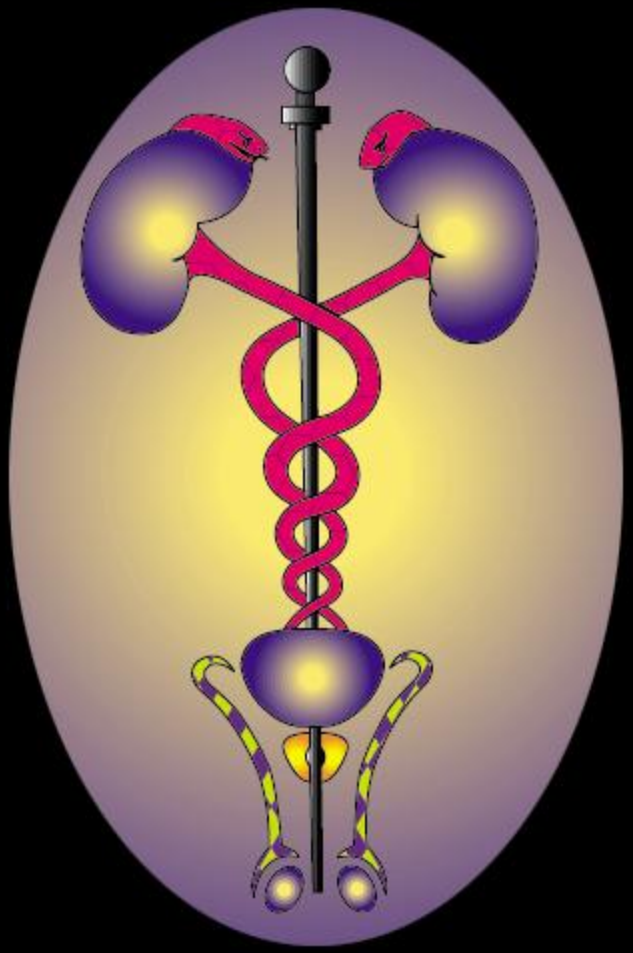
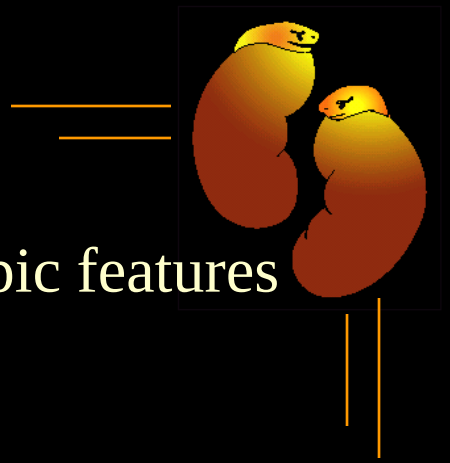


# The Adrenal Glands

Diane Hamele-Bena, M.D.



I. Normal adrenal gland: Gross and microscopic features

II. Hypoadrenalism

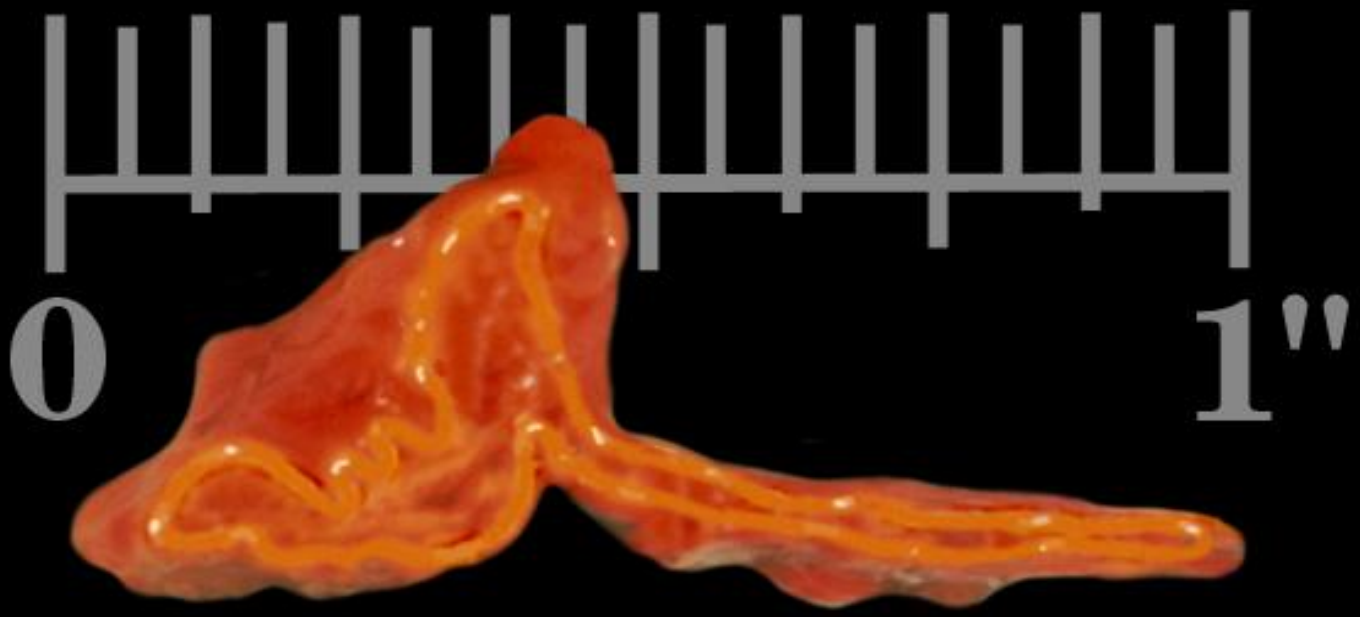
III. Hyperadrenalism

IV. Adrenal cortical neoplasms

V. Adrenal medulla

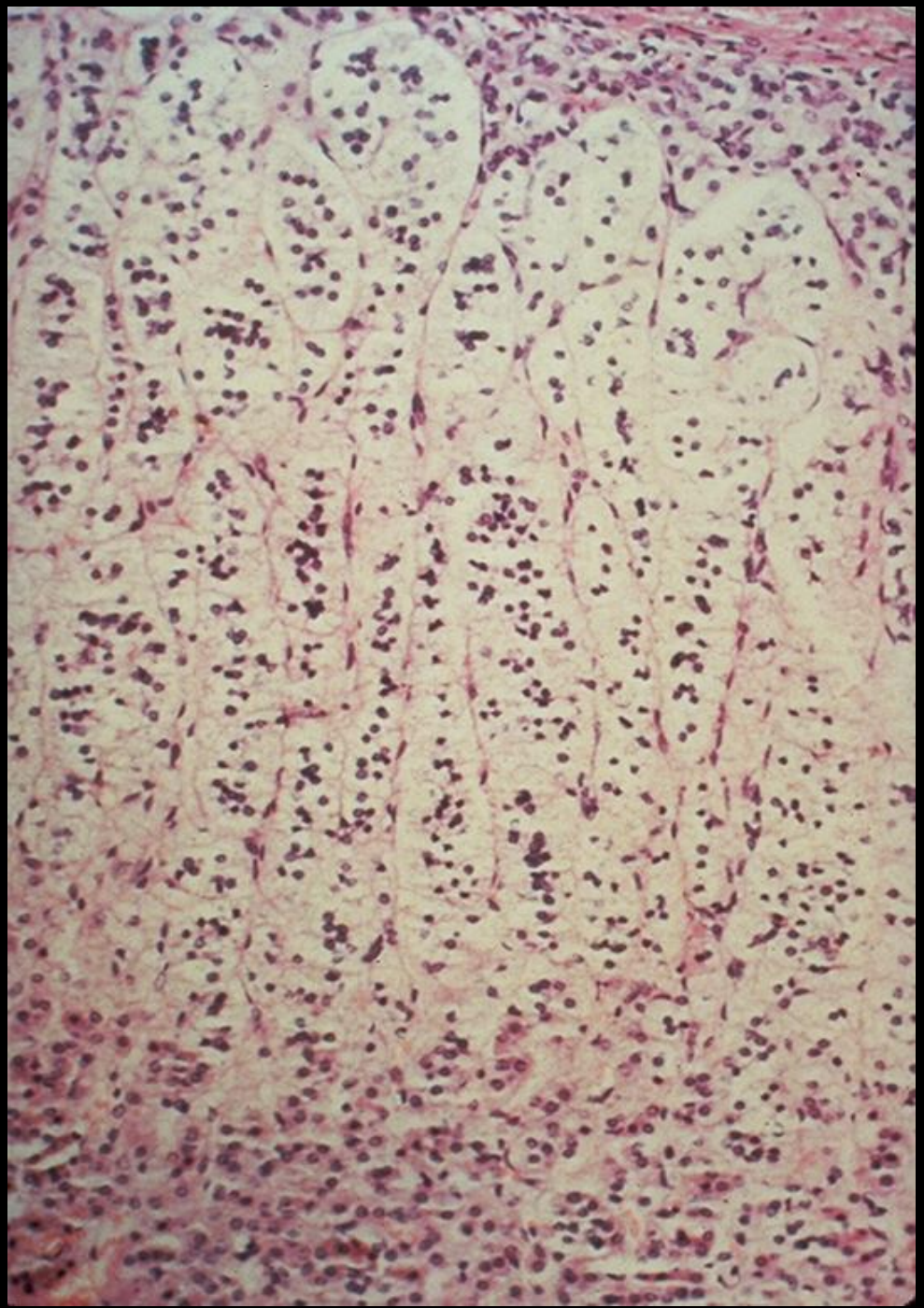
# Normal Adrenal Gland

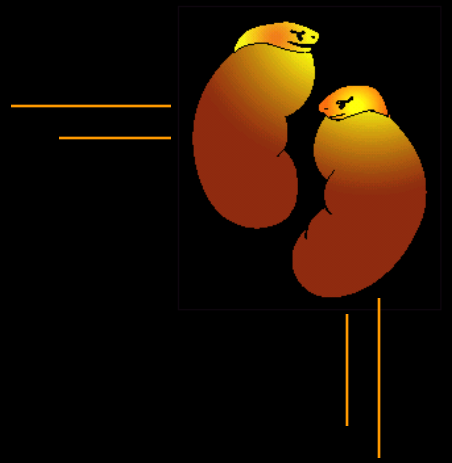
- Normal adult adrenal gland: 3.5 - 4.5 grams



# Adrenal Cortex Morphology

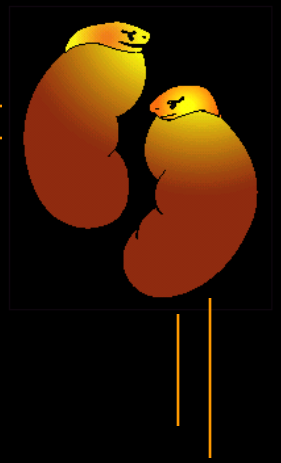
- Cortex: 3 zones:
  - Glomerulosa: mineralocorticoids (aldosterone)
  - Fasciculata :glucocorticoids; sex steroids (<)
  - Reticularis:androgens


Capsule
Glomerulosa
Fasciculata
Reticularis
CORTEX

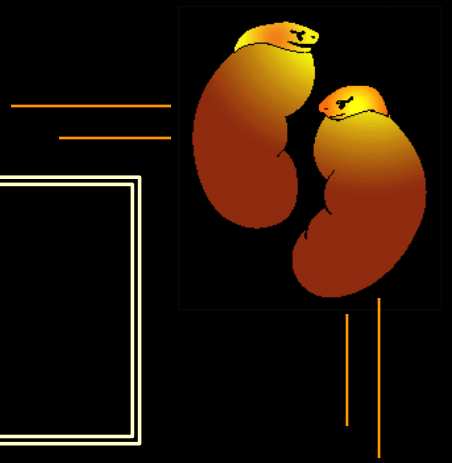


# Hypoadrenalism

# Hypoadrenalism

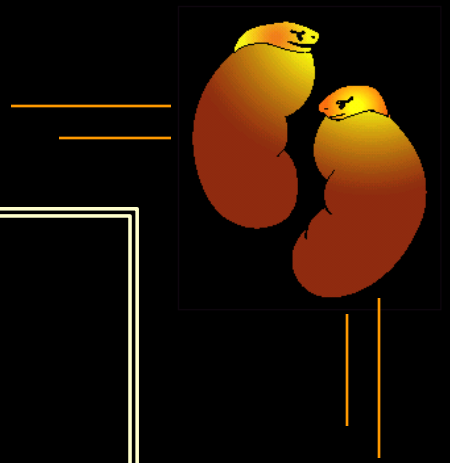


- Primary Adrenocortical Insufficiency
  - –Due to primary failure of adrenal glands
  - –ACTH is elevated
- Secondary Adrenocortical Insufficiency
  - –Due to disorder of hypothalamus or pituitary
  - –ACTH is decreased



# Hypoadrenalism
## Clinical Manifestations

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

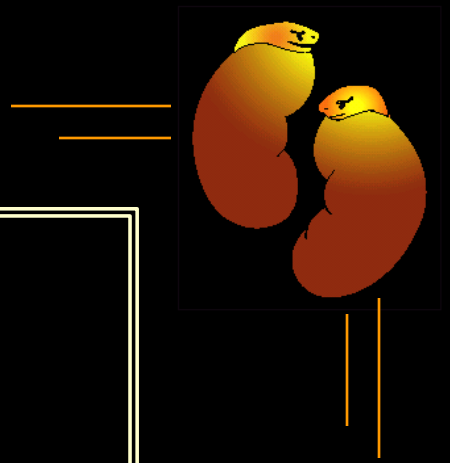


# Hypoadrenalism
# Clinical Manifestations

Primary adrenal insufficiency:

Deficiency of
glucocorticoids, mineralocorticoids, and androgens

| | *aldosterone* | |
|---|---|---|
| Hypoglycemia<br>Fatigue<br>Anorexia<br>Weight loss | Hyponatremia<br>Hyperkalemia<br>Hypotension<br>Dizziness | Reduced pubic and axillary hair in women |



