hormone synthesis, regulation & measurement

II. Hypoadrenalism

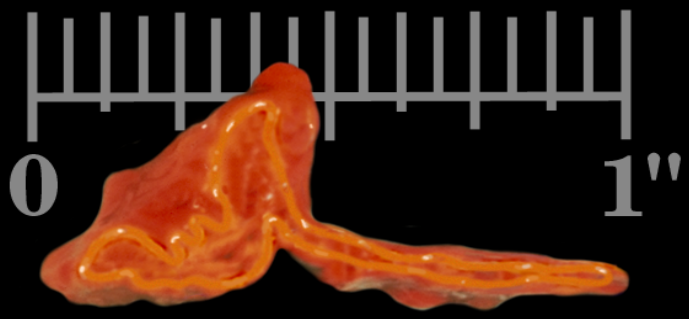
-- Break --

III. Hyperadrenalism; Adrenal cortical neoplasms

IV. Adrenal medulla

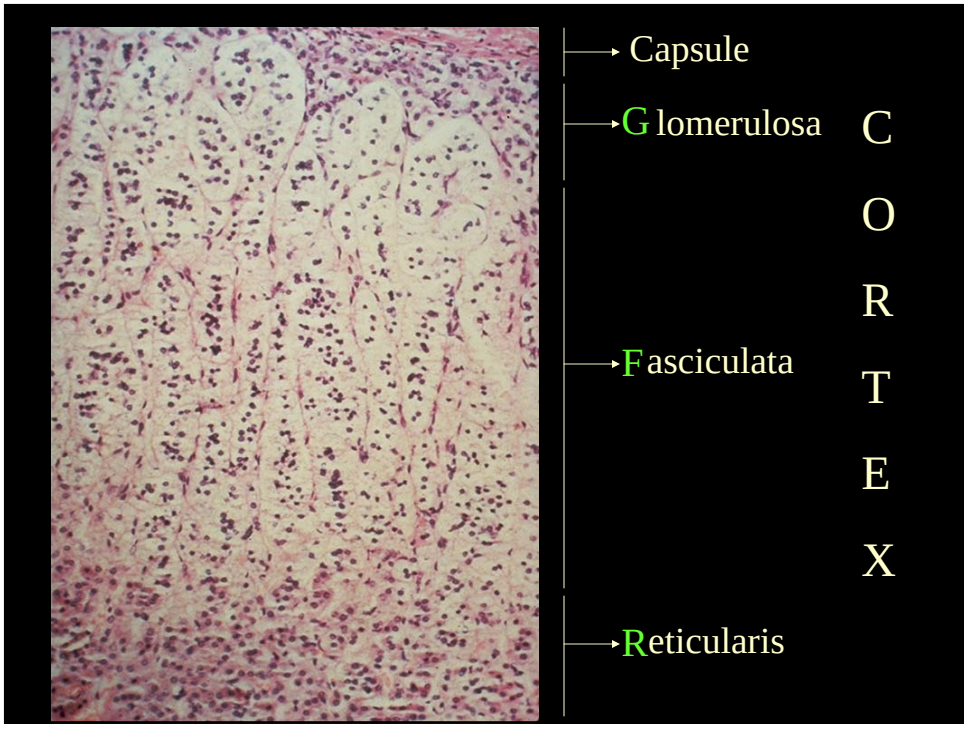
Normal Adrenal Gland

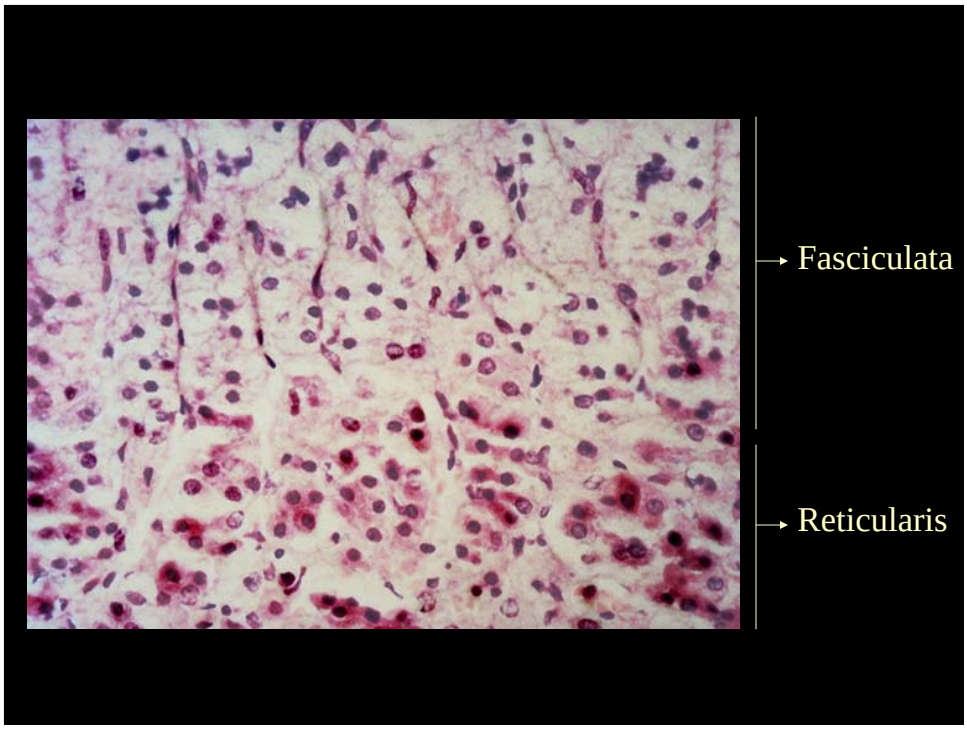
- Normal adult adrenal gland: 3.5 - 4.5 grams

