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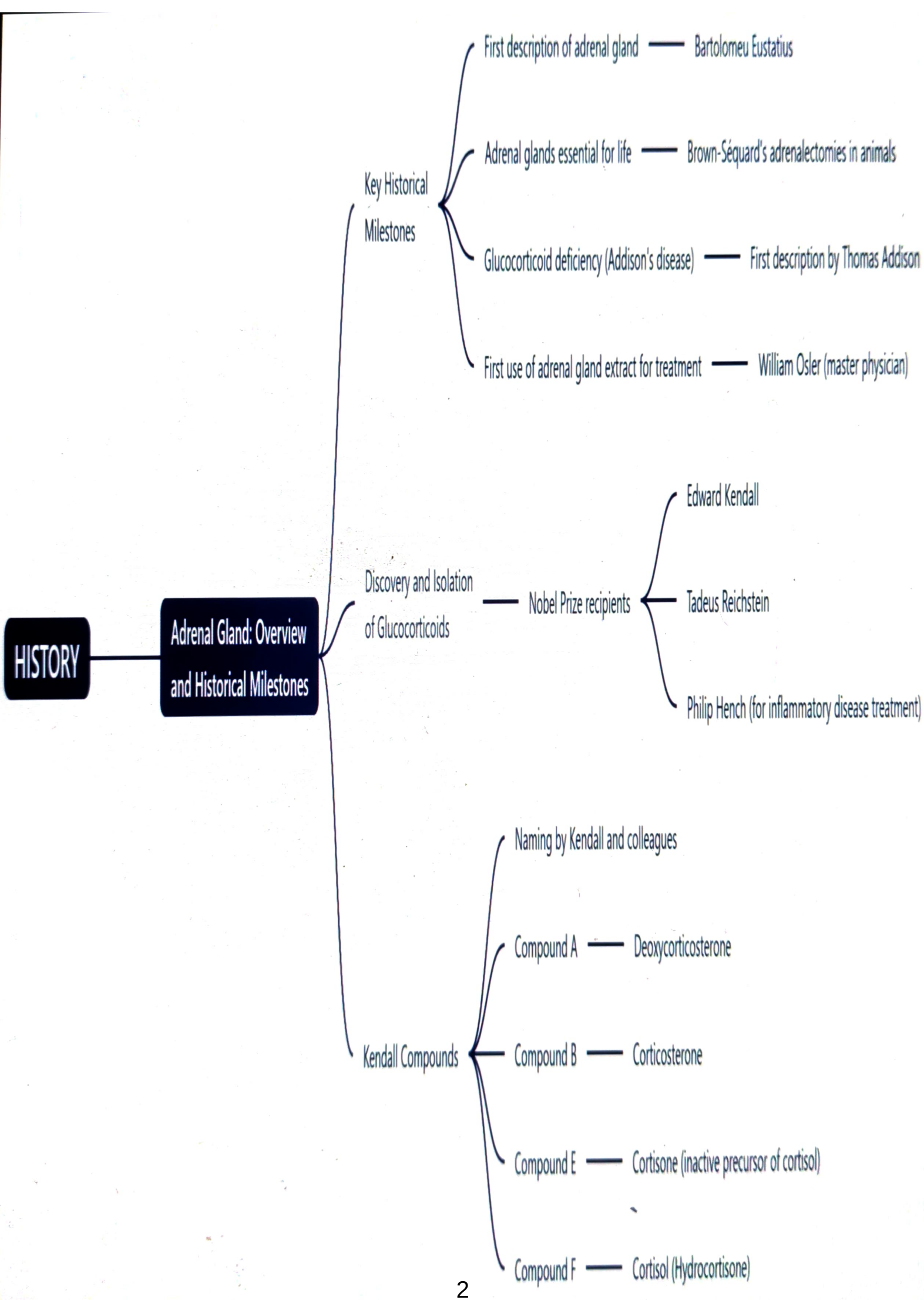


Endocrine

HISTORY

I. Adrenal Gland: Overview and Historical Milestones. 00:04:00

- **Key Historical Milestones of the Adrenal Gland:**
  - **First description of the adrenal gland: Bartolomeu Eustatius**
  - **Proposed adrenal glands are essential for life: Brown-Séquard.** He conducted adrenalectomies in animals, finding they could not survive long.
  - **First description of glucocorticoid deficiency (Addison's disease): Thomas Addison.**
  - **First used adrenal gland extract for Addison's disease treatment: William Osler** (also known as the master physician).
  - **Discovery and Isolation of Glucocorticoids & Nobel Prize:**
    1. **Edward Kendall and Tadeus Reichstein** were responsible for the discovery and isolation.
    2. **Philip Hench** was also awarded the Nobel Prize for identifying that glucocorticoids could treat inflammatory diseases, such as rheumatoid arthritis.
  - **Kendall Compounds:**
    1. Kendall and colleagues initially named the isolated compounds as "Kendall compounds".
    2. Compound A: Deoxycorticosterone.
    3. Compound B: Corticosterone.
    4. **Compound E: Cortisone** (an inactive form or precursor for cortisol).
    5. **Compound F: Cortisol** (also known as Hydrocortisone).

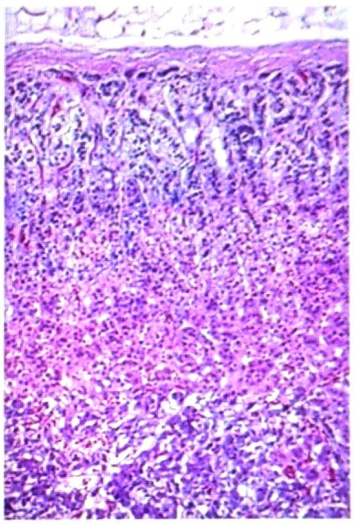

HISTORY
Adrenal Gland: Overview and Historical Milestones
Key Historical Milestones
First description of adrenal gland — Bartolomeu Eustatius
Adrenal glands essential for life — Brown-Séquard's adrenalectomies in animals
Glucocorticoid deficiency (Addison's disease) — First description by Thomas Addison
First use of adrenal gland extract for treatment — William Osler (master physician)
Discovery and Isolation of Glucocorticoids
Nobel Prize recipients
Edward Kendall
Tadeus Reichstein
Philip Hench (for inflammatory disease treatment)
Kendall Compounds
Naming by Kendall and colleagues
Compound A — Deoxycorticosterone
Compound B — Corticosterone
Compound E — Cortisone (inactive precursor of cortisol)
Compound F — Cortisol (Hydrocortisone)

ANATOMY & PHYSIOLOGY OF THE ADRENAL GLAND

Introduction 00:00:15

- The adrenal gland is a retroperitoneal structure composed of two main components: the cortex and the medulla. This division is significant for embryogenesis, structure, hormonal secretion, and function, leading to different clinical presentations and management strategies.