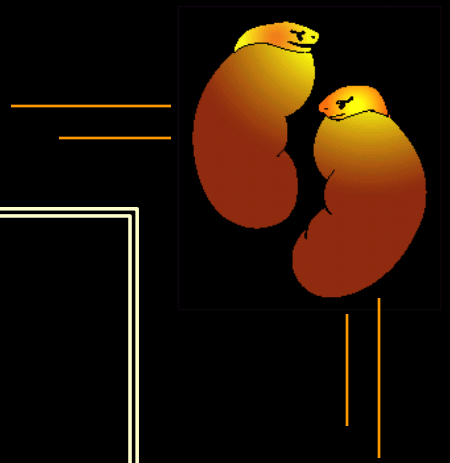
# Hypoadrenalism
# Clinical Manifestations

Primary adrenal insufficiency:

Concomitant hypersecretion of ACTH

MSH-like effect

Hyperpigmentation



# Hypoadrenalism
# Clinical Manifestations

Secondary adrenal insufficiency:

Deficiency of ACTH

↓

NO hyperpigmentation

# Pathology of Hypoadrenalism

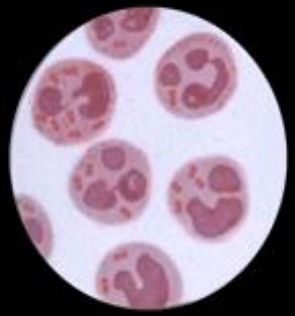
- Primary Adrenocortical Insufficiency
  - Acute
    - Waterhouse-Friderichsen Syndrome

      Acute hemorrhagic necrosis, most often due to Meningococci
  - Chronic = Addison Disease

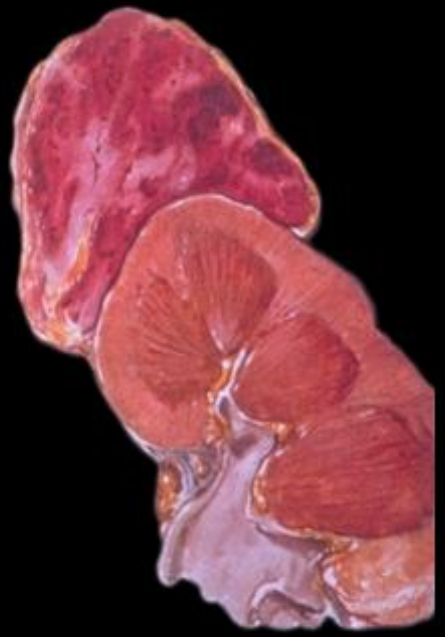
- Secondary Adrenocortical Insufficiency

# Waterhouse-Friderichsen Syndrome

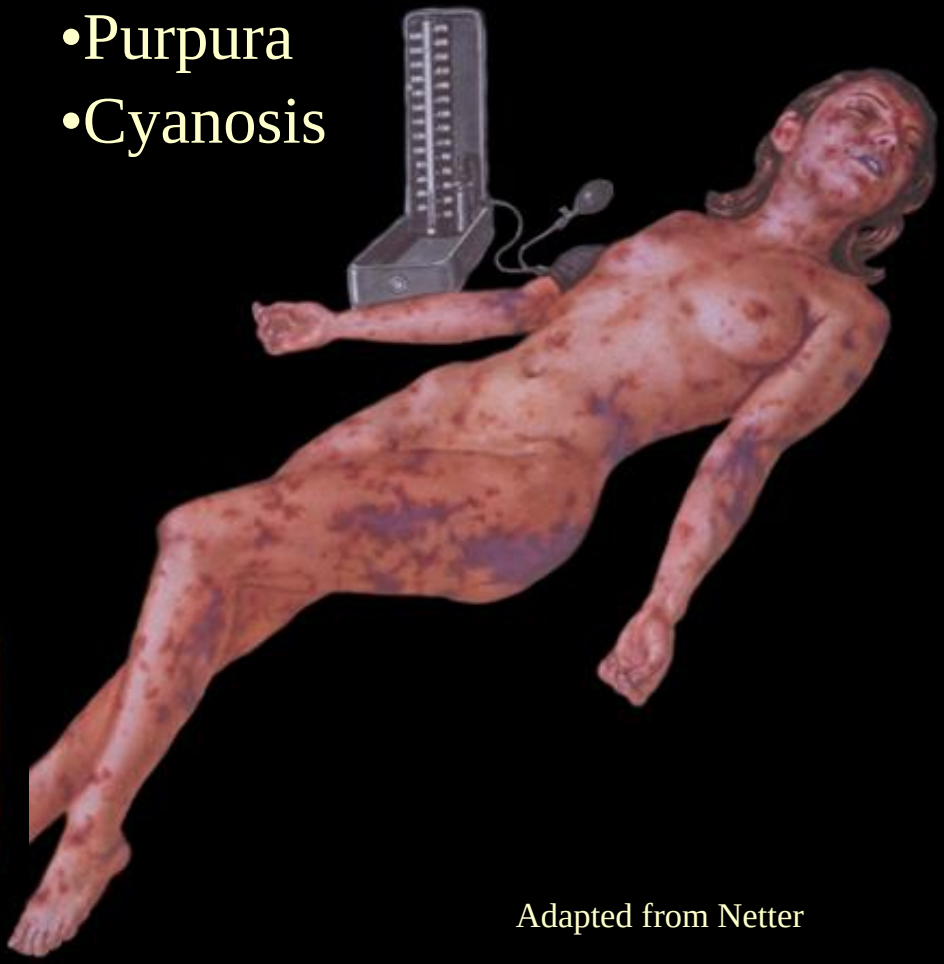
Massive adrenal hemorrhage



Meningococci

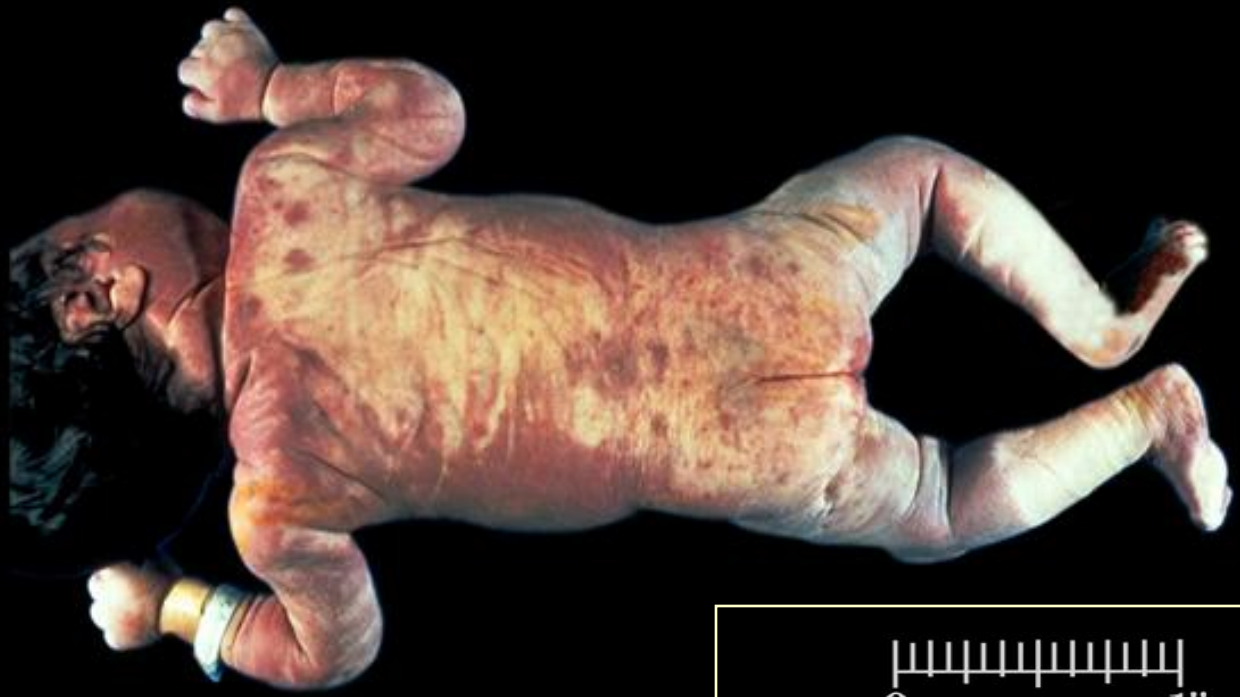


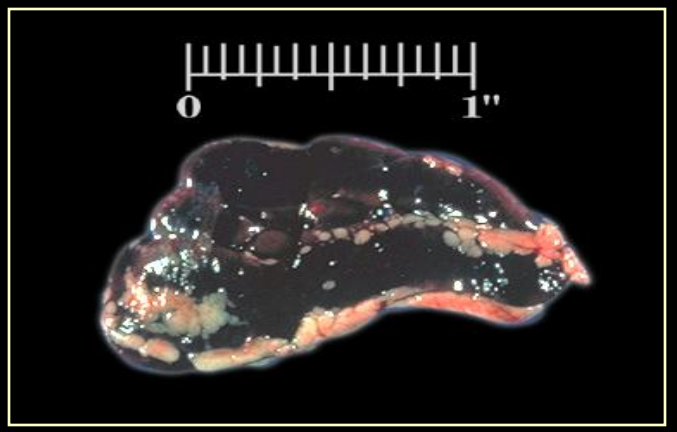
- Hypotension
- Purpura
- Cyanosis



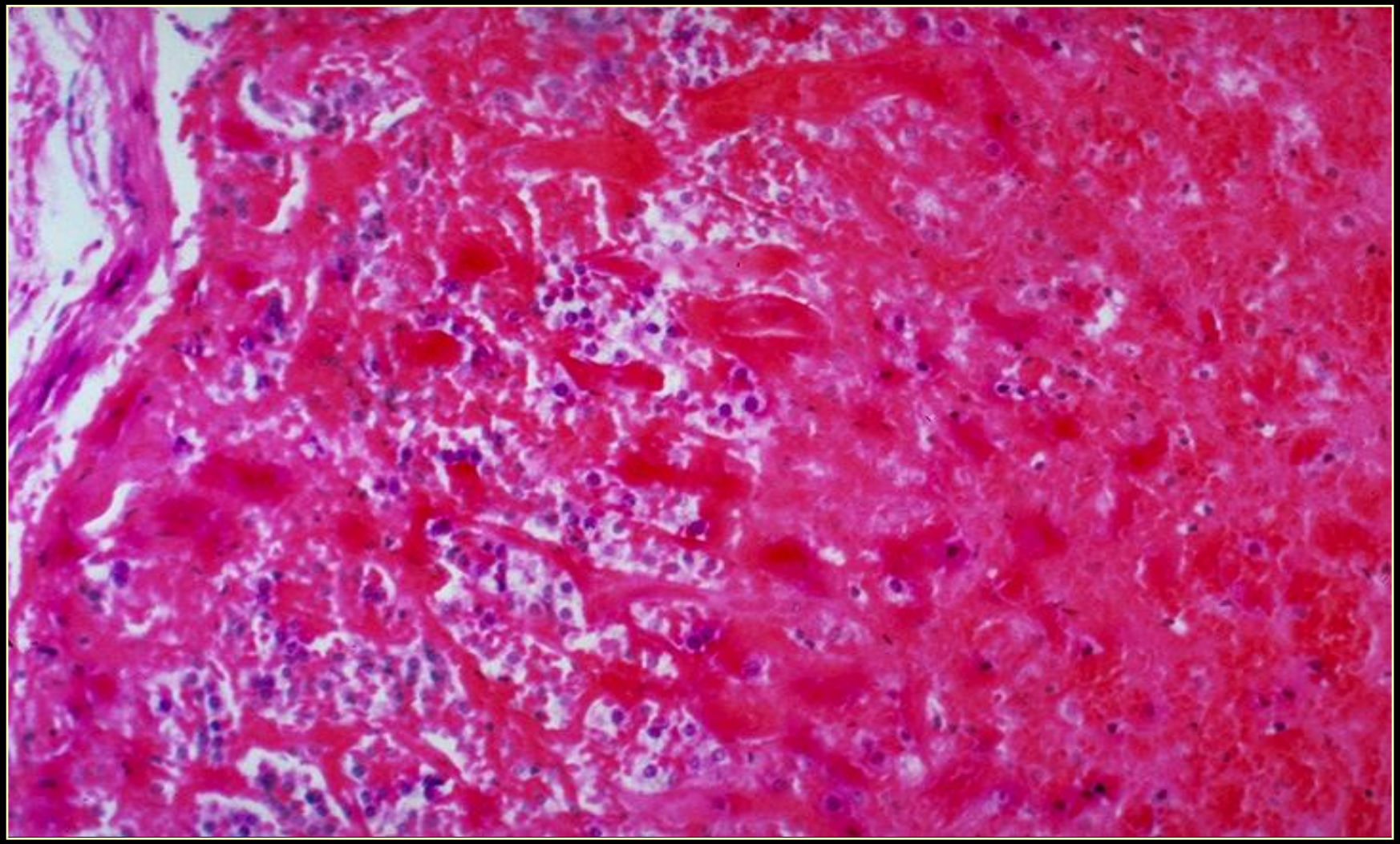
Adapted from Netter

# Waterhouse-Friderichsen Syndrome





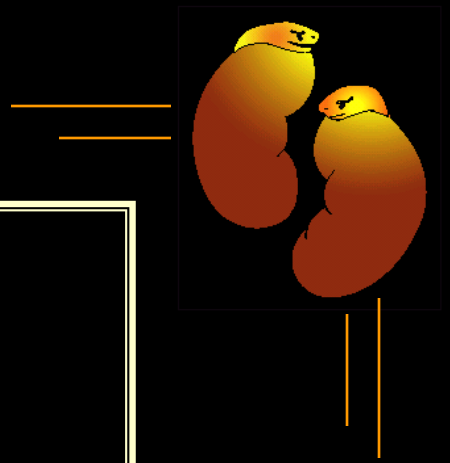
# Waterhouse-Friderichsen Syndrome



# Pathology of Hypoadrenalism

- Primary Adrenocortical Insufficiency
  - Acute
    - Waterhouse-Friderichsen Syndrome

      Acute hemorrhagic necrosis, most often due to Meningococci
  - Chronic = Addison Disease
    - Autoimmune adrenalitis
    - *Infections (e.g., tuberculosis, fungi)*
    - *Metastatic tumors*
    - *Other: Amyloidosis, hemochromatosis*