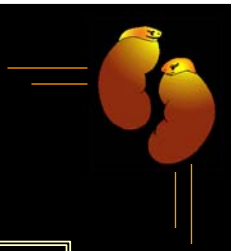


Adrenal Cortex Morphology

- Cortex: 3 zones:
  - Glomerulosa
  - Fasciculata
  - Reticularis

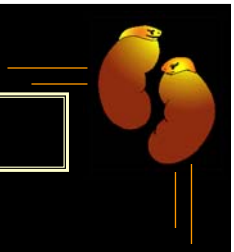

Capsule
Glomerulosa
Fasciculata
Reticularis
CORTEX


Fasciculata
Reticularis



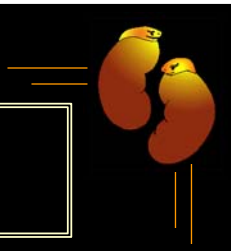
Hormone synthesis, regulation, and measurements

Hypoadrenalism



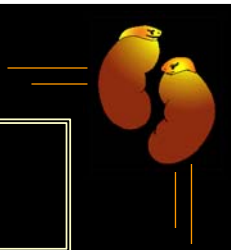
Hypoadrenalism

- Primary Adrenocortical Insufficiency
  - –Due to primary failure of adrenal glands
  - –ACTH is elevated
- Secondary Adrenocortical Insufficiency
  - –Due to disorder of hypothalamus or pituitary
  - –ACTH is decreased



Hypoadrenalism
Clinical Manifestations

- Fatigue, weakness, depression
- Anorexia
- Dizziness
- N&V, diarrhea
- Hyponatremia, hyperkalemia
- Hypoglycemia
- Hyperpigmentation

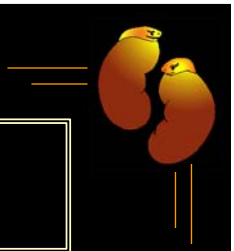


Hypoadrenalism
Clinical Manifestations

<u>Primary adrenal insufficiency:</u>

Deficiency of
glucocorticoids, mineralocorticoids, and androgens

	aldosterone	
↓	↓	↓
Hypoglycemia Fatigue Anorexia Weight loss	Hyponatremia Hyperkalemia Hypotension Dizziness	Reduced pubic and axillary hair in women



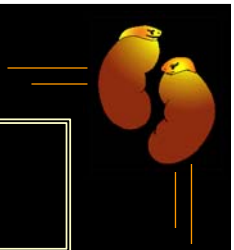
Hypoadrenalism
Clinical Manifestations

Primary adrenal insufficiency:
Concomitant hypersecretion of ACTH

MSH-like effect

↓

Hyperpigmentation



Hypoadrenalism
Clinical Manifestations

Secondary adrenal insufficiency:
Deficiency of ACTH

↓

NO hyperpigmentation

- Aldosterone secretion is usually normal and the renin-angiotensin system is preserved, so NO hyperkalemia
- Other manifestations of hypopituitarism may also be present, e.g., other endocrine deficiencies & visual field defects

Pathology of Hypoadrenalism

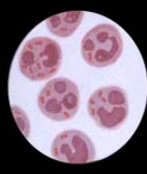
- Primary Adrenocortical Insufficiency
  - Acute
    - •Waterhouse-Friderichsen Syndrome
      Acute hemorrhagic necrosis, most often due to Meningococci
  - Chronic = Addison Disease

- Secondary Adrenocortical Insufficiency

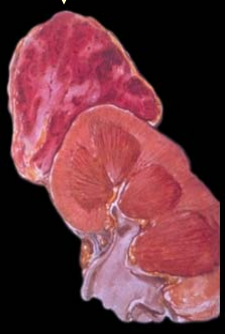
Waterhouse-Friderichsen Syndrome

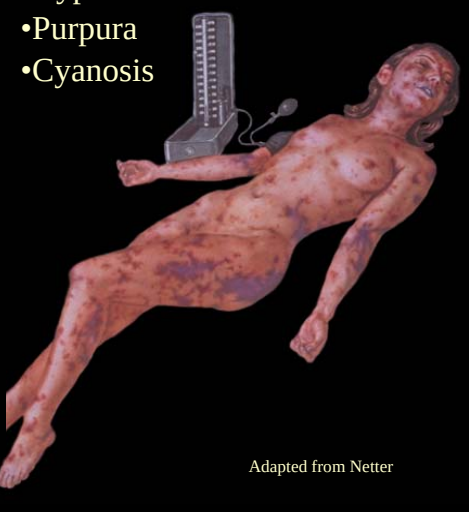
Massive adrenal hemorrhage

•Hypotension
•Purpura
•Cyanosis



Meningococci

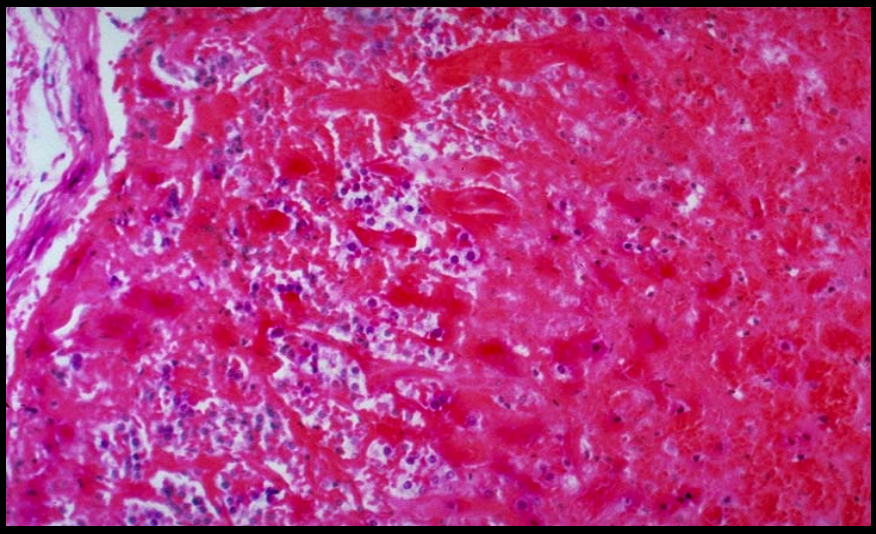




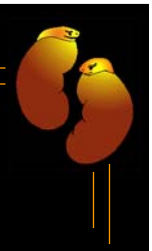
Adapted from Netter

Waterhouse-Friderichsen Syndrome

Waterhouse-Friderichsen Syndrome

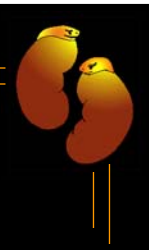


Pathology of Hypoadrenalism



- Primary Adrenocortical Insufficiency
  - Acute
    - Waterhouse-Friderichsen Syndrome
      Acute hemorrhagic necrosis, most often due to Meningococci
  - Chronic = Addison Disease
    - Autoimmune adrenalitis
    - *Tuberculosis*
    - *AIDS*
    - *Metastatic tumors*
    - *Other: fungi, amyloidosis, hemochromatosis*