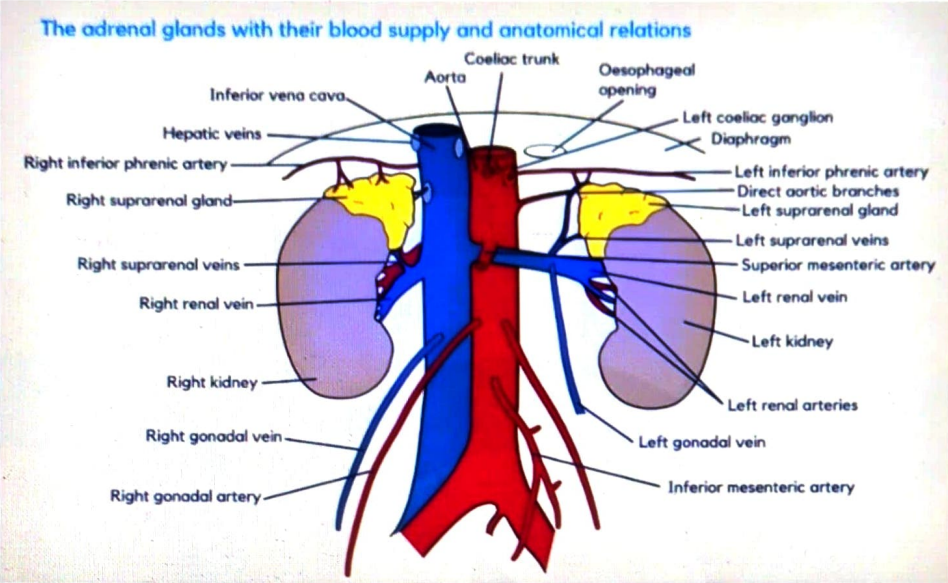
Microscopic Anatomy of the Adrenal Gland: 00:01:06



- The adrenal cortex develops from a single zone embryologically, progressing to a two-zone structure by 8-9 weeks, and finally to three distinct zones in the adult: the zona glomerulosa, zona fasciculata, and zona reticularis. The medulla is the innermost layer, which is encircled by the fetal cortex by the second trimester.
  - Zona Glomerulosa (Outermost Layer):
    - Corresponds to the definitive zone in the fetus.
    - Composed of small, closely packed, lipid-poor cells with moderate eosinophilic cytoplasm.
    - Accounts for approximately 15% of the adult cortex and forms an incomplete circumferential layer.
    - Responsible for mineralocorticoid secretion, primarily aldosterone.
    - Aldosterone regulates fluid volume and electrolyte balance by reabsorbing sodium and chloride, while exchanging potassium and hydrogen ions into the urine. It is part of the renin-angiotensin-aldosterone system (RAAS).
    - Clinical Relevance: Increased aldosterone secretion causes primary hyperaldosteronism (Conn syndrome if due to an adenoma), characterized by uncontrolled hypertension and episodic weakness of the lower limbs due to hypokalemia.
  - Zona Fasciculata (Middle Layer):
    - Corresponds to the transitional zone in the embryo.
    - Consists of clear, lipid-containing cells arranged in radial columns.
    - Forms the predominant part of the adult cortex, accounting for about 70%.
    - Responsible for glucocorticoid secretion, primarily cortisol.
    - Clinical Relevance: Excess glucocorticoid secretion can cause Cushing's syndrome.
  - Zona Reticularis (Innermost Cortical Layer):
    - Develops around 4-8 years of age, repopulating the fetal zone.
    - Composed of small, compactly arranged, eosinophilic cells.
    - Important for the production of sex steroids, such as dehydroepiandrosterone (DHEA).
  - Adrenal Medulla (Innermost Layer):
    - Arranged in clusters, nests, and cords.
    - Contains chromaffin cells, which produce a brownish color when reacting with chromium salts and are basophilic.
    - These cells possess secretory granules that contain epinephrine and norepinephrine.

Gross Anatomy of the Adrenal Gland 00:14:33

- The adrenal gland is a retroperitoneal, paravertebral structure located from the T11 to T12 vertebrae, superior to the kidney (hence "suprarenal gland"). It has an average weight of 4-6 grams and dimensions of approximately 5x3 cm.



- Right Adrenal Gland:
  - Typically triangular or pyramidal in shape, with its apex pointing superiorly and its base touching the upper pole of the kidney.
  - Relations:
    - Anterior: Posterior aspect of the liver (bare area).
    - Posterior: Diaphragm and pleura.
    - Medial: Inferior Vena Cava (IVC) and duodenum.
    - Inferior: Upper pole of the kidney.
  - The hilum is on its anterior surface and contains the right adrenal vein, a short (~0.5 cm), broad vessel that drains directly into the posterior part of the IVC.
- Left Adrenal Gland:
  - Semilunar or concentric in shape, positioned more medially and higher than the right adrenal gland.
  - Relations:
    - Anterior: Stomach and pancreas.
    - Posterior: Diaphragm and pleura.
    - Medial: Abdominal aorta.
    - Superior: Spleen.
    - Inferior: Upper pole of the left kidney.
  - Predominantly covered by the peritoneum of the lesser sac, making surgical access more challenging.
  - The left adrenal vein is longer and typically drains into the left renal vein, sometimes joined by the inferior phrenic vein.
  - Clinical Relevance: Left-sided adrenal tumors can extend thrombi into the renal vein and potentially the gonadal vein, leading to a varicocele.