# Addison Disease
## Clinical findings

### Mineralocorticoid deficiency

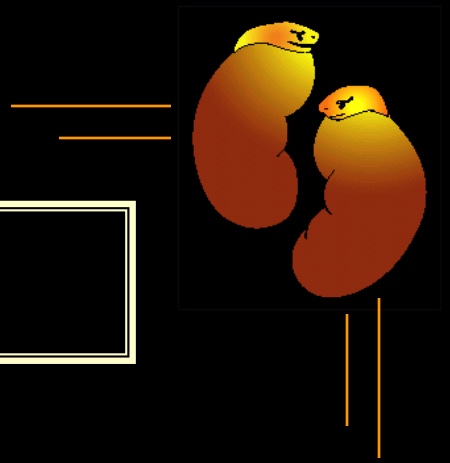
- Hypotension
- Hyponatremia
- Hyperkalemia

### Androgenic deficiency

- Loss of pubic and axillary hair in women

### Glucocorticoid deficiency

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

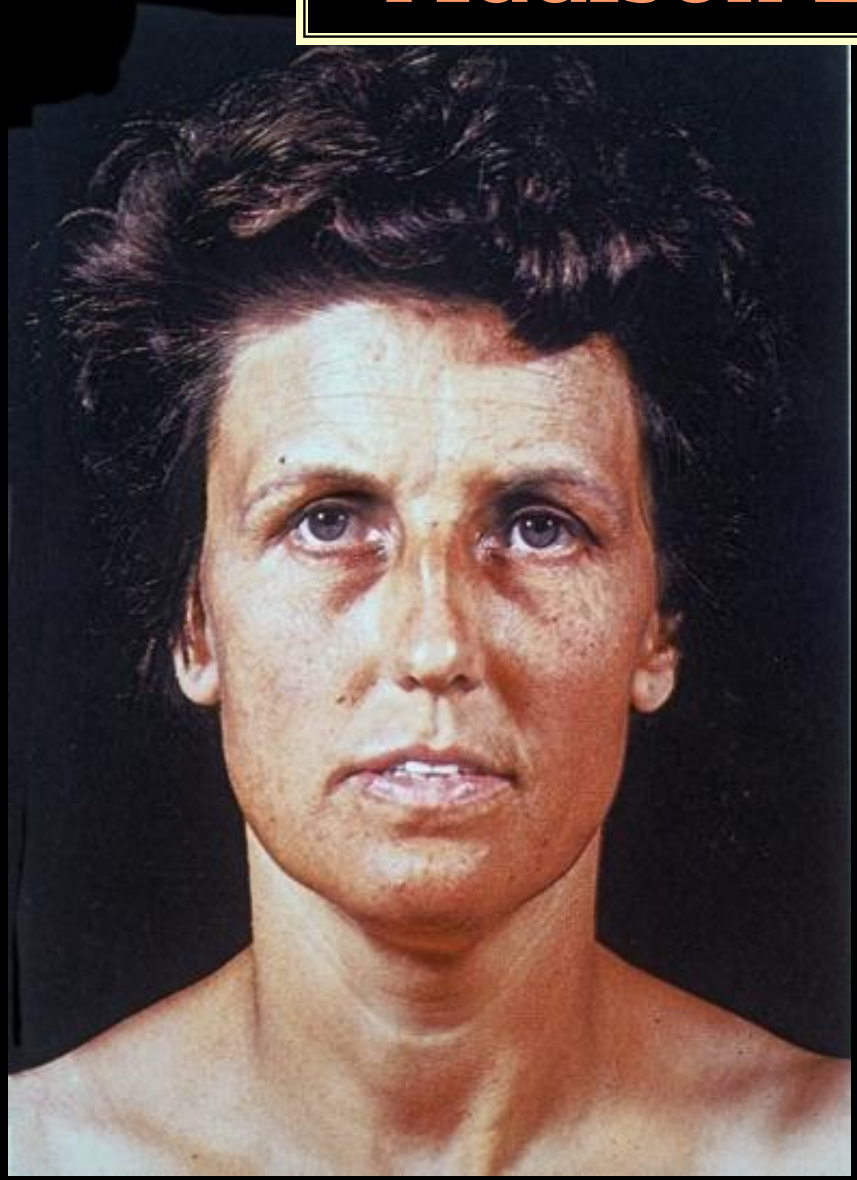


# Autoimmune Adrenalitis

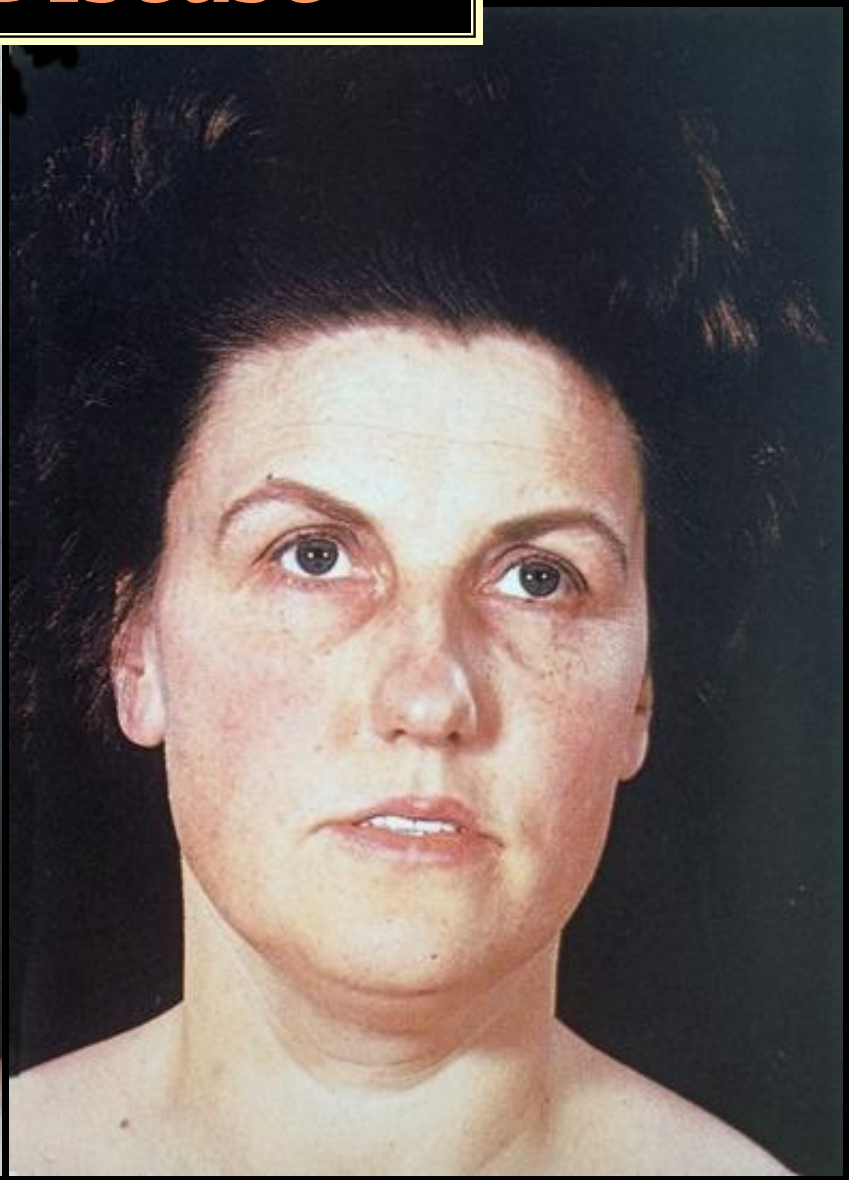
Three settings:

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

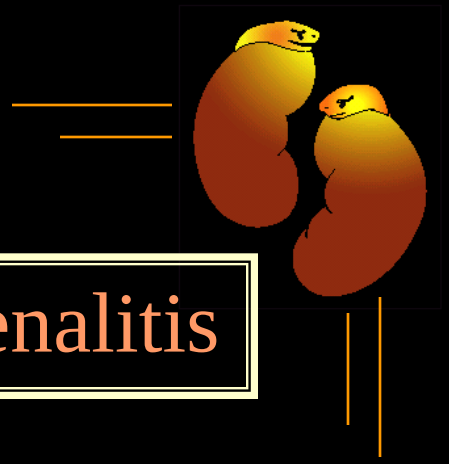
# Addison Disease



Before treatment



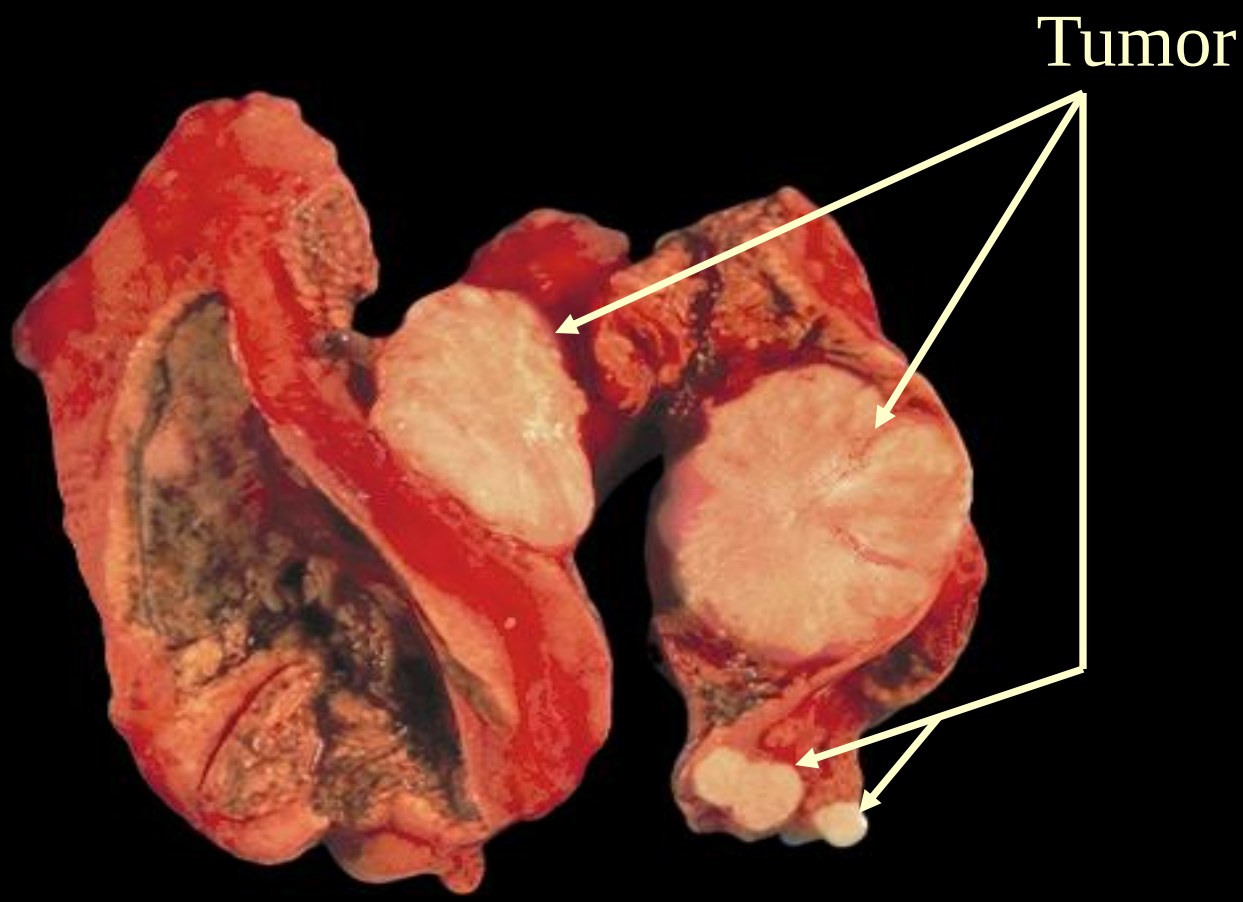
After treatment



# Pathologic Changes in Autoimmune Adrenalitis

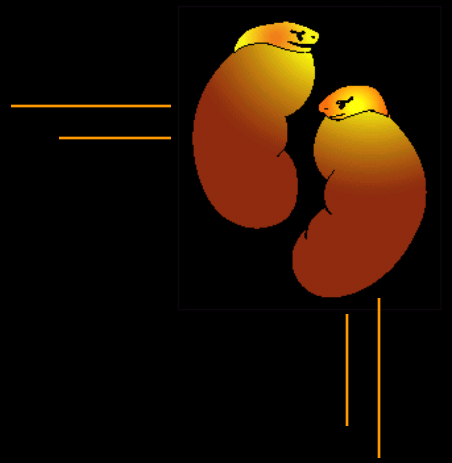
- Gross:
  - –Very small glands (1 - 1.5 grams)
  - –Cortices markedly thinned
- Micro:
  - –Diffuse atrophy of *all* cortical zones
  - –Lymphoplasmacytic infiltrate
  - –Medulla is unaffected

# Metastatic carcinoma in adrenal

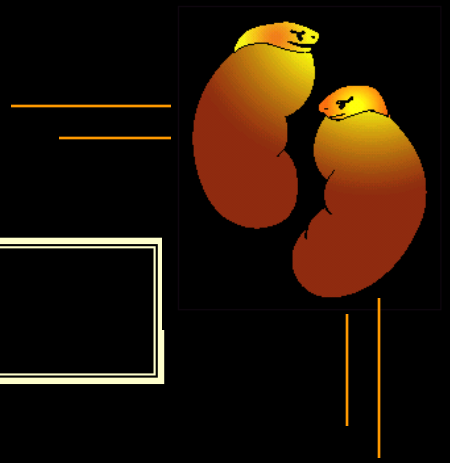


# Pathology of Hypoadrenalism

- 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



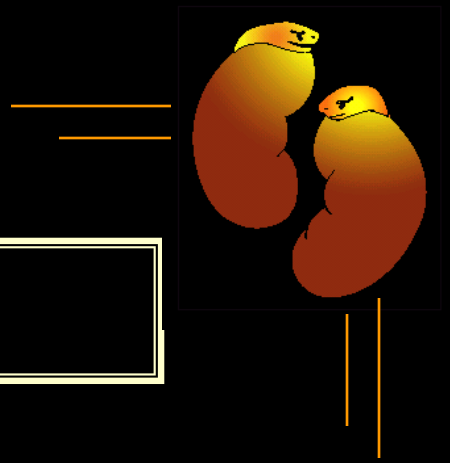
# Hyperadrenalism



# Hyperadrenalism

Three distinctive clinical syndromes:

- Excess cortisol: Cushing Syndrome
- Excess aldosterone: Conn Syndrome
- (Excess androgens: Adrenogenital or Virilizing Syndrome)



# 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

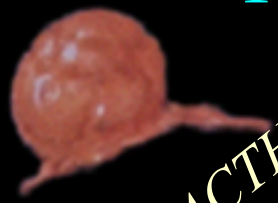
70-80%

*ACTH-dependent*

Pituitary adenoma

*Cushing Disease*

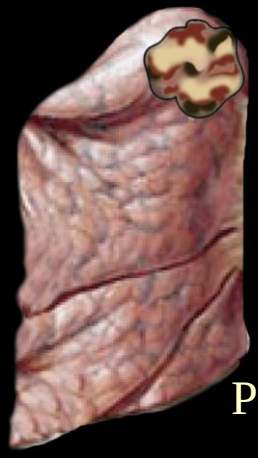
10-20%



*ACTH-independent*

Adrenal neoplasm

10%



*ACTH-dependent*

Paraneoplastic Syndrome

ACTH-producing tumor

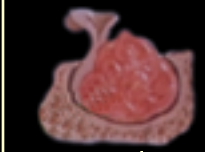
## Exogenous (Iatrogenic)

*Most common*

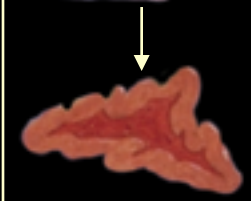
# “Endogenous” Cushing Syndrome

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

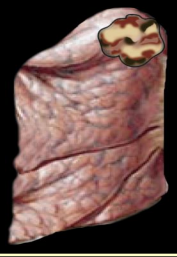
# Cushing Syndrome



Pituitary adenoma

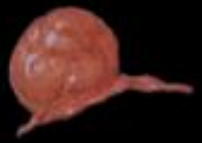


Adrenal cortical hyperplasia



ACTH-producing tumor

Adrenal carcinoma



Adrenal adenoma

CORTISOL

Dorsal fat pad

Ecchymoses

Thin skin

Moon face

Striae

Pendulous abdomen

Thin arms & legs

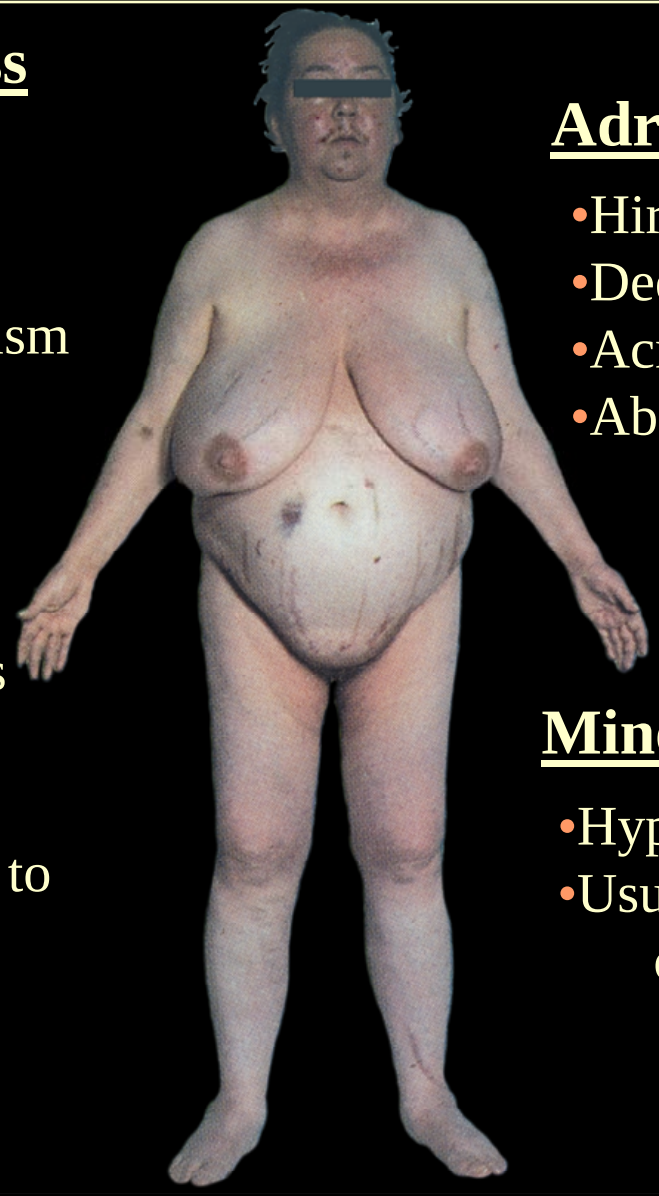
Poor wound healing

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



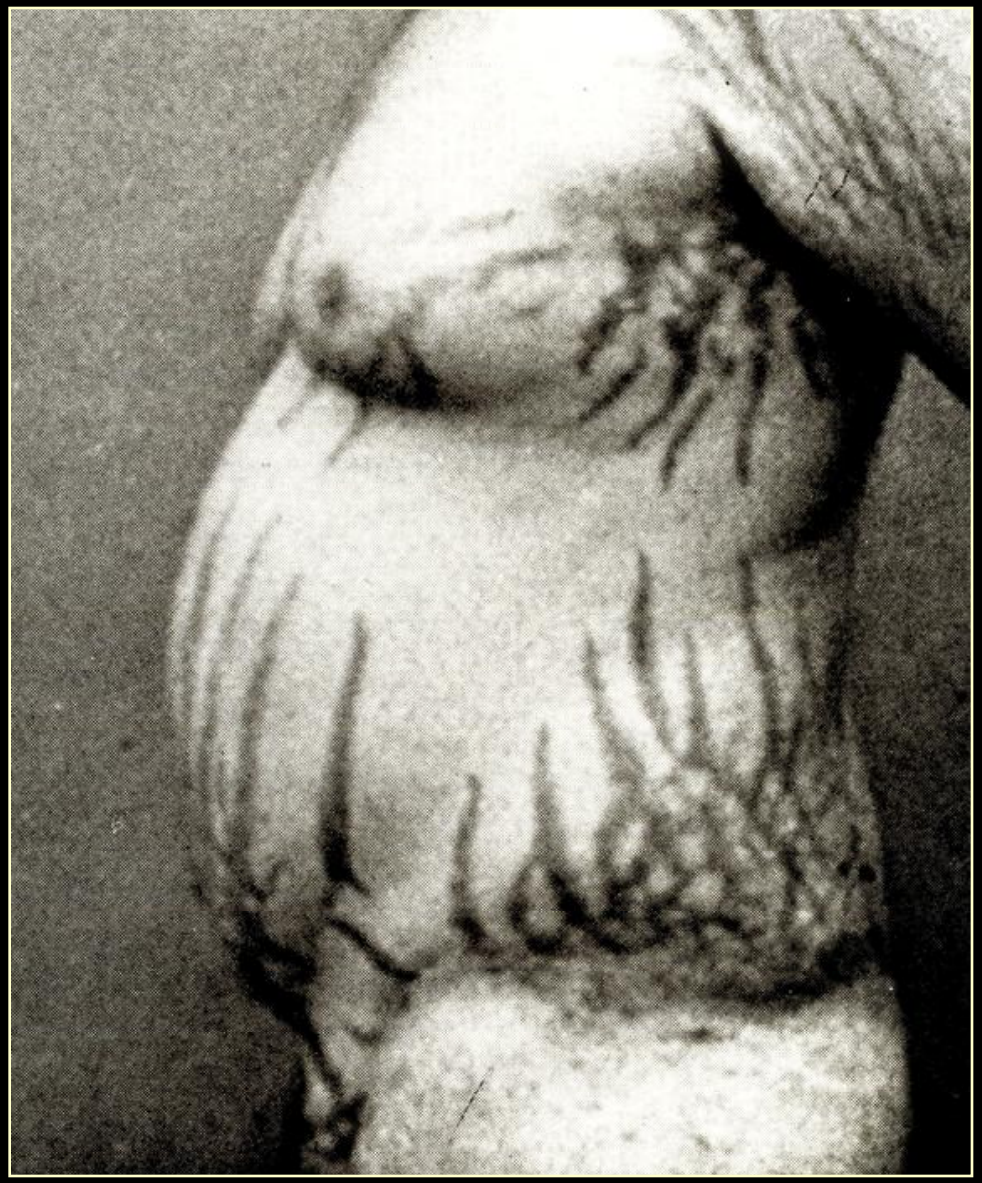
## Adrenal Androgen Excess

- Hirsutism
- Deepened voice in women
- Acne
- Abnormal menses

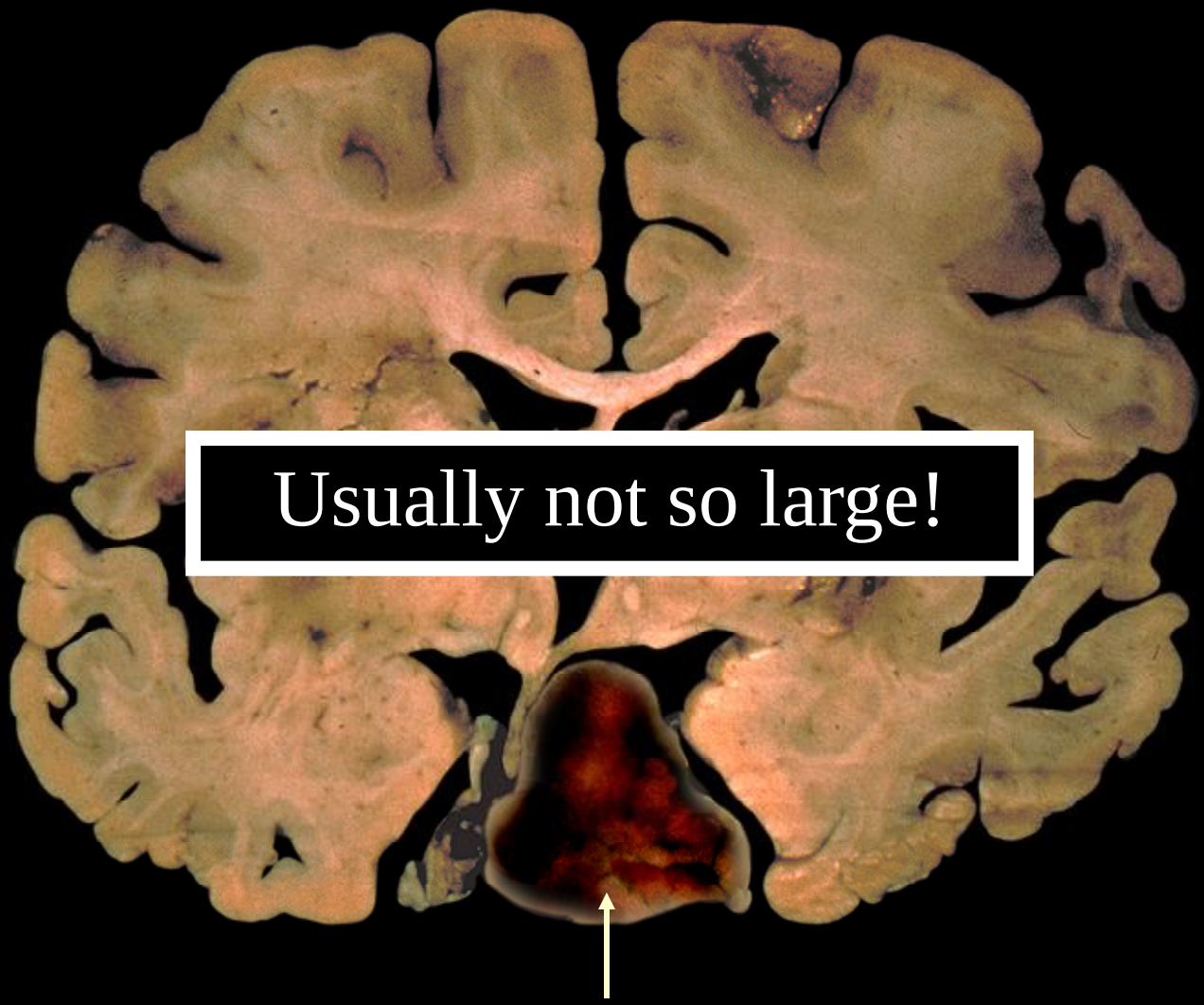
## Mineralocorticoid Excess

- Hypokalemia with alkalosis
- Usually occurs in cases of ectopic ACTH production