Addison Disease
Clinical findings



Mineralocorticoid deficiency

- Hypotension
- Hyponatremia
- Hyperkalemia

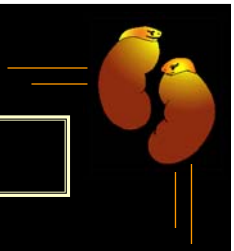
Glucocorticoid deficiency

- Weakness and fatigue
- Weight loss
- Hyponatremia
- Hypoglycemia
- Pigmentation
- Abnormal H_2O metabolism
- Irritability and mental sluggishness

Androgenic deficiency

- Loss of pubic and axillary hair in women

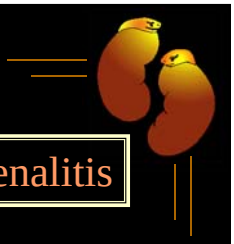
Autoimmune Adrenalitis



Three settings:

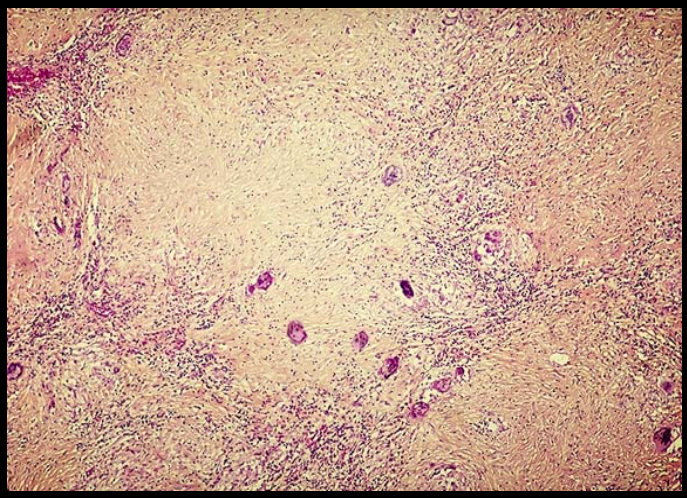
- Autoimmune Polyendocrine Syndrome type 1 (APS1) = Autoimmune Polyendocrinopathy, Candidiasis, and Ectodermal Dysplasia (APECED)
- Autoimmune Polyendocrine Syndrome type 2 (APS2)
- Isolated Autoimmune Addison Disease

Pathologic Changes in Autoimmune Adrenalitis



- Gross:
  - –Very small glands (1 - 1.5 grams)
  - –Cortices markedly thinned
- Micro:
  - –Diffuse atrophy of *all* cortical zones
  - –Lymphoplasmacytic infiltrate
  - –Medulla is unaffected

Tuberculosis involving adrenal

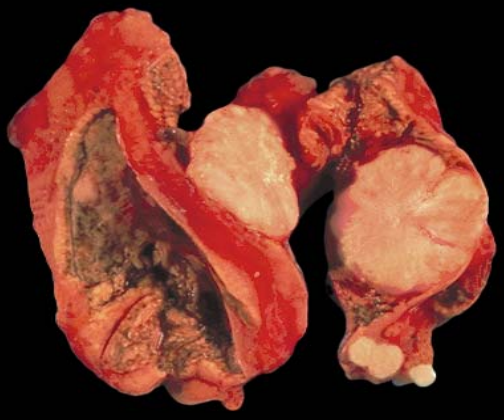


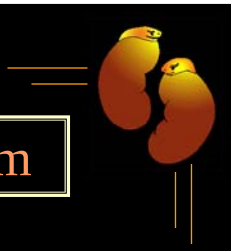
Multinucleated giant cells

Cortex and medulla are affected

Metastatic carcinoma in adrenal

ıor





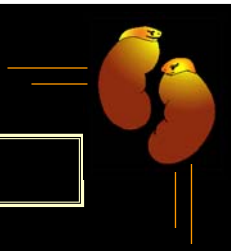
Pathology of Hypoadrenalism

- Primary Adrenocortical Insufficiency
  - Acute
    - Waterhouse-Friderichsen Syndrome
  - Chronic = Addison Disease
- Secondary Adrenocortical Insufficiency
  - Any disorder of the hypothalamus or pituitary leading to diminished ACTH; e.g., infection; pituitary tumors, including metastatic carcinoma; irradiation

Diagnosis of Hypoadrenalism


Hyperadrenalism

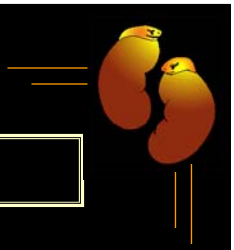
Hyperadrenalism



Three distinctive clinical syndromes:

- Cushing Syndrome: excess cortisol
- Hyperaldosteronism
- Adrenogenital or Virilizing Syndrome: excess androgens

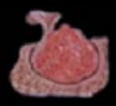
Hyperadrenalism



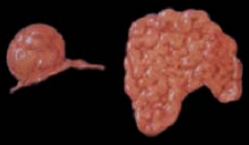
In clinical practice, most cases of Cushing Syndrome are the result of administration of exogenous glucocorticoids ("exogenous" or iatrogenic Cushing Syndrome).