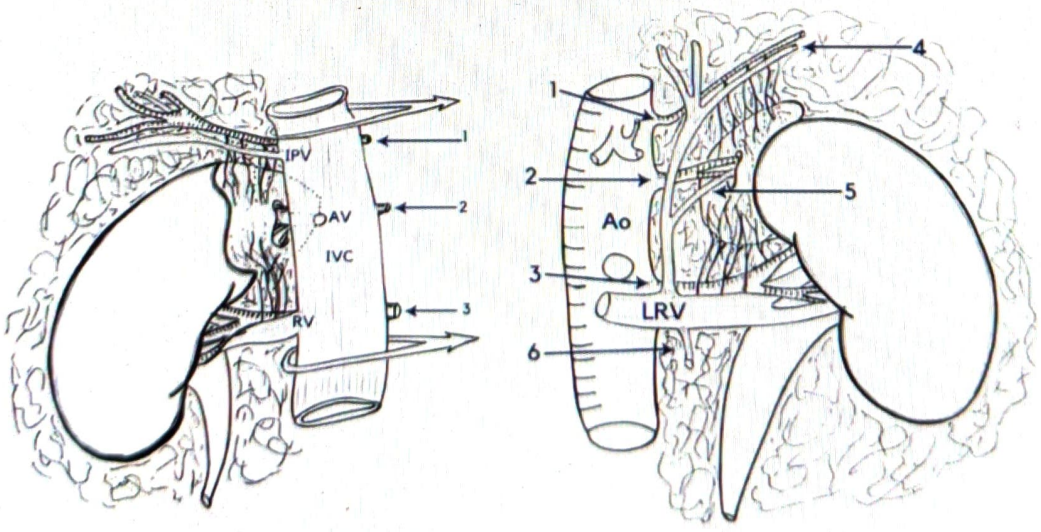
Right adrenal			Left adrenal	
Surface	Area	Description	Area	Description
Anterior	Medial	Not covered by peritoneum, posterior to the inferior vena cava	Superior	Covered with the peritoneum of the omental bursa, which separates it from the cardia and sometimes from the posterior extremity of the spleen
	Lateral	Upper part is in contact with the inferomedial angle of the bare area of the liver; lower part may be covered by peritoneum, reflected onto it from the inferior layer of the coronary ligament	Inferior	Not covered by peritoneum, in direct contact with the tail of pancreas and splenic artery
Posterior	Upper	Rests against the diaphragm	Medial	In contact with left crus of diaphragm
	Lower	In contact with the superior pole and the adjacent area of the anterior surface of the right kidney	Lateral	Close to the kidney
Medial border		Right celiac ganglion Right inferior phrenic artery		Left celiac ganglion Left inferior phrenic artery Left gastric arteries

Blood Supply

00:21:22

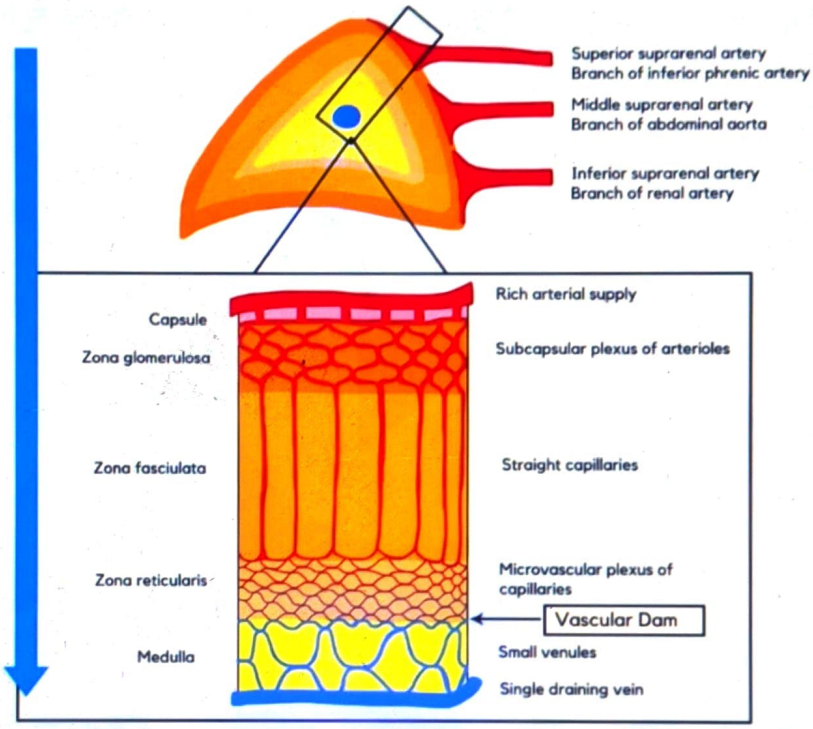
The adrenal gland has a rich blood supply.

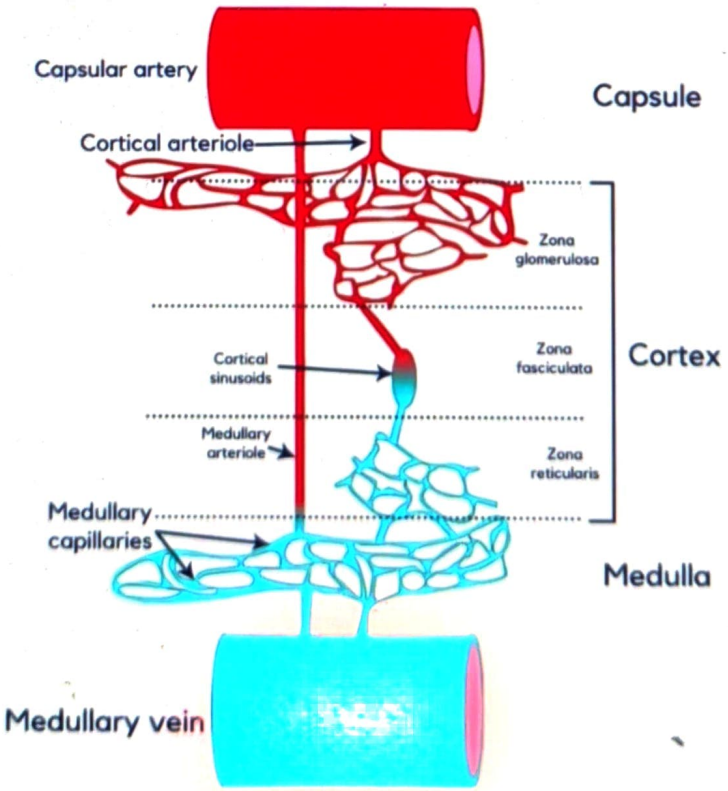
- Arterial Supply: Consists of three main branches on each side:
  - Superior adrenal artery, derived from the inferior phrenic artery.
  - The middle adrenal artery, a direct branch from the aorta.
  - Inferior adrenal artery, a branch from the renal artery.
  - Smaller feeder vessels may also arise from intercostal, ovarian/gonadal, or internal somatic arteries. Adrenal arterial vessels are generally small.
- Venous Drainage: Unlike the arteries, the adrenal veins are large vessels.
  - The right adrenal vein is short and drains directly into the posterior IVC.
  - The left adrenal vein is longer and drains into the left renal vein.
  - The adrenal vein is a crucial structure during adrenalectomy for pheochromocytoma because its ligation leads to a sudden drop in blood pressure, requiring careful management of intraoperative hemodynamics.