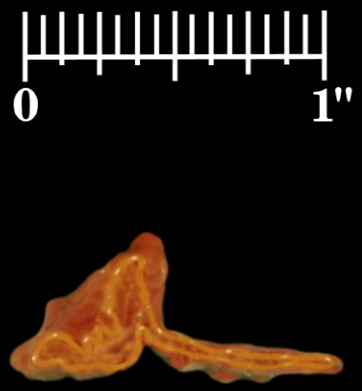
# Cushing Syndrome



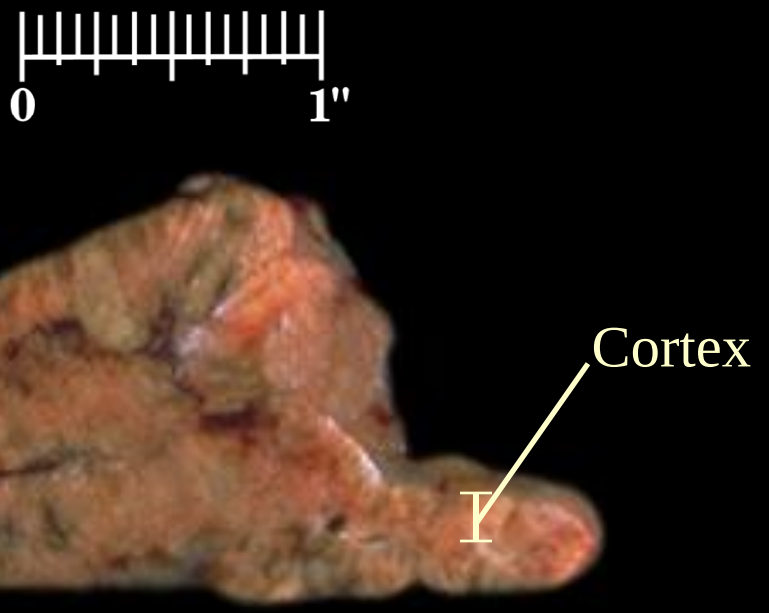
# Cushing *Disease*



# Adrenal cortical hyperplasia

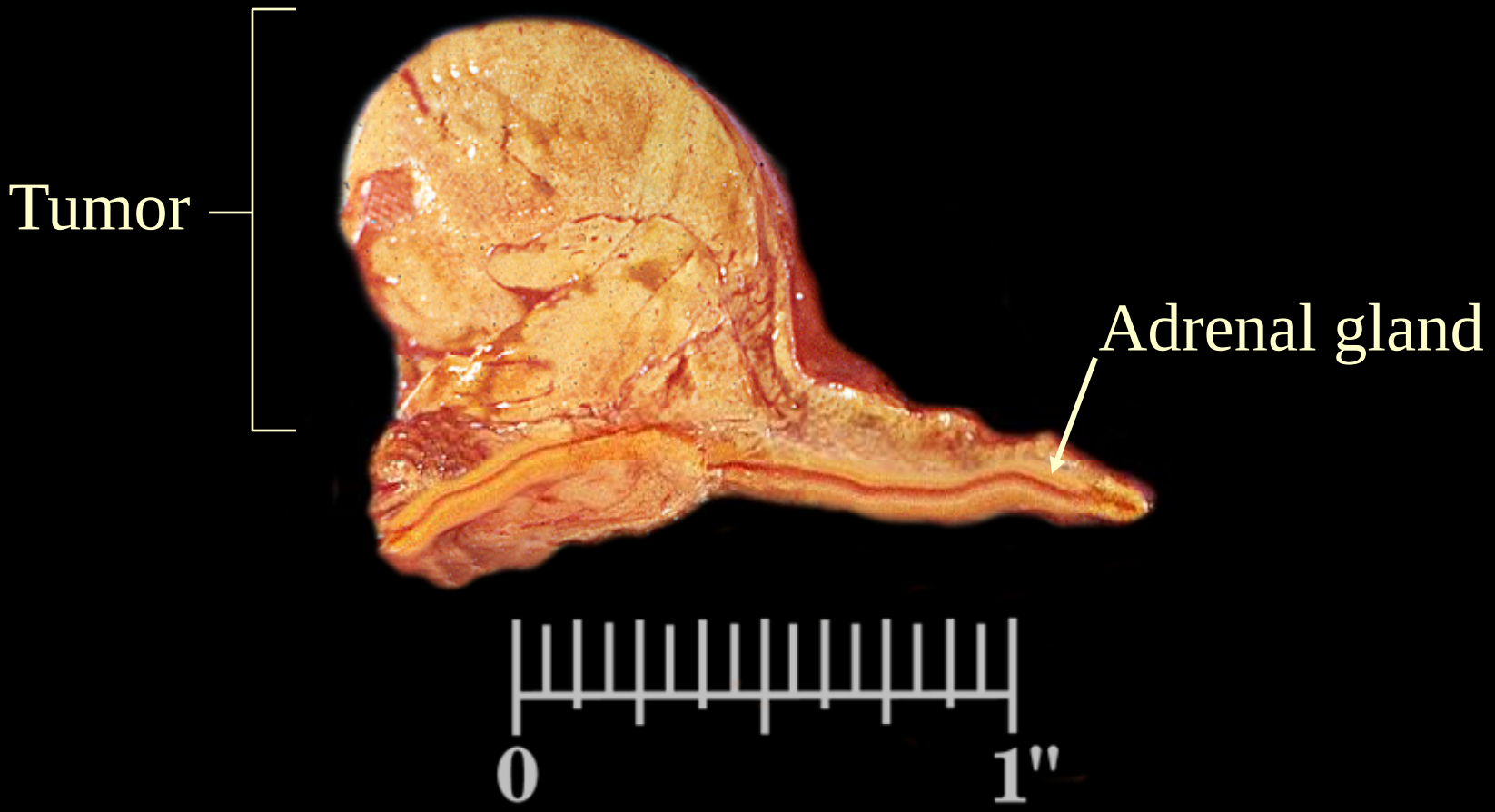


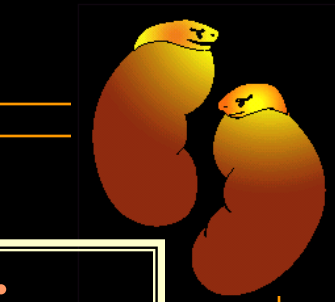

Normal




Cortical hyperplasia

# Adrenal cortical adenoma

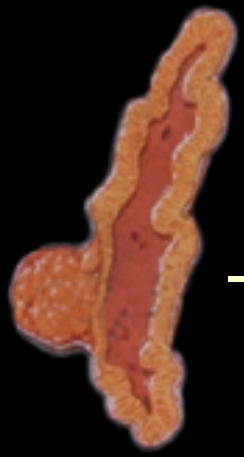




# Pathology of Primary Hyperaldosteronism

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

# Conn Syndrome



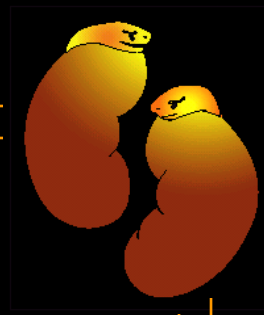
Adrenal adenoma

→ Aldosterone →

- Hypertension
- Polydipsia
- Polyuria
- Hypernatremia
- Hypokalemia

Adapted from Netter

# Cortical Neoplasms



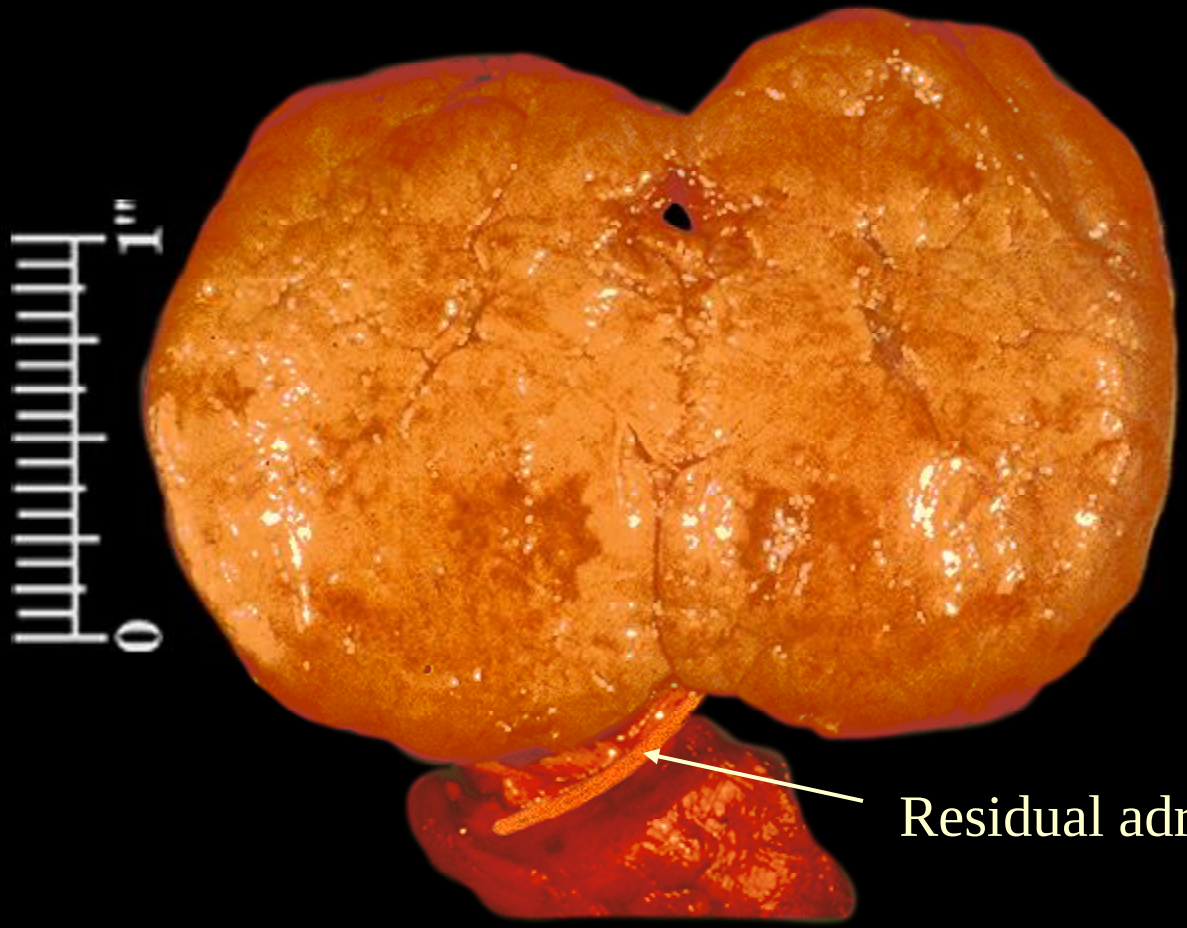
Adenomas and Carcinomas
- Functioning *
- Non-functioning

* May produce:
- Cortisol (Cushing Syndrome)
- Sex steroids
- Aldosterone (Conn Syndrome)