Cushing Syndrome

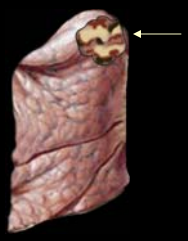
Endogenous



Pituitary adenoma



Adrenal neoplasm or hyperplasia

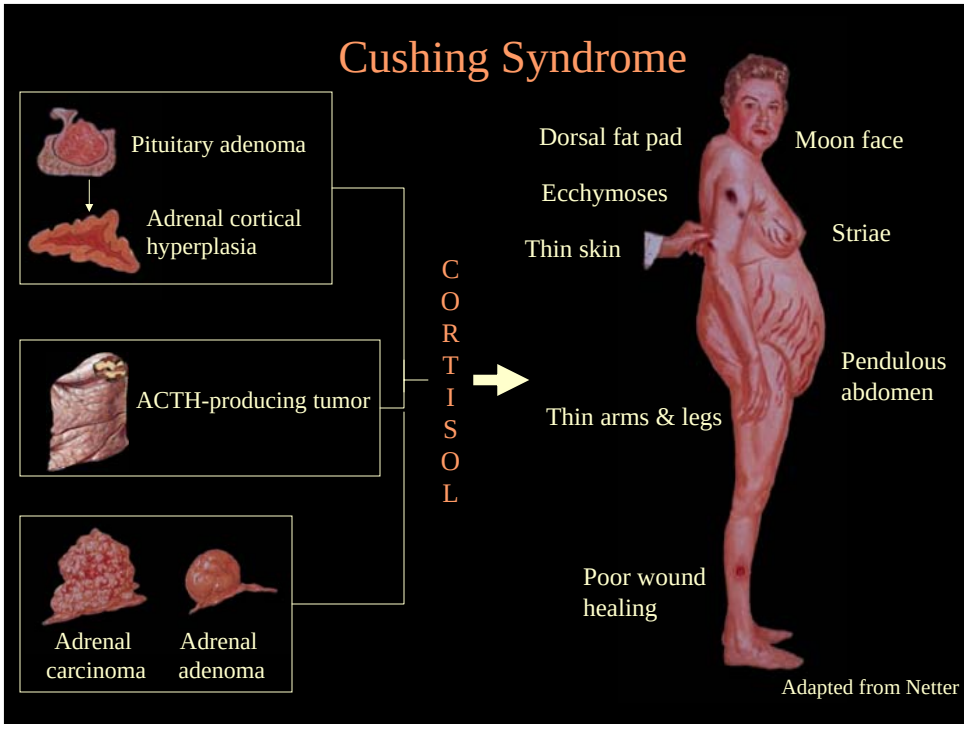


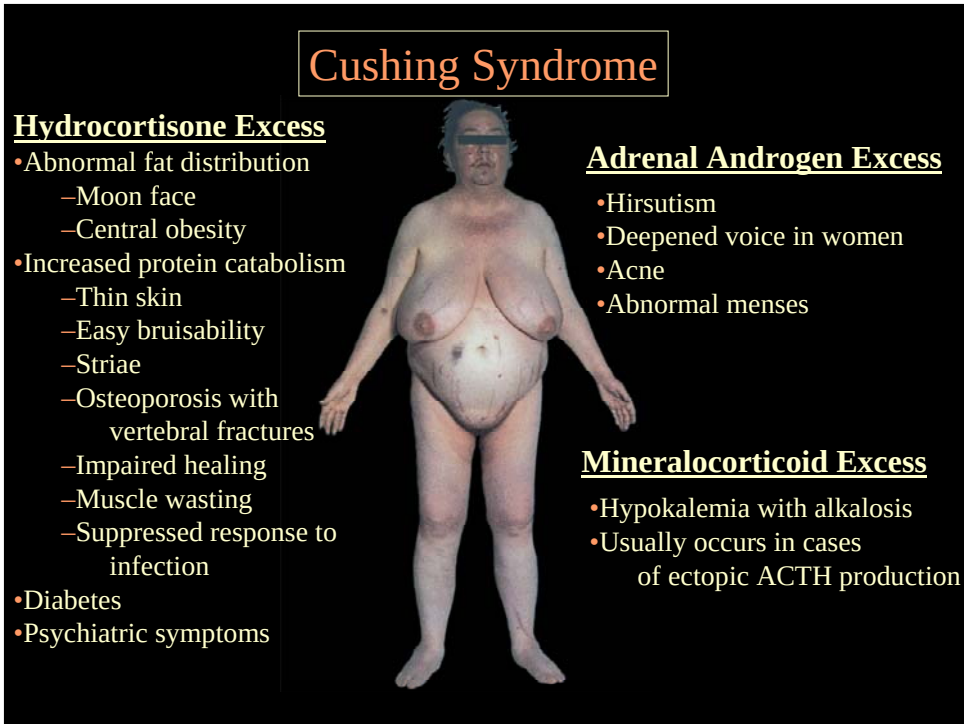
ACTH-producing tumor

Exogenous (Iatrogenic)

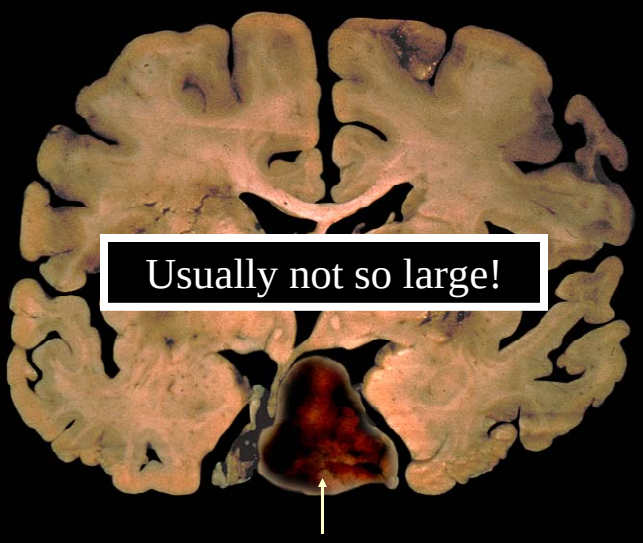
"Endogenous" Cushing Syndrome

Etiology	Pathology
I. ACTH-dependent:	
•Cushing *Disease*	Pituitary adenoma or hyperplasia → Adrenal cortical hyperplasia
•Ectopic ACTH production	Extra-adrenal ACTH-producing tumor → Adrenal cortical hyperplasia
II. ACTH-independent:	
•Hypersecretion of cortisol by adrenal neoplasm or autonomous adrenal cortical hyperplasia	Adrenal neoplasm or cortical hyperplasia