Microcirculation 00:30:00

- Adrenal arteries branch before piercing the capsule and form a subcapsular plexus in the zona glomerulosa. The blood flow is centripetal, moving from the periphery (outside) to the center (inside). Straight capillaries are found in the zona fasciculata, while a deep capillary plexus exists in the zona reticularis. This deep plexus eventually drains into the medullary veins. Cortisol, produced in the cortex, reaches the adrenal medulla via this pathway, acting as a cofactor for the enzyme phenylethanolamine N-methyltransferase (PNMT), which converts norepinephrine to epinephrine. The medulla has a dual blood supply: over 95% is indirect via the cortical pathway, and less than 5% is direct. Muscular fibers at the corticomedullary junction help regulate blood flow.





Lymphatic Drainage 00:36:32

- The adrenal gland has two main lymphatic plexuses: a subcapsular plexus and a medullary plexus. The primary lymphatic drainage is to the paracaval territory, specifically the lateral aortic and preaortic lymph nodes up to the diaphragm. Some lymphatic vessels can cross the diaphragm and drain into the mediastinum, serving as a route for adrenal cortical cancer metastasis.

Nerve Supply 00:37:38

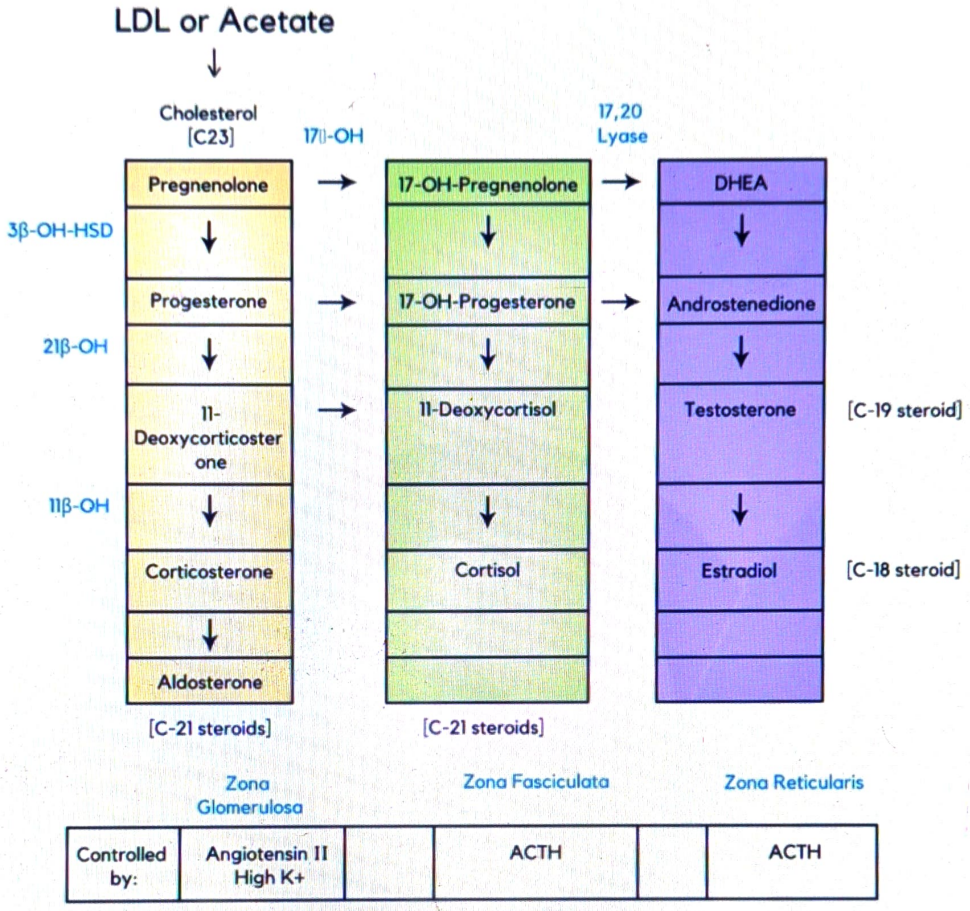
- The adrenal medulla is a neuroendocrine organ that converts electrical nerve signals (action potentials) into endocrine chemical signals. Presynaptic splanchnic nerves (sympathetic fibers) connect directly to the chromaffin cells in the medulla, which are analogous to postganglionic sympathetic neurons. Acetylcholine release at these junctions causes calcium influx, triggering the exocytosis of secretory granules and hormone release. Pheochromocytomas, however, lack innervation and thus release hormones without requiring a neuronal stimulus. This principle is used in the clonidine suppression test for diagnosing pheochromocytoma, as clonidine (a centrally acting agent that blocks neuronal signals) does not suppress hormone output from an innervated tumor.