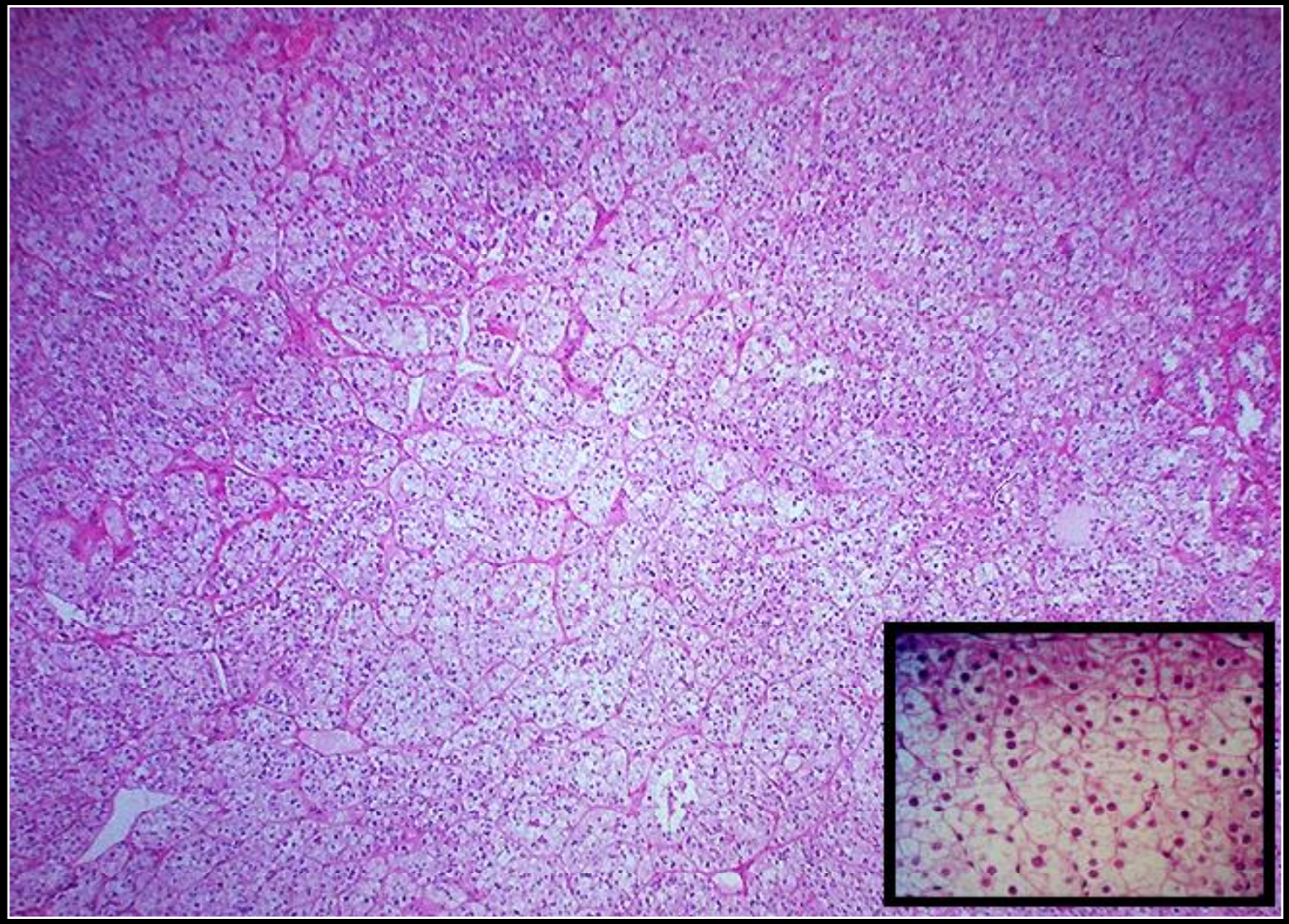
# Cortical Neoplasms

- 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

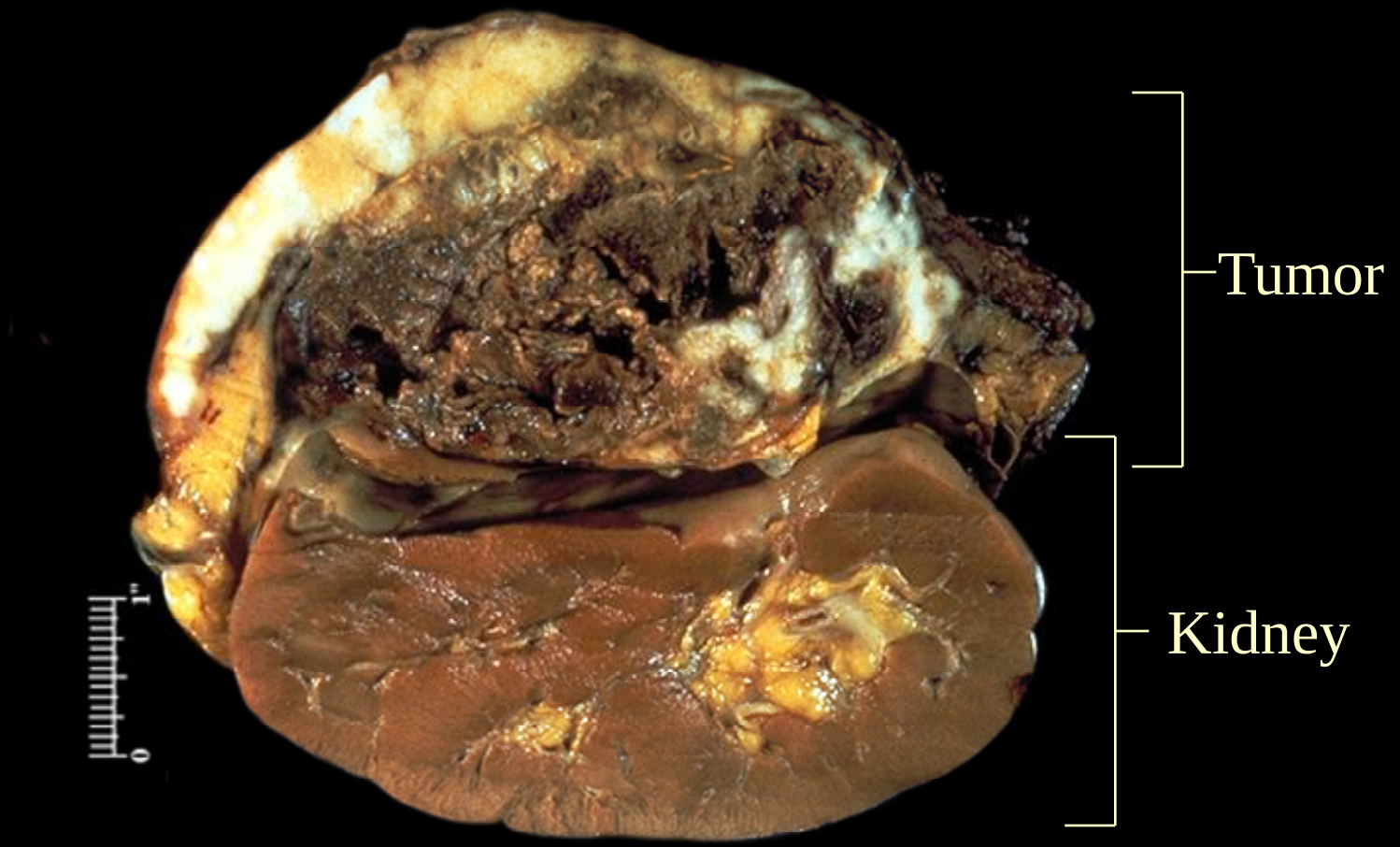
# Adrenal cortical adenoma



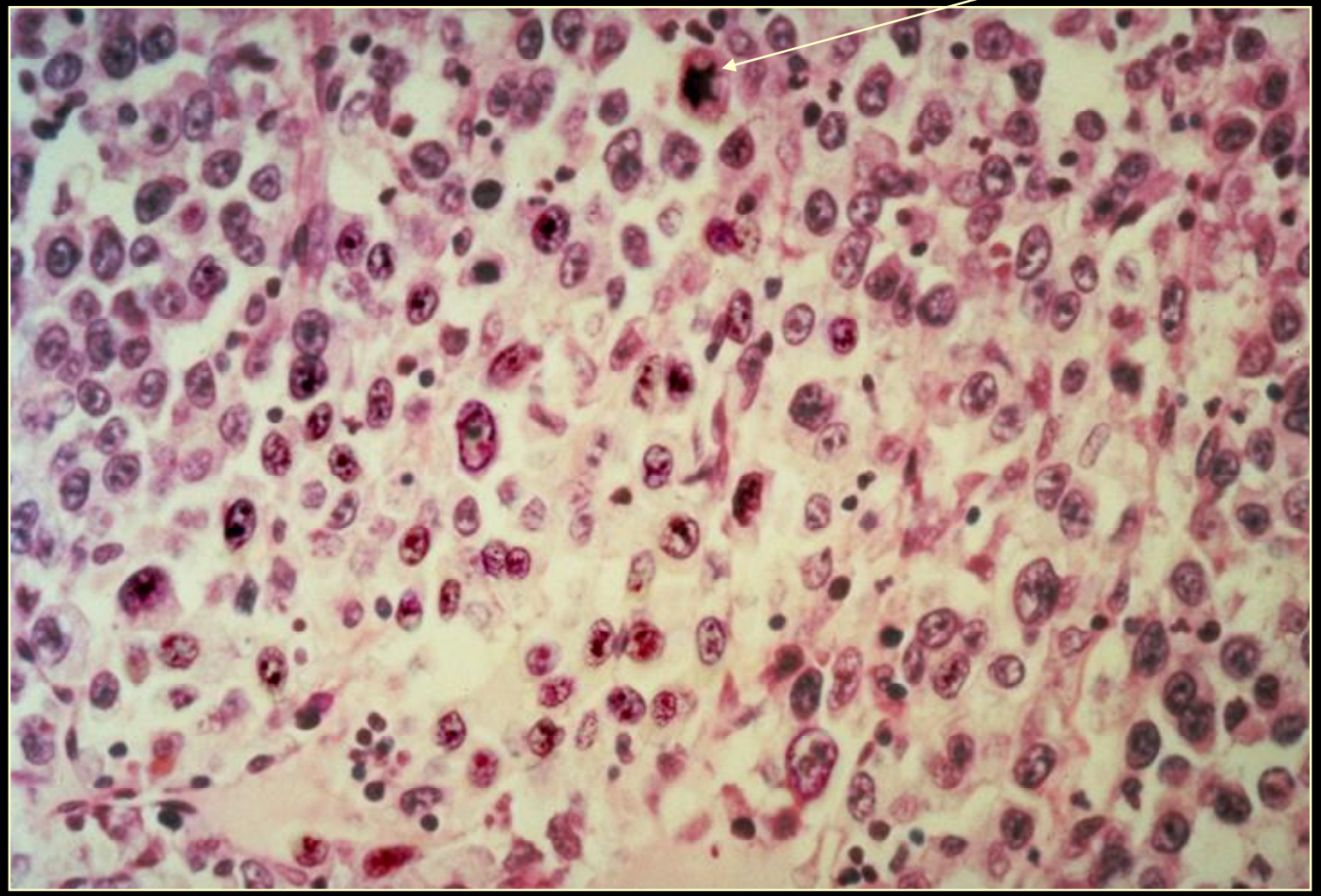
# Adrenal cortical adenoma

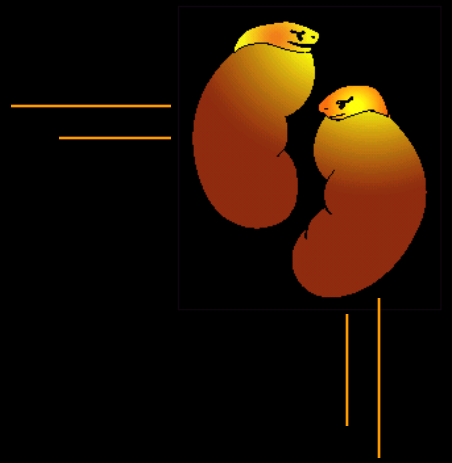


# Adrenal cortical carcinoma

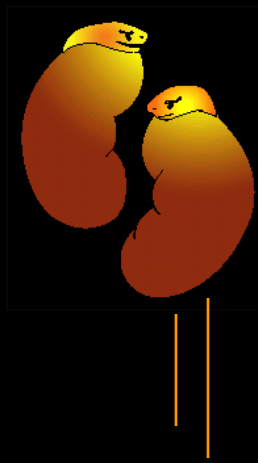


# Adrenal cortical carcinoma





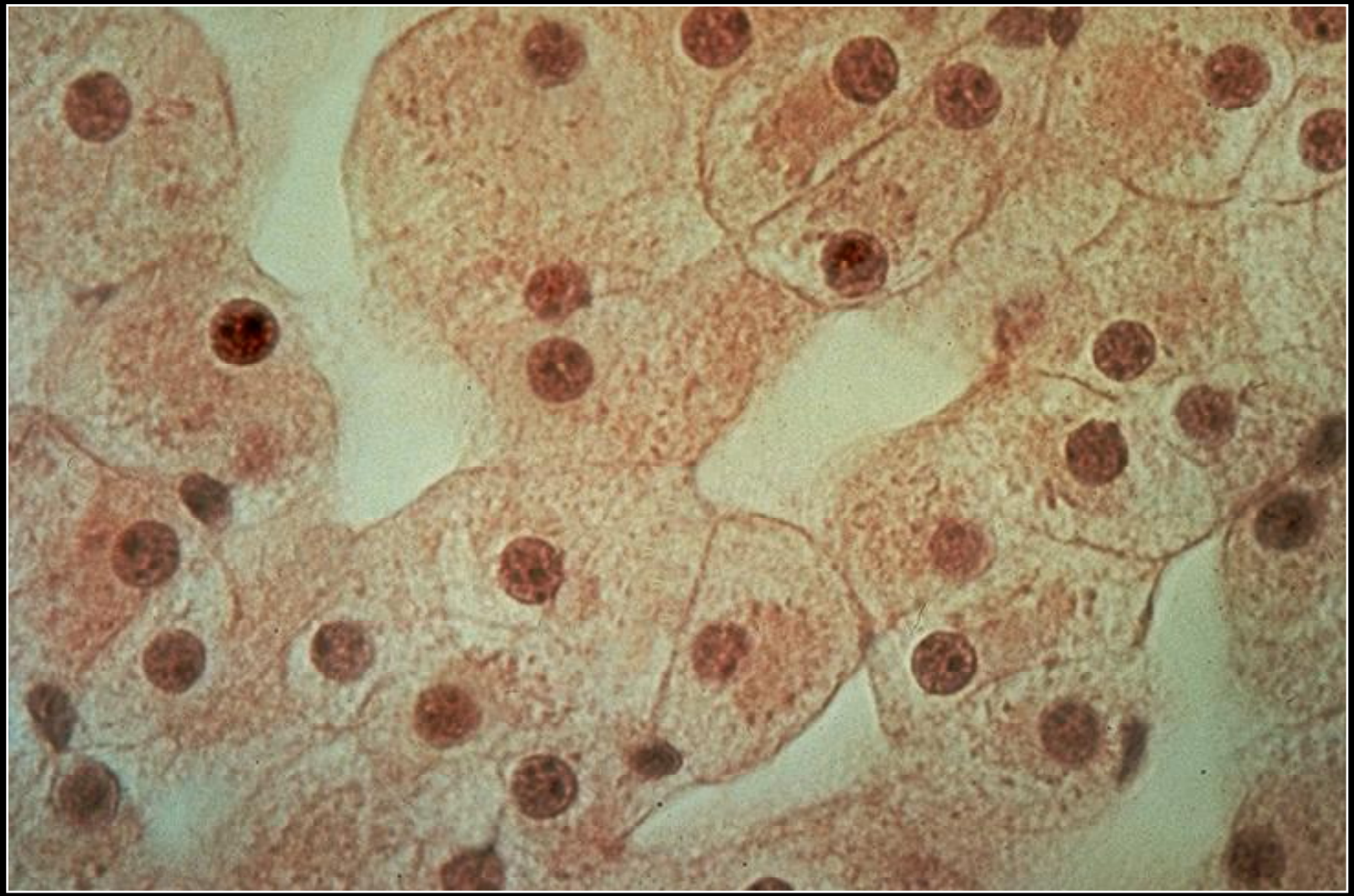
# Adrenal Medulla



# 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)

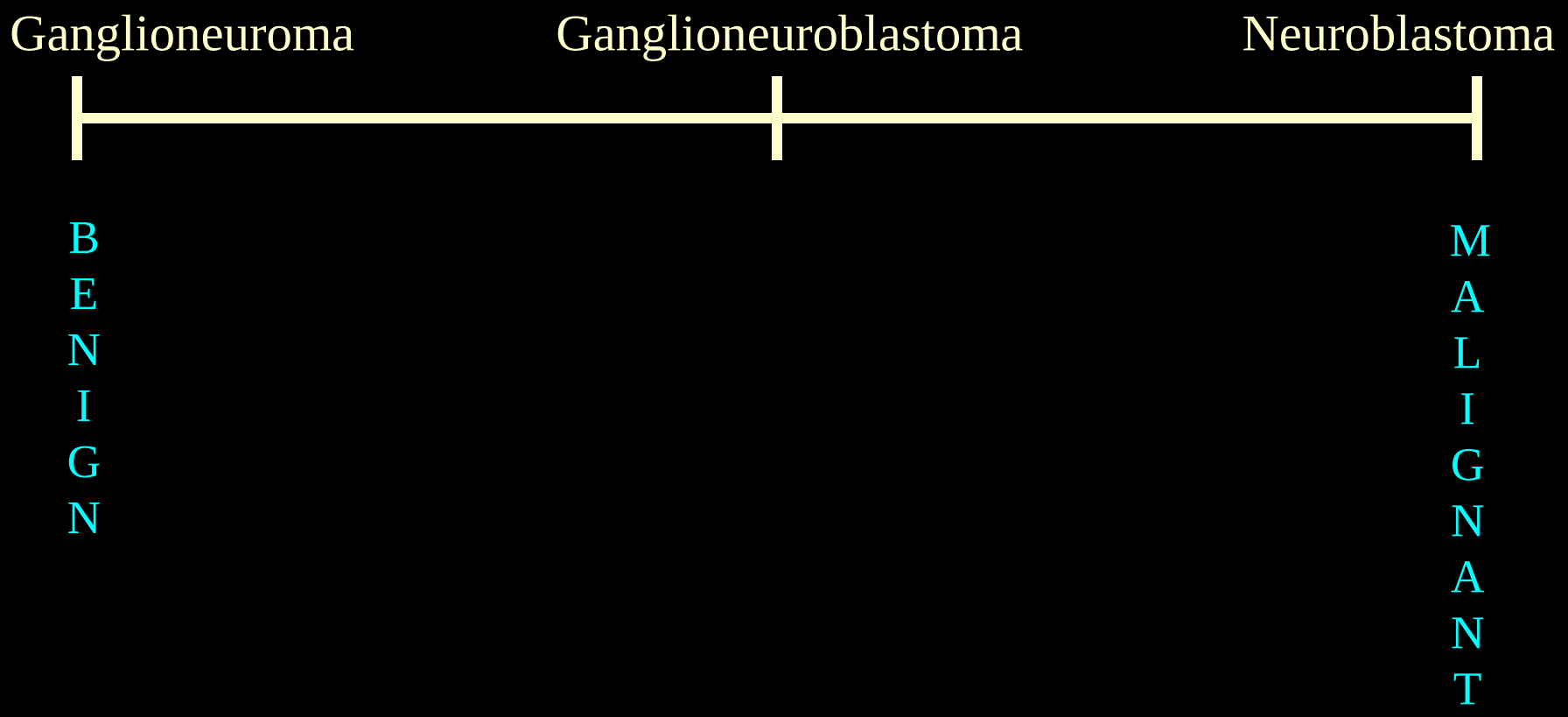
# Adrenal Medulla



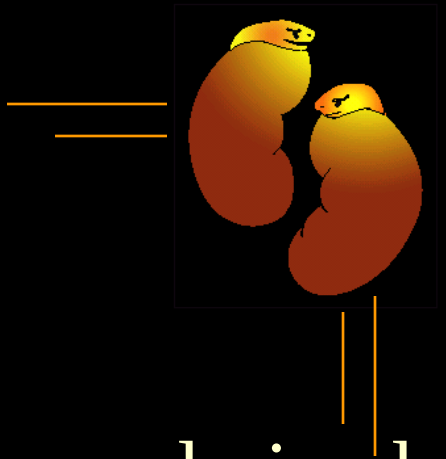
# Tumors of the Adrenal Medulla

- Neuroblastoma
- Ganglioneuroblastoma
- Ganglioneuroma

- Pheochromocytoma