Cushing Syndrome
Pituitary adenoma
Adrenal cortical hyperplasia
ACTH-producing tumor
Adrenal carcinoma
Adrenal adenoma
CORTISOL
Dorsal fat pad
Moon face
Ecchymoses
Striae
Thin skin
Pendulous abdomen
Thin arms & legs
Poor wound healing
Adapted from Netter


Cushing Syndrome
Hydrocortisone Excess
•Abnormal fat distribution
–Moon face
–Central obesity
•Increased protein catabolism
–Thin skin
–Easy bruisability
–Striae
–Osteoporosis with vertebral fractures
–Impaired healing
–Muscle wasting
–Suppressed response to infection
•Diabetes
•Psychiatric symptoms
Adrenal Androgen Excess
•Hirsutism
•Deepened voice in women
•Acne
•Abnormal menses
Mineralocorticoid Excess
•Hypokalemia with alkalosis
•Usually occurs in cases of ectopic ACTH production

Cushing *Disease*



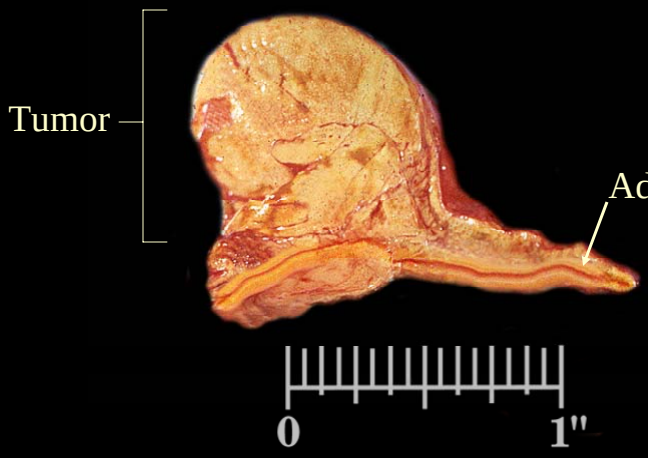
Usually not so large!

Pituitary adenoma

Adrenal cortical hyperplasia

Normal

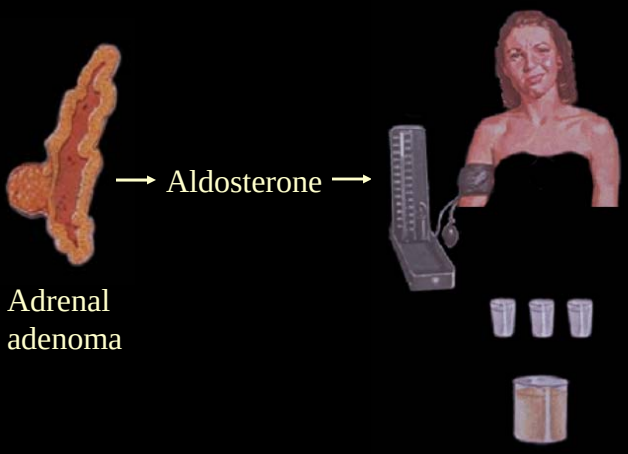
Adrenal cortical adenoma



Pathology of Primary Hyperaldosteronism

- Aldosterone-secreting adenoma
  - *Conn Syndrome*
- Bilateral idiopathic cortical hyperplasia
- Adrenal cortical carcinoma
  - Uncommon cause of hyperaldosteronism

Conn Syndrome



Adrenal adenoma → Aldosterone →

- Hypertension
- Polydipsia
- Polyuria
- Hypernatremia
- Hypokalemia

Adapted from Netter

Cortical Neoplasms

Adenomas and Carcinomas → Functioning *

Adenomas and Carcinomas → Non-functioning

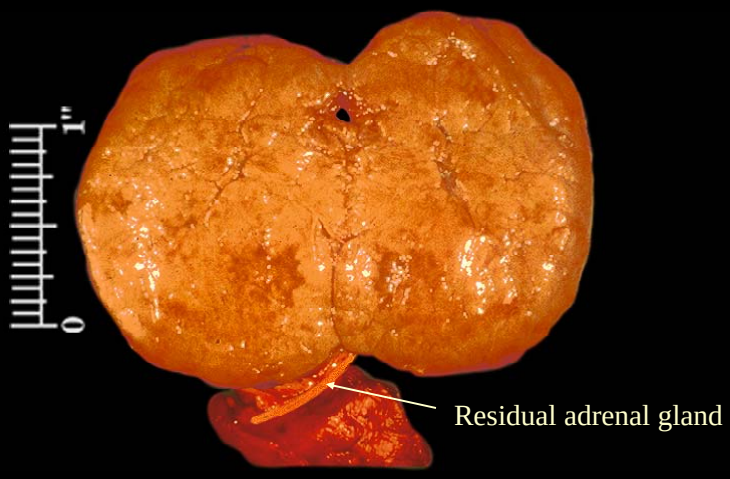
* May produce:

- Cortisol (Cushing Syndrome)
- Sex steroids
- Aldosterone (Conn Syndrome)

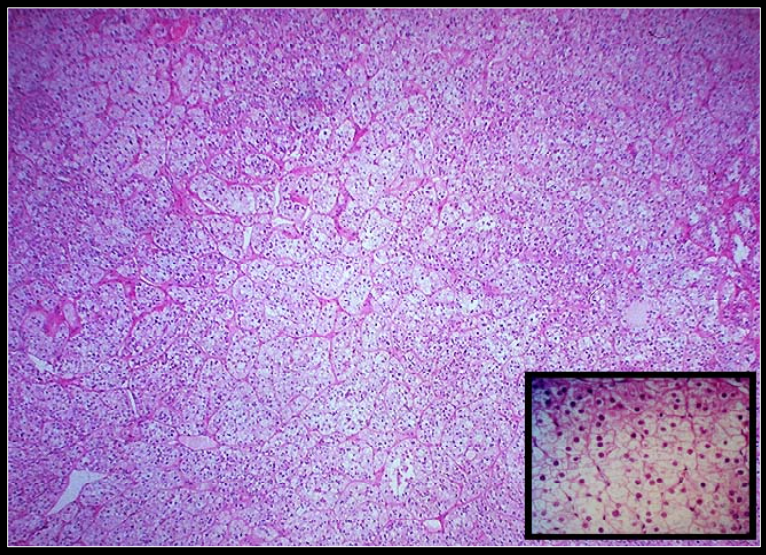
Cortical Neoplasms

- Adenomas
  - Gross:
    - Discrete, but often unencapsulated
    - Small (up to 2.5 cm)
    - Most <30 grams
    - Yellow-orange, usually without necrosis or hemorrhage
  - Micro:
    - Lipid-rich & lipid-poor cells with little size variation
- Carcinomas
  - Gross:
    - Usually unencapsulated
    - Large (many >20 cm)
    - Frequently > 200-300 grams
    - Yellow, with hemorrhagic, cystic, & necrotic areas
  - Micro:
    - Ranges from mild atypia to wildly anaplastic