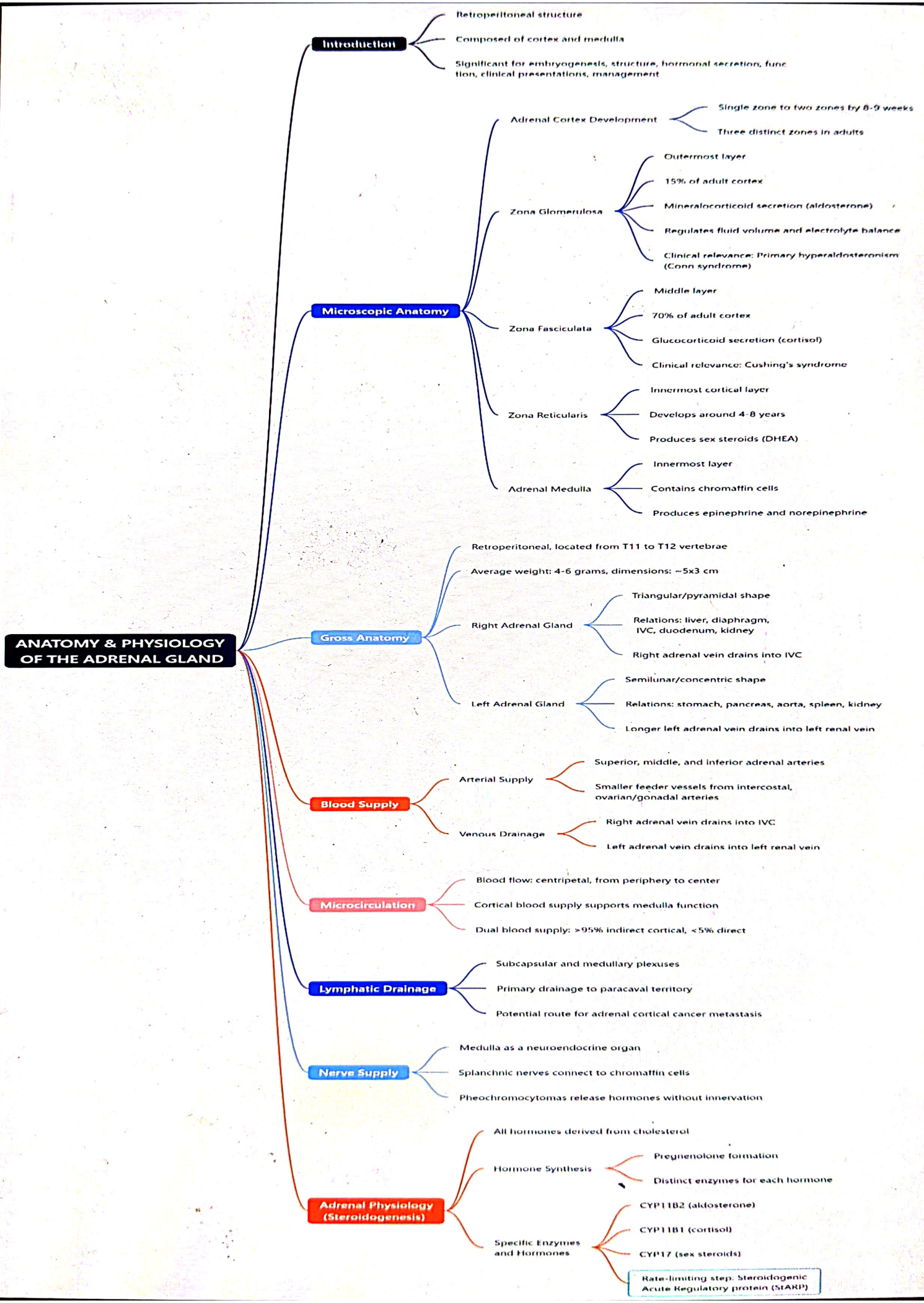
Adrenal Physiology (Steroidogenesis) 00:40:45

- All adrenal cortical hormones are derived from cholesterol, which is considered the "mother of all adrenal cortical hormones". The synthesis of these hormones (steroidogenesis) occurs in the inner mitochondrial membrane, requiring cholesterol to be transported from the cytoplasm to this membrane. This transport is facilitated by the Steroidogenic Acute Regulatory protein (StARP), which is the rate-limiting step in steroidogenesis.
  - Cholesterol first undergoes side-chain cleavage to form pregnenolone.
  - Different hormones are produced in specific adrenal cortical zones due to the presence of distinct enzymes:
    - CYP11B2 is found only in the zona glomerulosa and is responsible for aldosterone formation.
    - CYP11B1 is present in the zona fasciculata and is responsible for cortisol formation.
    - CYP17 (17-alpha hydroxylase) is found in both the zona fasciculata and zona reticularis, responsible for the formation of sex steroids (androgens).
  - Steroids are classified by carbon configuration: C-21 steroids have mineralocorticoid activity, C-19 steroids have androgenic activity, and C-18 steroids have estrogenic activity.
  - Pregnenolone is a precursor that is converted into various hormones depending on the location and specific enzymes present.
  - In the physical layers, pregnenolone is converted by C by p 17 to form sex steroids and cortisol.
  - In the zona glomerulosa, pregnenolone undergoes a series of reactions to form aldosterone.
  - Specific Enzymes and their Hormones:
    - SIB 17 is responsible for androgen formation and sex steroids.
    - KP 11 B two (SIB 11 b two) is responsible for the formation of aldosterone.

➢ Sipi 11 B one (11 B one) is responsible for the formation of cortisol.

- The rate-limiting enzyme in steroidogenesis is the Star (Steroidal Acute Regulatory protein).