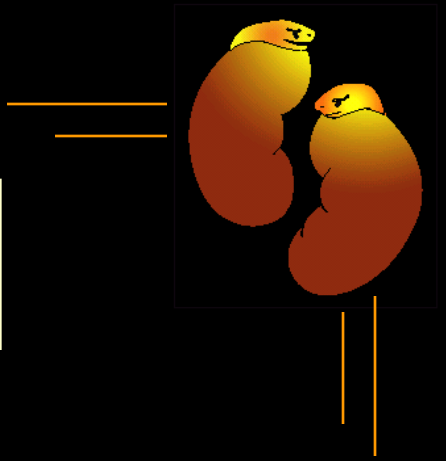

Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma
BENIGN
MALIGNANT

# Neuroblastoma



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

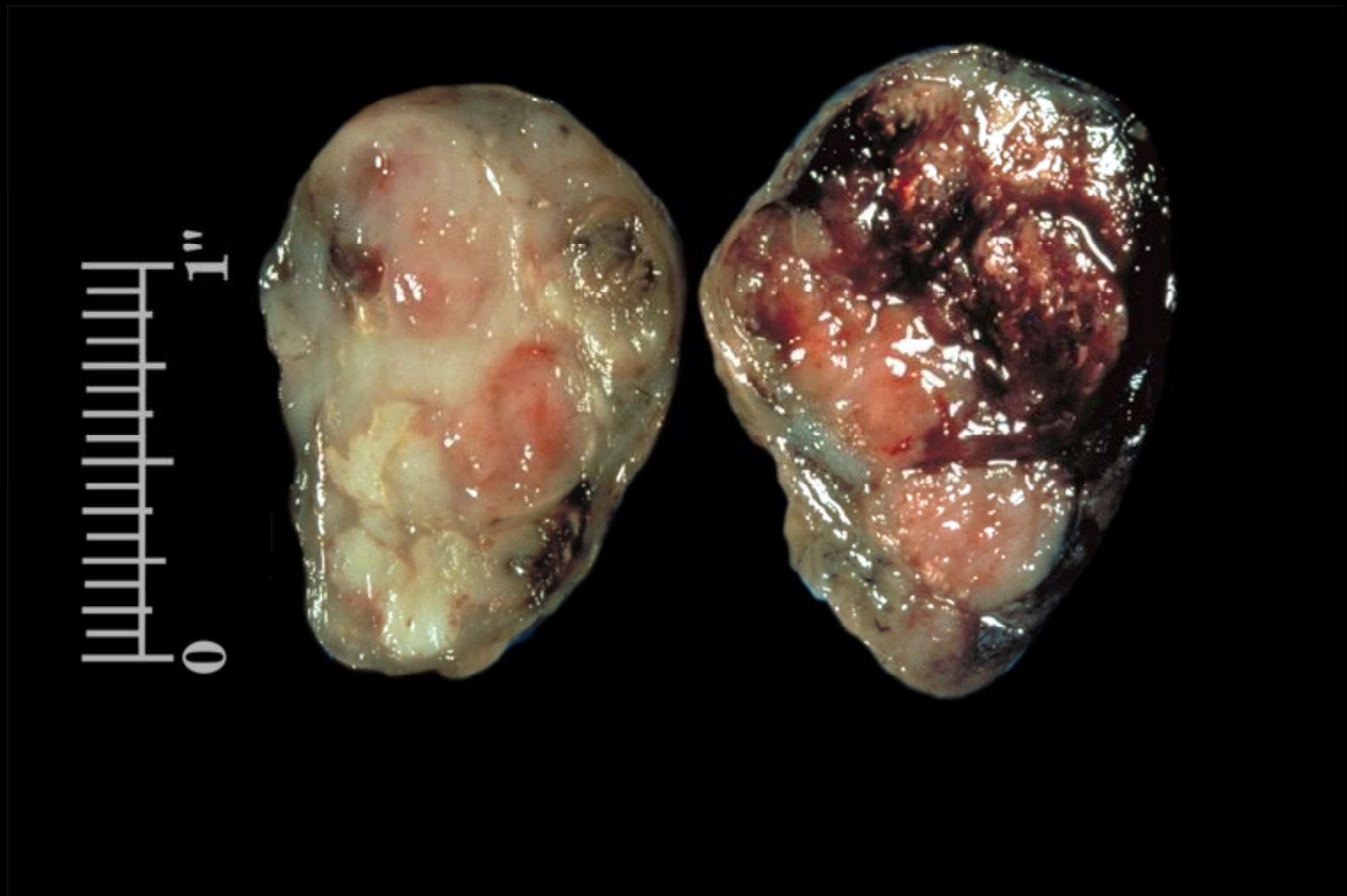
| | |
|---|---|
| Rhabdomyosarcoma | Lymphoma |
| Retinoblastoma | Wilms tumor |
| Ewing sarcoma/PNET | Medulloblastoma |



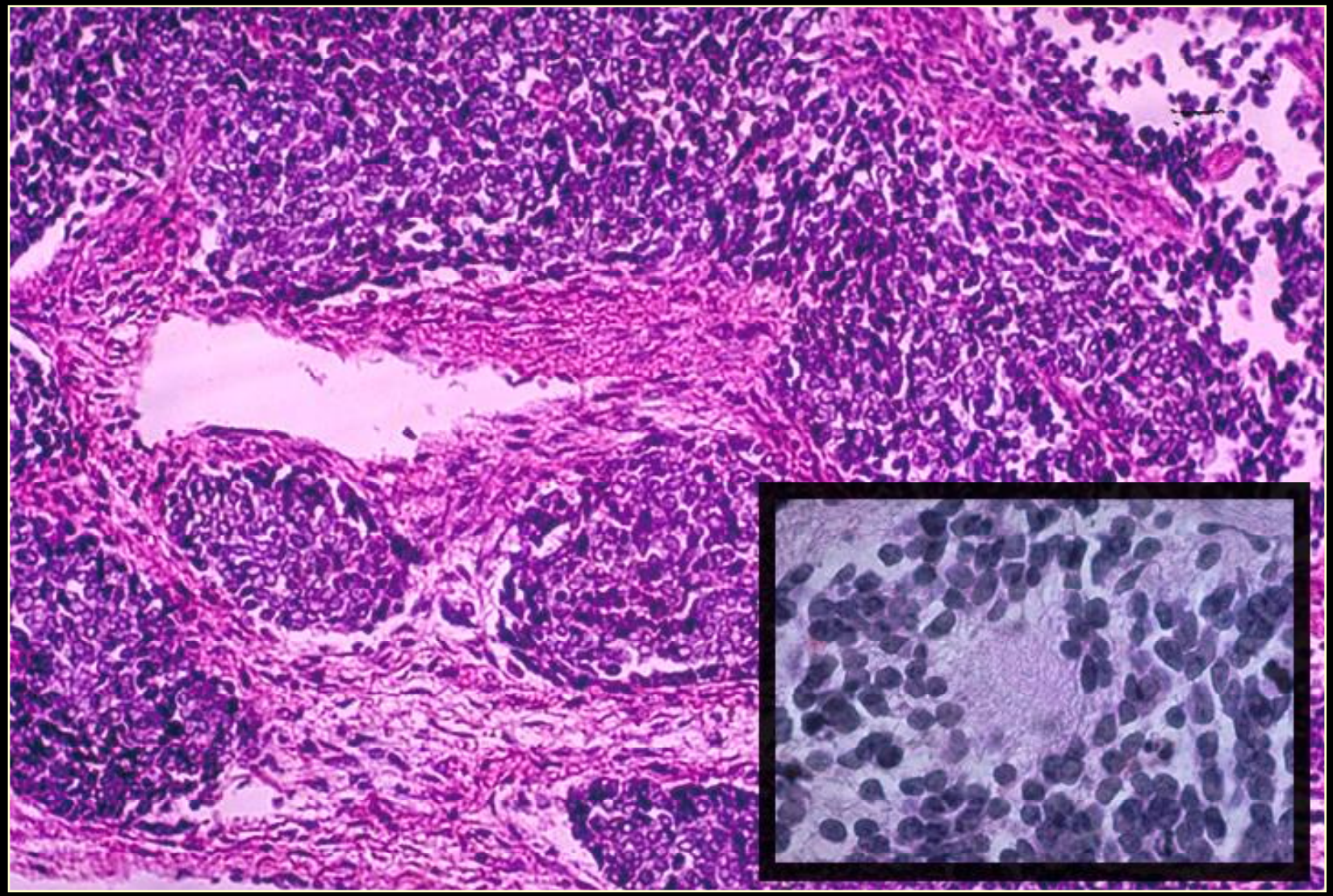
# Neuroblastoma: Pathology

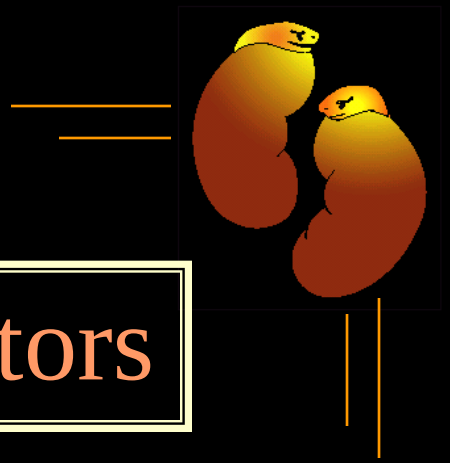
- Gross:
  - Large tumor with hemorrhage, necrosis, & calcification
- Micro:
  - Undifferentiated small cells resembling lymphocytes ("Small, round, blue cell tumor")
  - May show areas of *differentiation (larger cells with more cytoplasm and Schwannian stroma)*