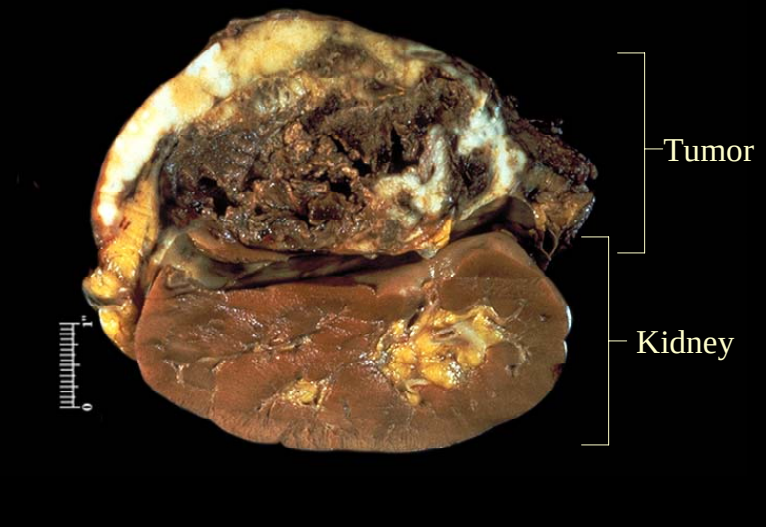
Adrenal cortical adenoma



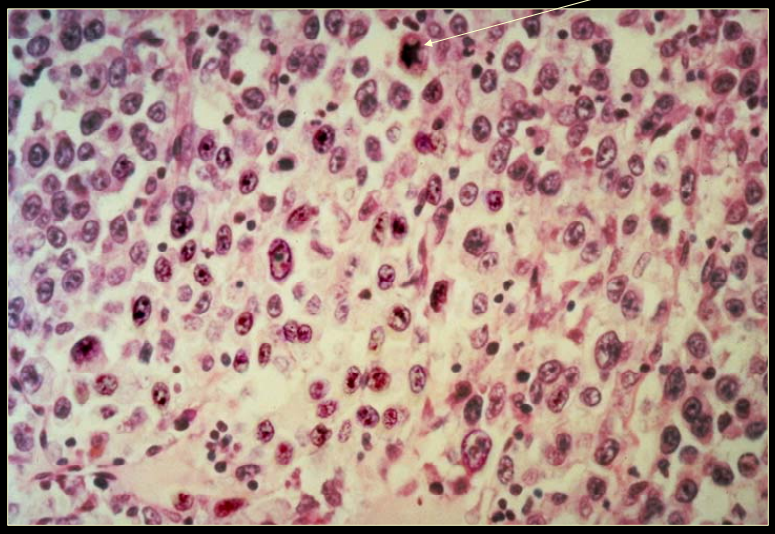
Adrenal cortical adenoma

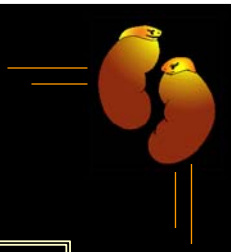


Adrenal cortical carcinoma

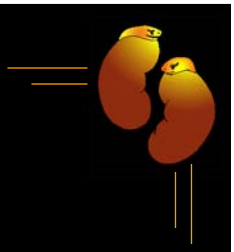


Adrenal cortical carcinoma





Diagnosis of Hyperadrenalism

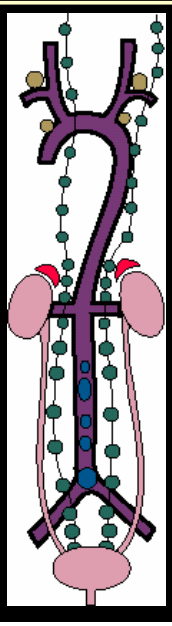


Adrenal Medulla

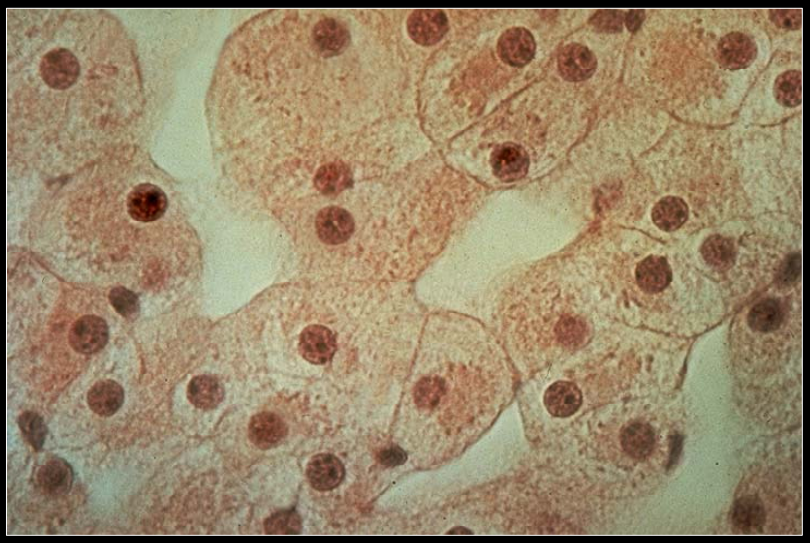
Adrenal Medulla

- Specialized neural crest (neuroendocrine) cells
- Part of the chromaffin system, which includes the adrenal medullae & paraganglia
- Major source of catecholamines (epi, norepi, & dopamine)