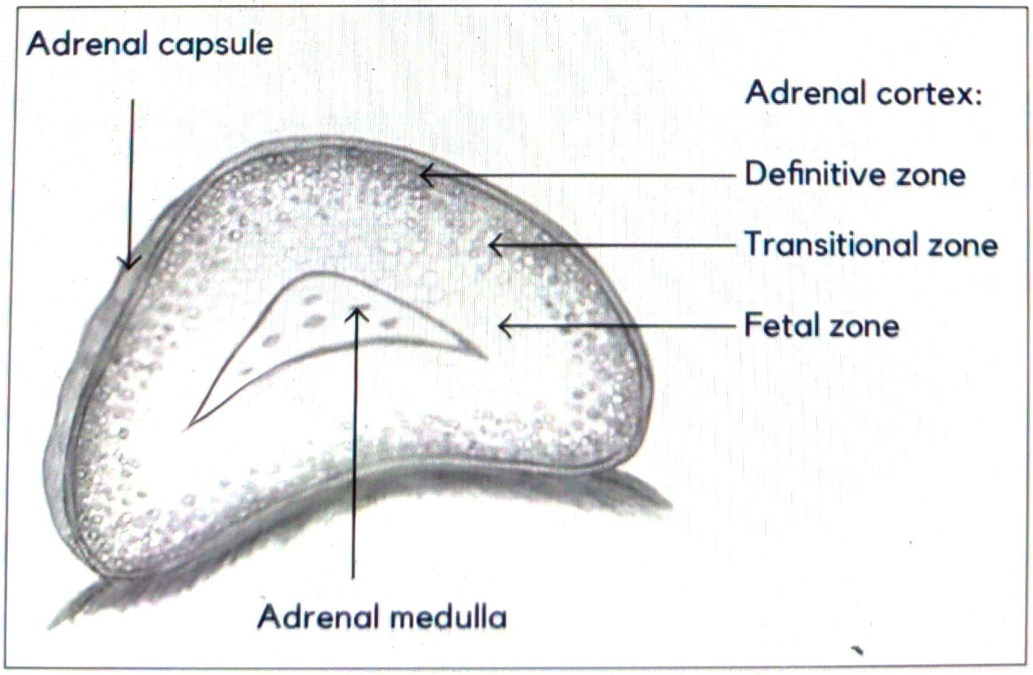

ANATOMY & PHYSIOLOGY OF THE ADRENAL GLAND
Introduction
Retroperitoneal structure
Composed of cortex and medulla
Significant for embryogenesis, structure, hormonal secretion, function, clinical presentations, management
Microscopic Anatomy
Adrenal Cortex Development
Single zone to two zones by 8-9 weeks
Three distinct zones in adults
Zona Glomerulosa
Outermost layer
15% of adult cortex
Mineralocorticoid secretion (aldosterone)
Regulates fluid volume and electrolyte balance
Clinical relevance: Primary hyperaldosteronism (Conn syndrome)
Zona Fasciculata
Middle layer
70% of adult cortex
Glucocorticoid secretion (cortisol)
Clinical relevance: Cushing's syndrome
Zona Reticularis
Innermost cortical layer
Develops around 4-8 years
Produces sex steroids (DHEA)
Adrenal Medulla
Innermost layer
Contains chromaffin cells
Produces epinephrine and norepinephrine
Gross Anatomy
Retroperitoneal, located from T11 to T12 vertebrae
Average weight: 4-6 grams, dimensions: ~5x3 cm
Right Adrenal Gland
Triangular/pyramidal shape
Relations: liver, diaphragm, IVC, duodenum, kidney
Right adrenal vein drains into IVC
Left Adrenal Gland
Semilunar/concentric shape
Relations: stomach, pancreas, aorta, spleen, kidney
Longer left adrenal vein drains into left renal vein
Blood Supply
Arterial Supply
Superior, middle, and inferior adrenal arteries
Smaller feeder vessels from intercostal, ovarian/gonadal arteries
Venous Drainage
Right adrenal vein drains into IVC
Left adrenal vein drains into left renal vein
Microcirculation
Blood flow: centripetal, from periphery to center
Cortical blood supply supports medulla function
Dual blood supply: >95% indirect cortical, <5% direct
Lymphatic Drainage
Subcapsular and medullary plexuses
Primary drainage to paracaval territory
Potential route for adrenal cortical cancer metastasis
Nerve Supply
Medulla as a neuroendocrine organ
Splanchnic nerves connect to chromaffin cells
Pheochromocytomas release hormones without innervation
Adrenal Physiology (Steroidogenesis)
All hormones derived from cholesterol
Hormone Synthesis
Pregnenolone formation
Distinct enzymes for each hormone
Specific Enzymes and Hormones
CYP11B2 (aldosterone)
CYP11B1 (cortisol)
CYP17 (sex steroids)
Rate-limiting step: Steroidogenic Acute Regulatory protein (StARP)

Adrenal Gland Development 00:00:10

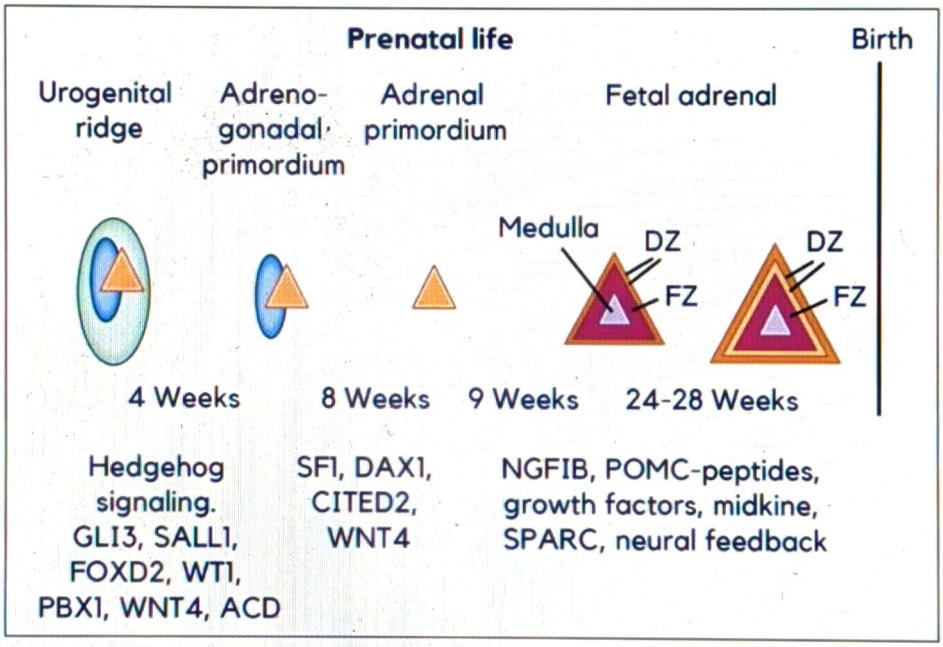
- **Origin:**
  - The **adrenal cortex** originates from the **intermediate mesoderm**.
  - The **adrenal medulla** develops from **neural crest cells** that migrate and invade the developing adrenal primordial at nine weeks.
- **Key Developmental Stages:**
  - At **four weeks** of gestation, the intermediate mesoderm gives rise to the **urogenital ridge**.
  - At **eight weeks**, the urogenital ridge forms the **adrenal gonadal primordial**, which soon after splits into adrenal primordial (containing cortical precursors) and gonadal primordial.
  - At **nine weeks**, neural crest cells invade the adrenal primordial to form the medulla.
- **Essential Transcription Factors:**
  - **SF1 (Steroidogenic Factor 1)**
  - **DAX1 (Dosage-sensitive sex reversal adrenal hypoplasia congenita gene located in the X chromosome)**
  - **WNT4**
  - Inactivating mutations in these transcription factors can result in **adrenal insufficiency**.
  - Specifically, SF1 mutation can lead to **gonadal dysgenesis with adrenal insufficiency**.
  - Inactivating mutation of DAX1 results in **congenital adrenal hypoplasia**.

Fetal Adrenal Gland Anatomy and Function 00:05:05

- **Structure:**
  - The fetal adrenal gland, like the adult, has an adrenal capsule.
  - The fetal adrenal cortex has an **outer definitive zone**, a **middle transitional zone** (whose clear distinction is debated), and an **inner fetal zone**.



- **Size:**
  - During the fetal period, the **fetal zone occupies the maximum volume**.
  - The fetal adrenal gland is significantly larger than the adult adrenal, with a weight **four times greater than the adult adrenal**.
  - After 20 weeks of gestation, the fetal adrenal gland may **outgrow the fetal kidney**.
  - It reaches its maximum size around 24 to 28 **weeks of gestation**, even outgrowing the fetal kidney.
- **Hormone Production by Fetal Zones:**
  - **Fetal Zone:** Produces **sex steroids**, especially **DHEA (dehydroepiandrosterone)**. DHEA is the **most abundant steroid in fetal life**. This DHEA is converted to androstenedione and then to estrogen by the placenta to sustain pregnancy and ensure fetal well-being.
  - **Definitive Zone:** Produces **mineralocorticoids**, but the necessary enzymes (like CYP11B2) are not expressed until 24 to 26 weeks of gestation.
  - **Transitional Zone:** Said to be involved in **glucocorticoid synthesis**.