# Neuroblastoma



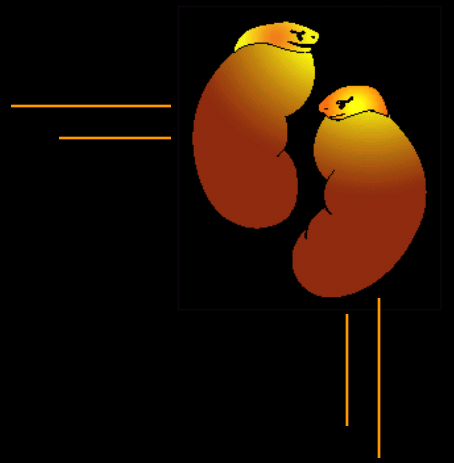
# Neuroblastoma





# Neuroblastoma: Prognostic Factors

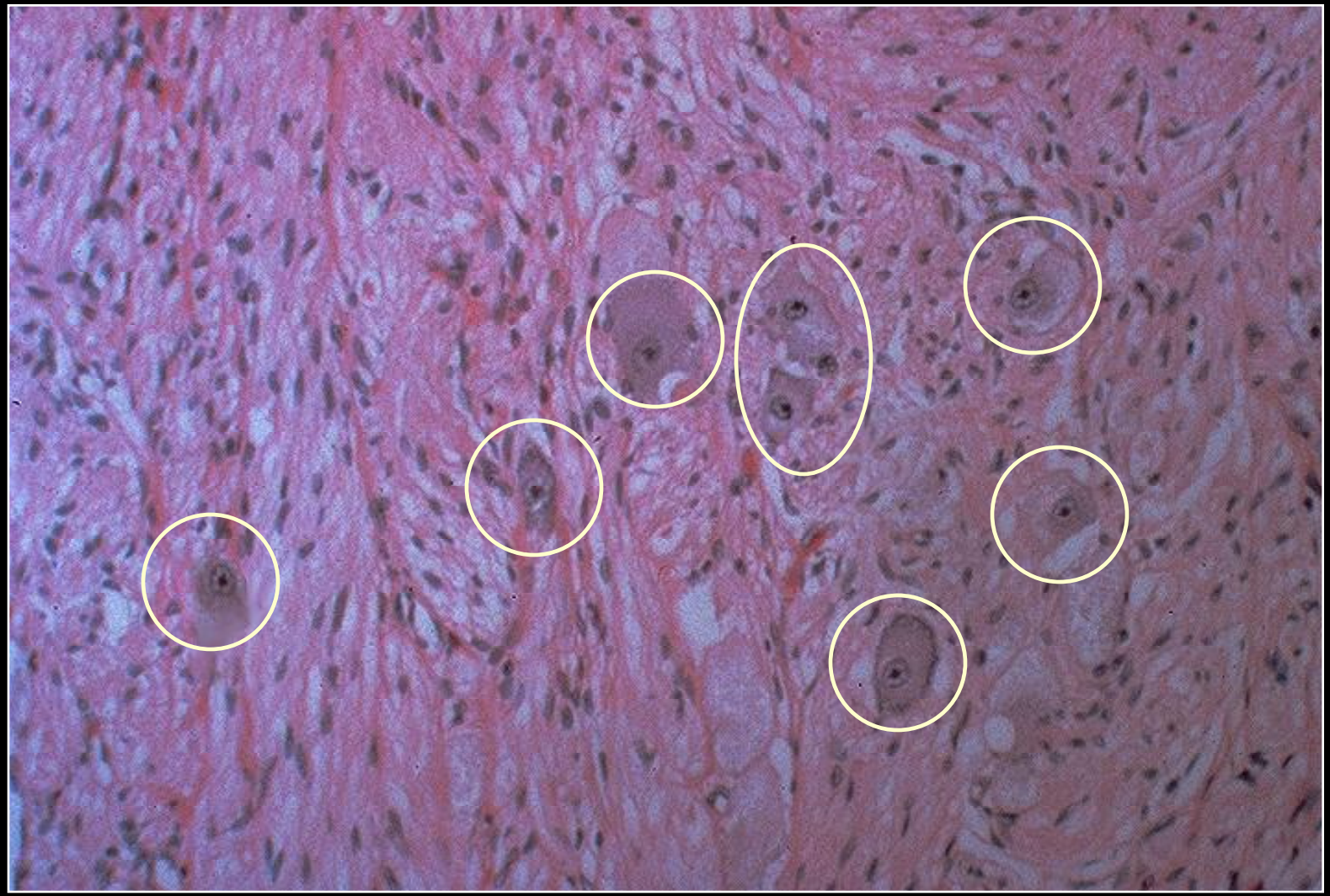
- Patient age
- Stage
- Site of $1^0$ involvement
- Histologic grade
- DNA ploidy
- N-myc oncogene amplification
- Others: Chromosome 17q gain, Chromosome 1p loss, Trk-A expression, Telomerase expression, MRP expression, CD44 expression

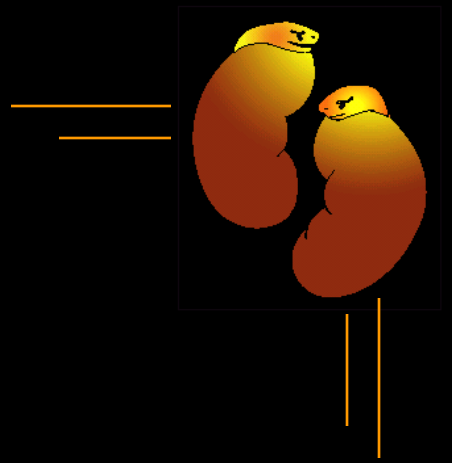


# Ganglioneuroma

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

# Ganglioneuroma

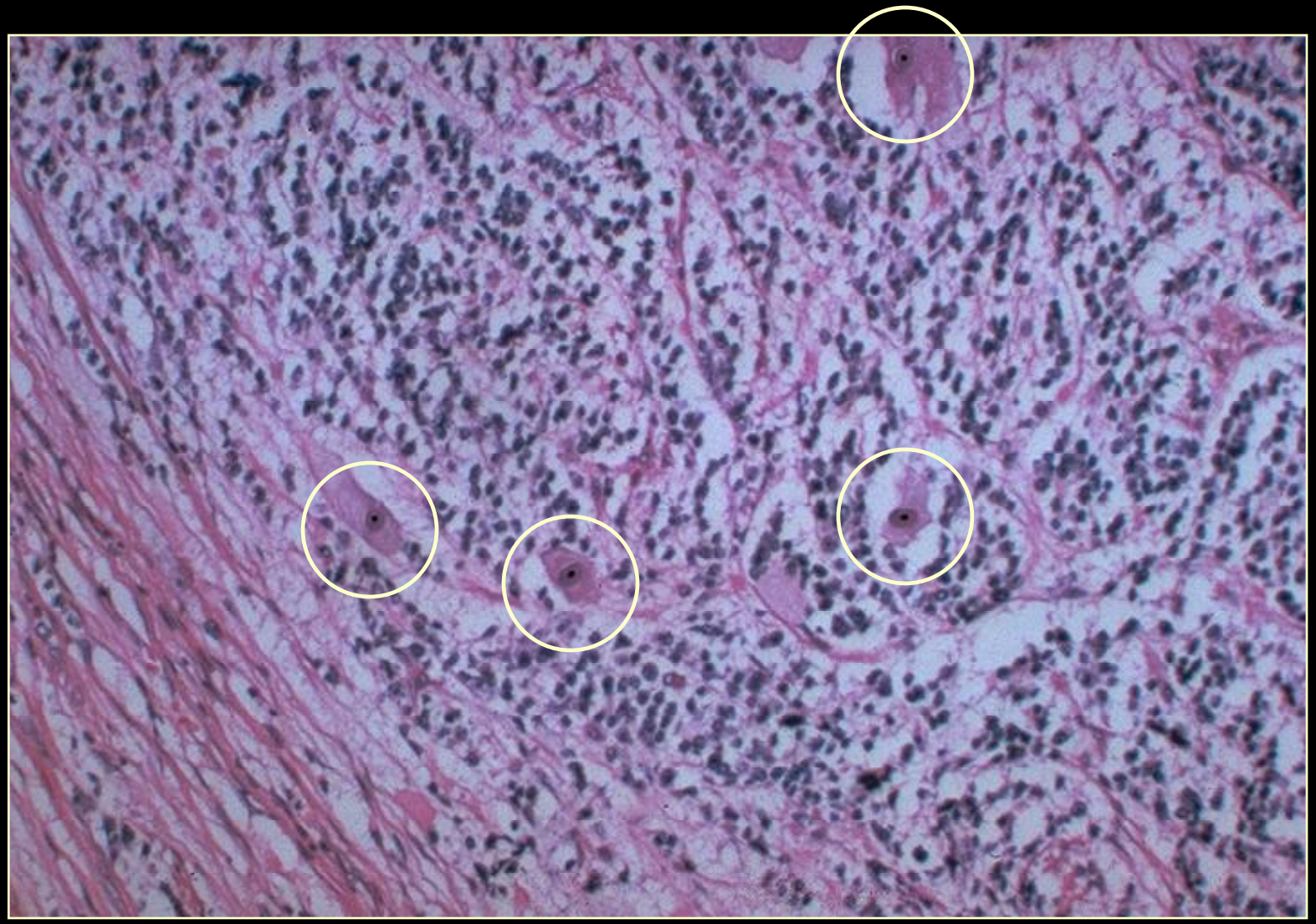




# Ganglioneuroblastoma

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

# Ganglioneuroblastoma



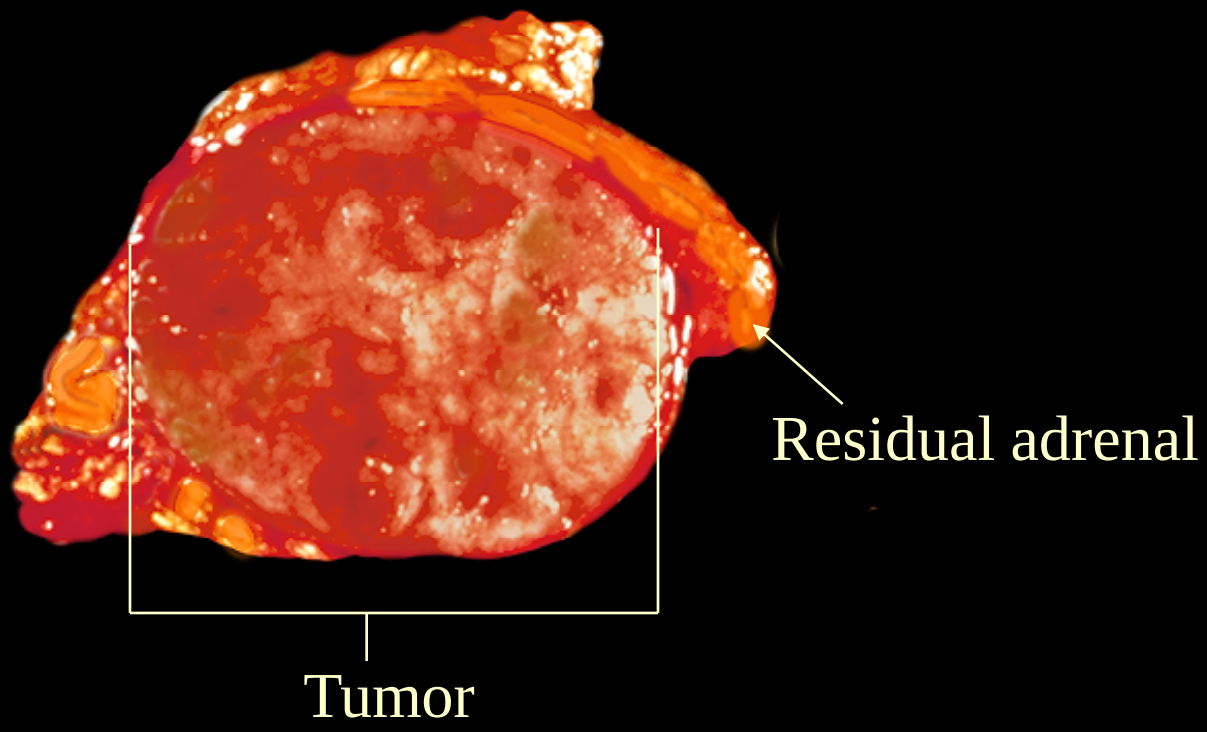
# Pheochromocytoma

- 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”

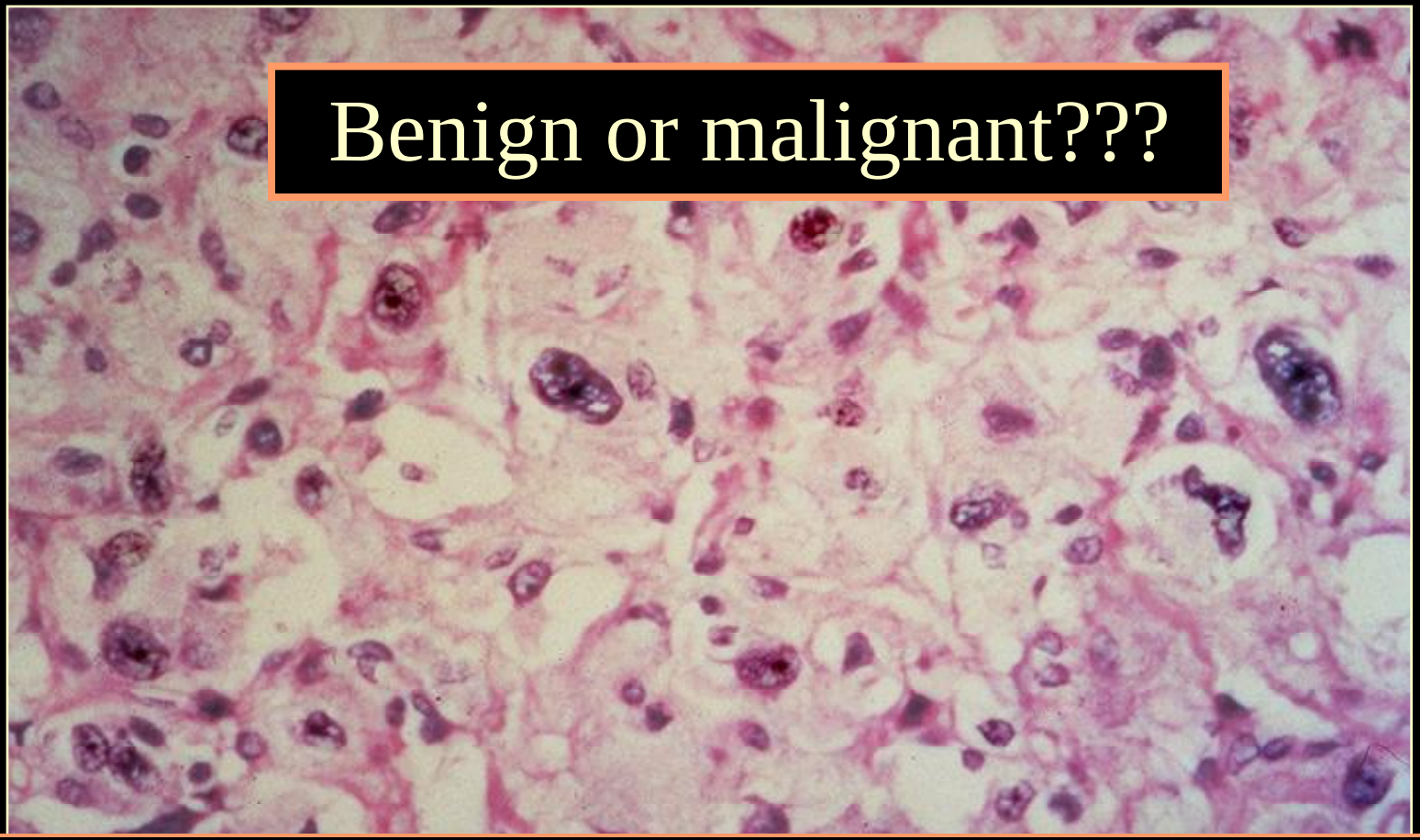
# Pheochromocytoma: Pathology

- 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




Benign & malignant tumors are histologically identical; the only absolute criterion for malignancy is *metastasis*.