Paraganglion System



Adrenal Medulla



Tumors of the Adrenal Medulla

- Neuroblastoma
- Ganglioneuroblastoma
- Ganglioneuroma
- Pheochromocytoma

Ganglioneuroma — Ganglioneuroblastoma — Neuroblastoma

BENIGN

MALIGNANT

Neuroblastoma

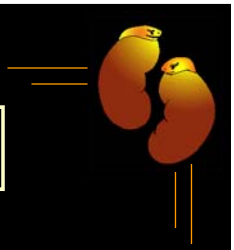
- *Poorly differentiated* malignant neoplasm derived from neural crest cells
- Usually occurs in infants & small children
- "Small round blue cell tumor" of childhood

Rhabdomyosarcoma	Lymphoma
Retinoblastoma	Wilms tumor
Ewing sarcoma/PNET	Medulloblastoma

Neuroblastoma: primary sites

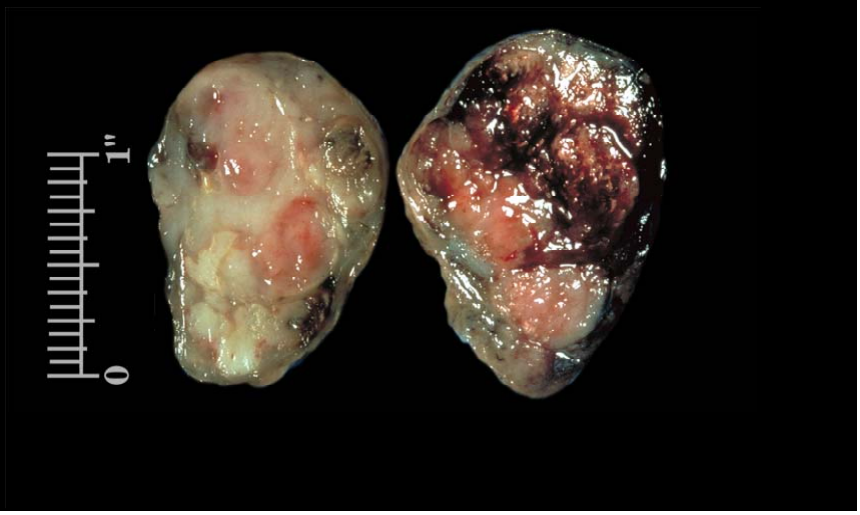
•Head	2%
•Neck	5%
•Chest	13%
•Adrenal	~ 40%
•Abdomen, nonadrenal	18%
•Pelvis	4%
•Other sites & unknown	21%

Neuroblastoma: Pathology

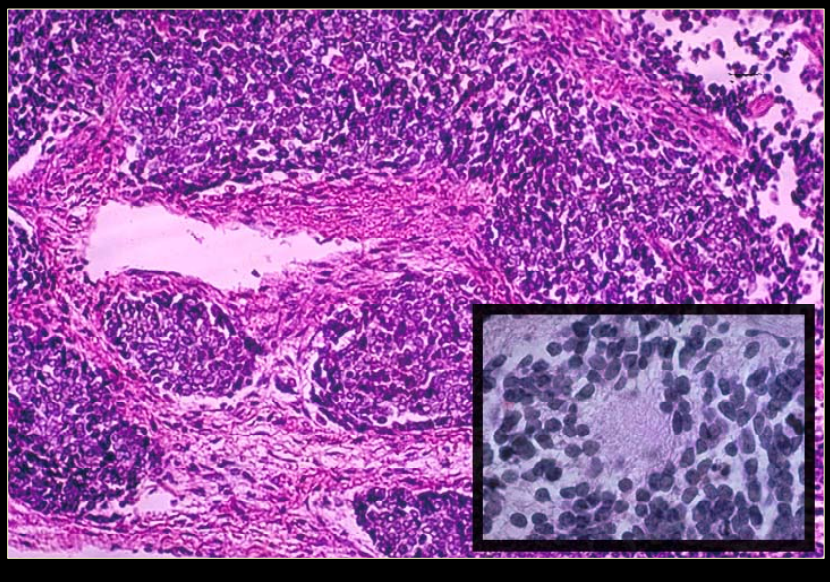


- Gross:
  - Large tumor with hemorrhage, necrosis, & calcification
- Micro:
  - Undifferentiated small cells resembling lymphocytes ("Small, round, blue cell tumor")
  - May show areas of *differentiation (larger cells with more cytoplasm and Schwannian stroma)*

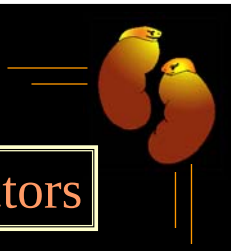
Neuroblastoma



Neuroblastoma

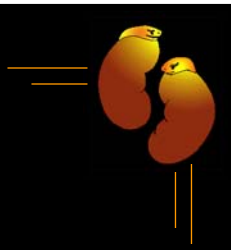


Neuroblastoma: Prognostic Factors



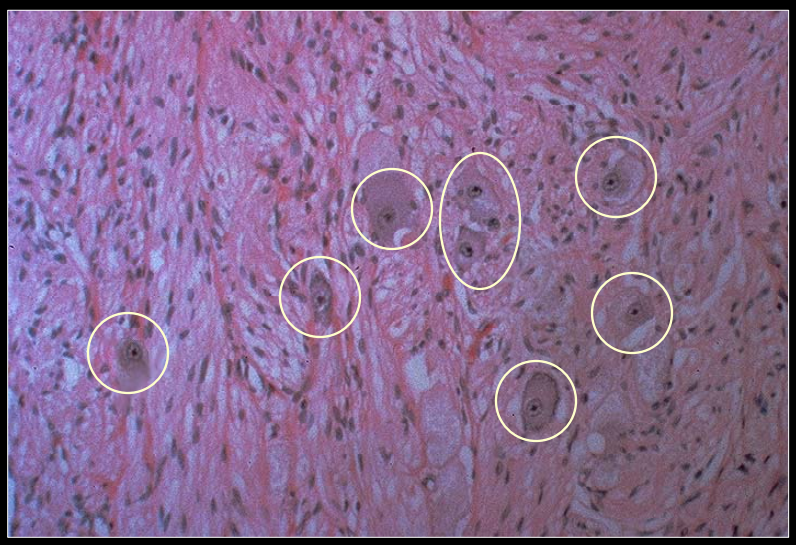
- Patient age
- Stage
- Site of 1^0 involvement
- Histologic grade
- DNA ploidy
- N-myc oncogene amplification
- Others: Chromosome 17q gain, Chromosome 1p loss, Trk-A expression, Telomerase expression, MRP expression, CD44 expression