Post-Natal Adrenal Changes 00:10:50

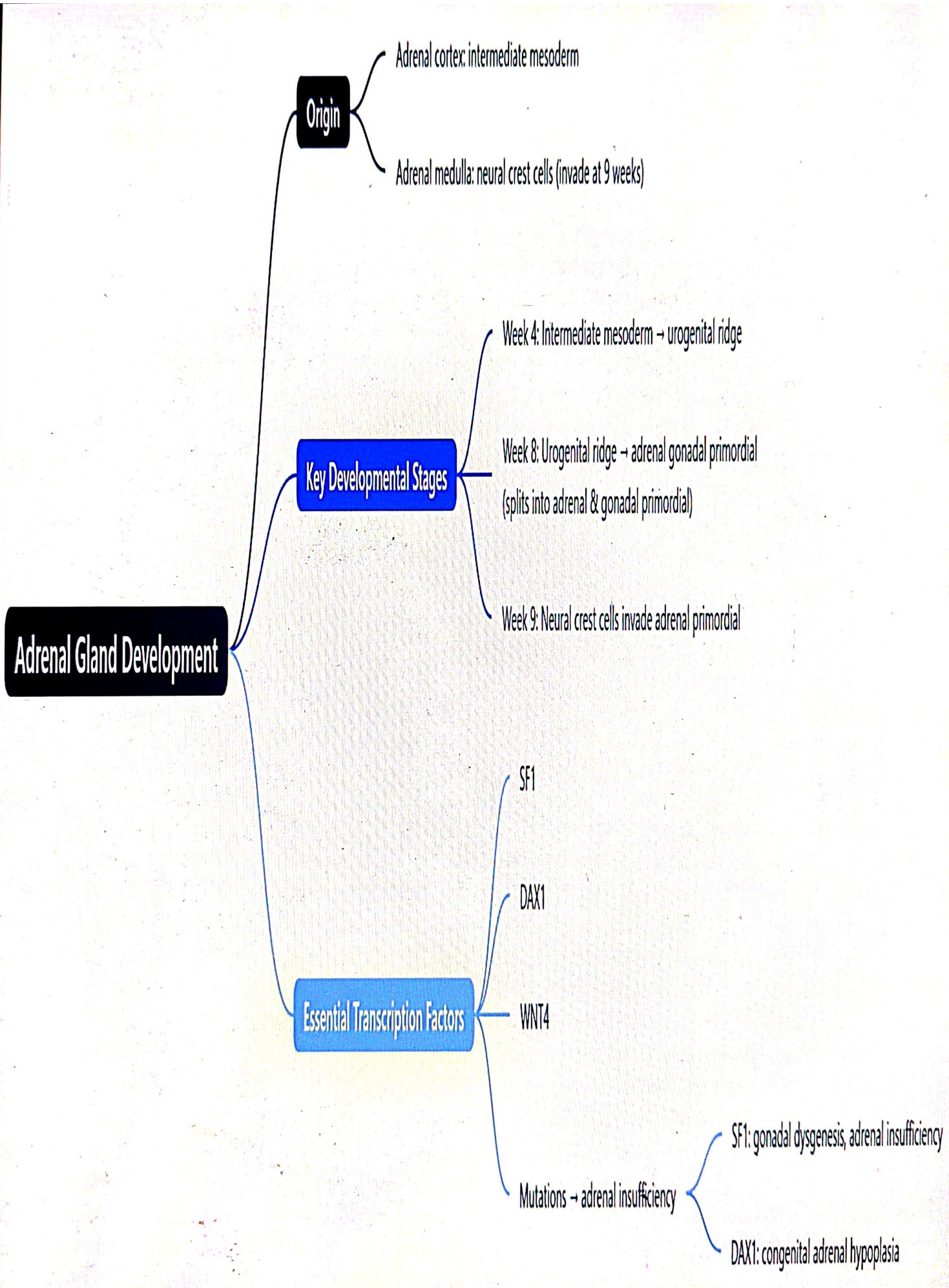
- **Fetal Zone Disintegration:** After birth, the fetal zone begins to disintegrate within 1 to 2 weeks and **completely disappears by six months**.
- **Definitive Zone Development:** The definitive zone increases in size and becomes the future adrenal cortex.
- **Zona Reticularis Development:**
  - The **zona reticularis is absent at birth**.
  - It starts development around 2 **to** 3 **years** of age.
  - It begins to function and produce sex steroids (adrenal androgens) by 6 **to** 8 **years**.
  - Its maturation continues and is completed by approximately 16 **to** 20 **years of age**, reaching adult levels of DHEA.

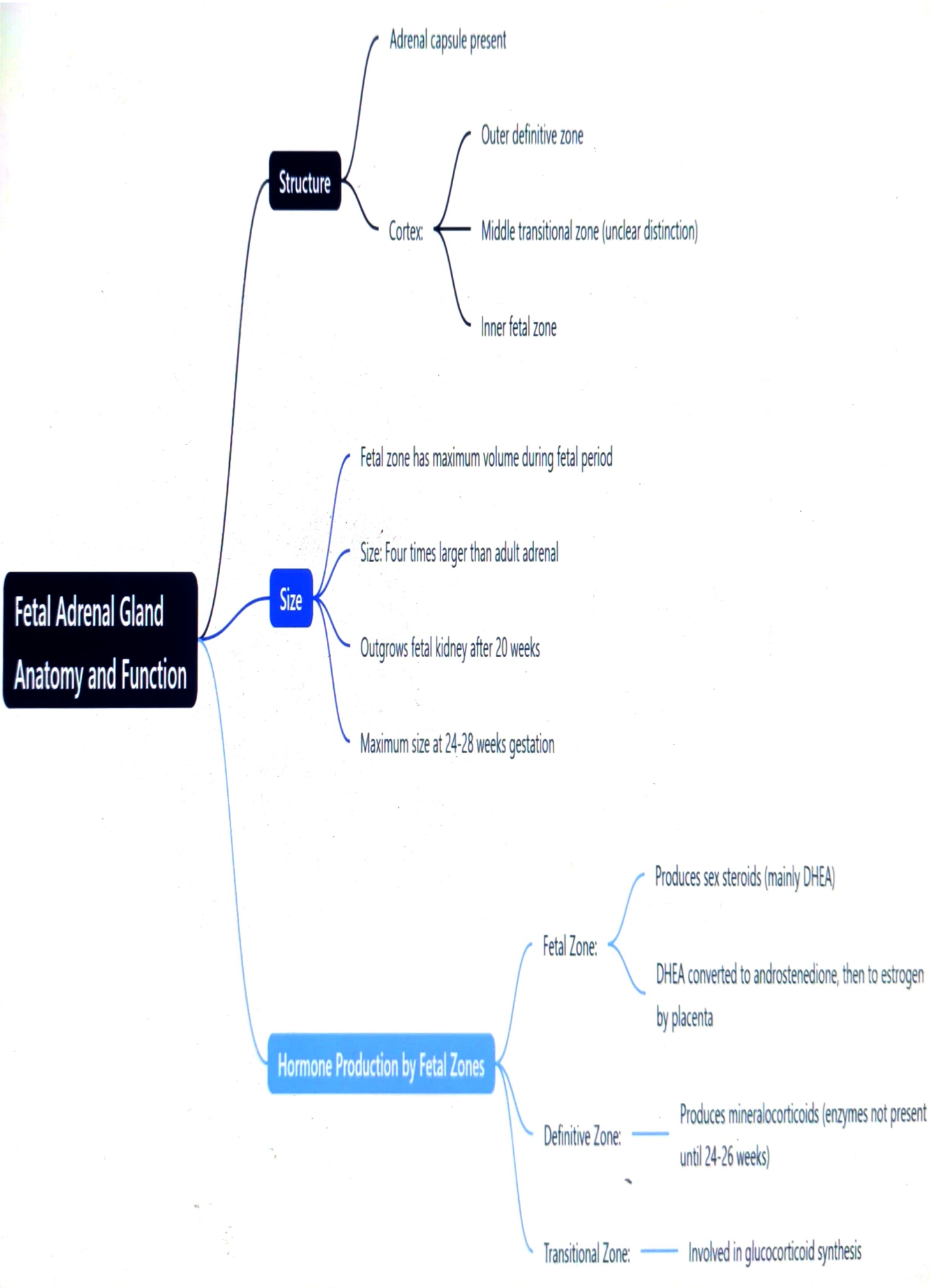
Clinical Relevance of Adrenal-Gonadal Development 00:12:35