Ganglioneuroma

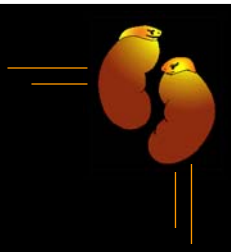


- *Differentiated* neoplasm of neural crest origin
- Benign
- Occurs in older age group
- Pathology:
  - Gross: Encapsulated, white, firm
  - Micro: Ganglion cells & Schwann cells

Ganglioneuroma

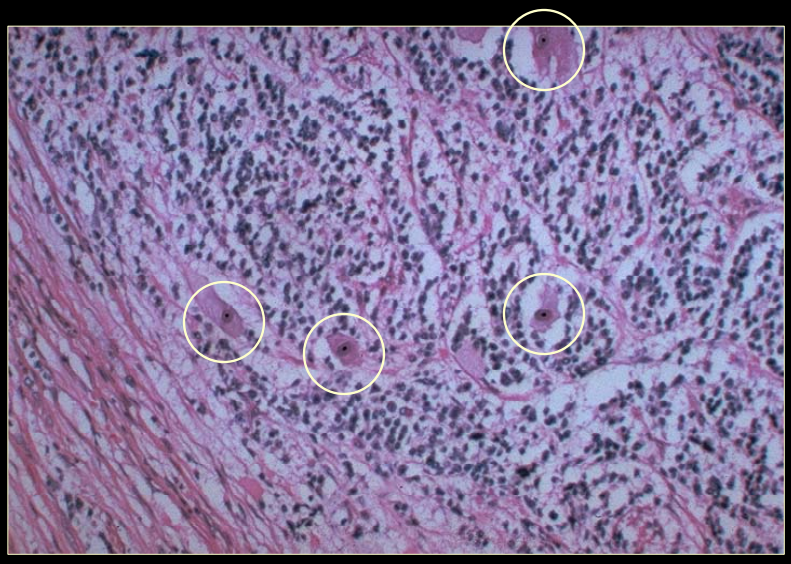


Ganglioneuroblastoma

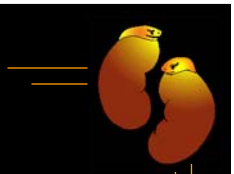


- Composed of malignant neuroblastic elements & ganglioneuromatous elements
- Prognosis depends on % of neuroblasts

Ganglioneuroblastoma

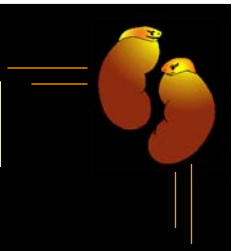


Pheochromocytoma



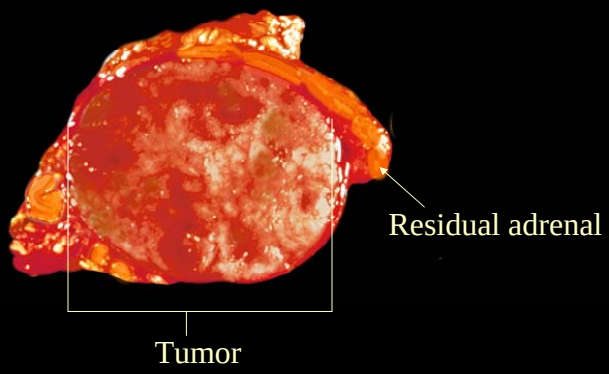
- Catecholamine-secreting neoplasm: HYPERTENSION
- Rare, but important: surgically curable form of hypertension
- May arise in association with familial syndromes, e.g., MEN2, von Hippel-Lindau, von Recklinghausen (NF1)
- May be "sporadic": ~24% have germline mutations, including mutations of RET, VHL, SDH-B, and SDH-D genes
- Extra-adrenal tumors (e.g., carotid body) are called "paragangliomas"

Pheochromocytoma: Pathology

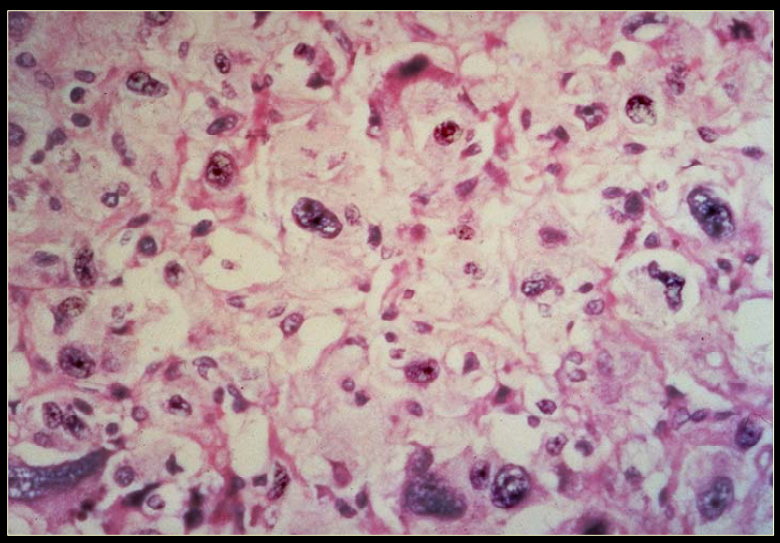


- Gross:
  - 1 - 4000 grams (average = 100 grams)
  - Areas of hemorrhage, necrosis, & cystic degeneration
- Micro:
  - Balls of cells resembling cells of medulla, with bizarre, hyperchromatic nuclei; richly vascular stroma
- Benign & malignant tumors are histologically identical; the only absolute criterion for malignancy is *metastasis*.

Pheochromocytoma



Pheochromocytoma



Pheochromocytoma: Clinical aspects