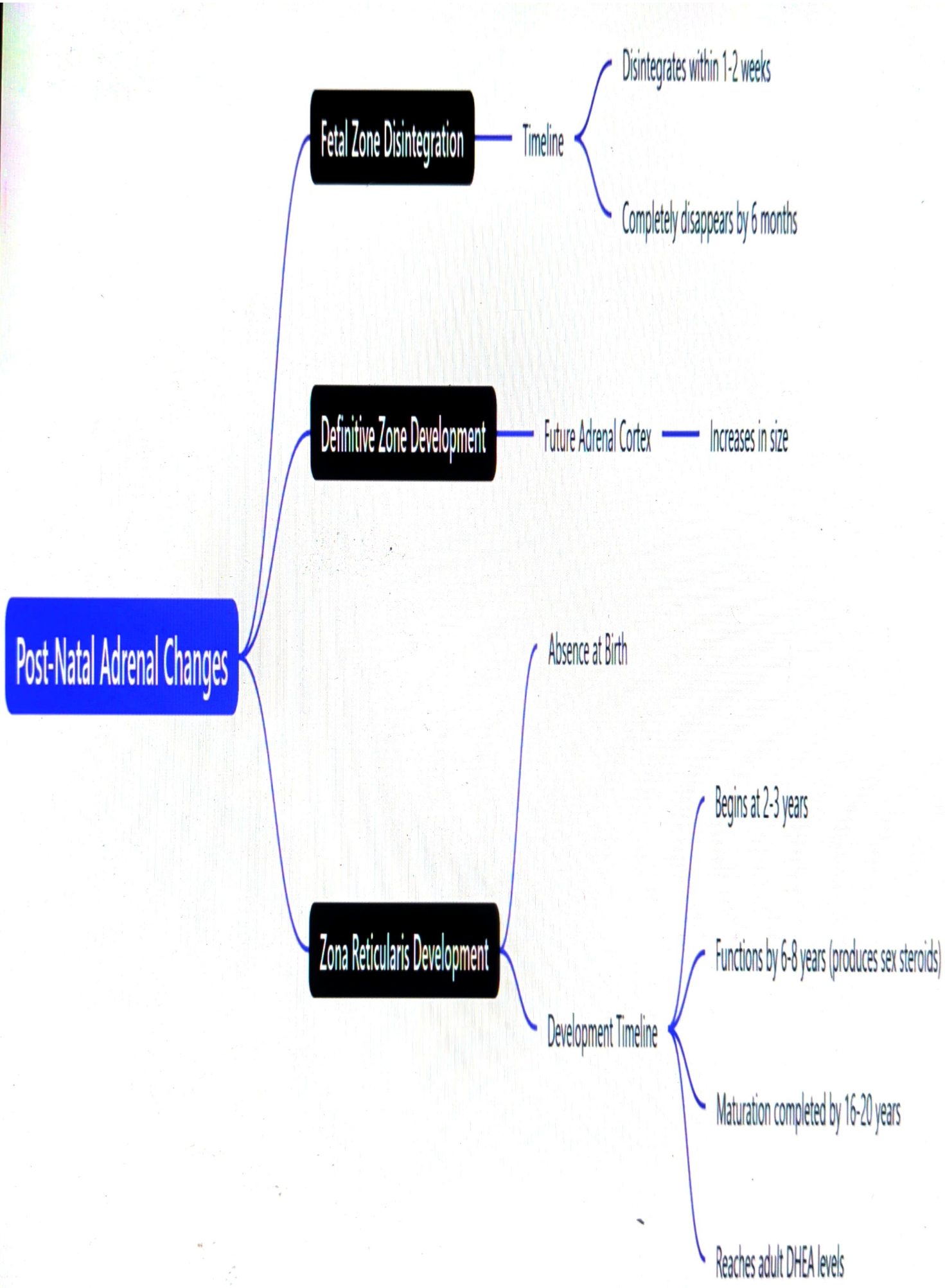
- **Transcription factors**: SF 1 transcription factor mutation causes gonadal dysgenesis and adrenal insufficiency. An inactivating mutation of DAX 1 results in congenital adrenal hypoplasia. WNT 4 can also be involved.
- **Testicular Adrenal Rest Tumors (TARTs)**:
  - Adrenals and gonads originate from a **common adrenal-gonadal primordial**.
  - During splitting, some adrenal cells can get **trapped in the gonads** (e.g., testes in males, ovaries in females).
  - In patients with **congenital adrenal hyperplasia (CAH)**, reduced cortisol production leads to **increased ACTH**.
  - This increased ACTH stimulates the trapped adrenal cells (adrenal rest) within the gonads, causing them to **enlarge in size**.
  - These enlarged adrenal rests can compress testicular tissue, potentially resulting in **infertility**.

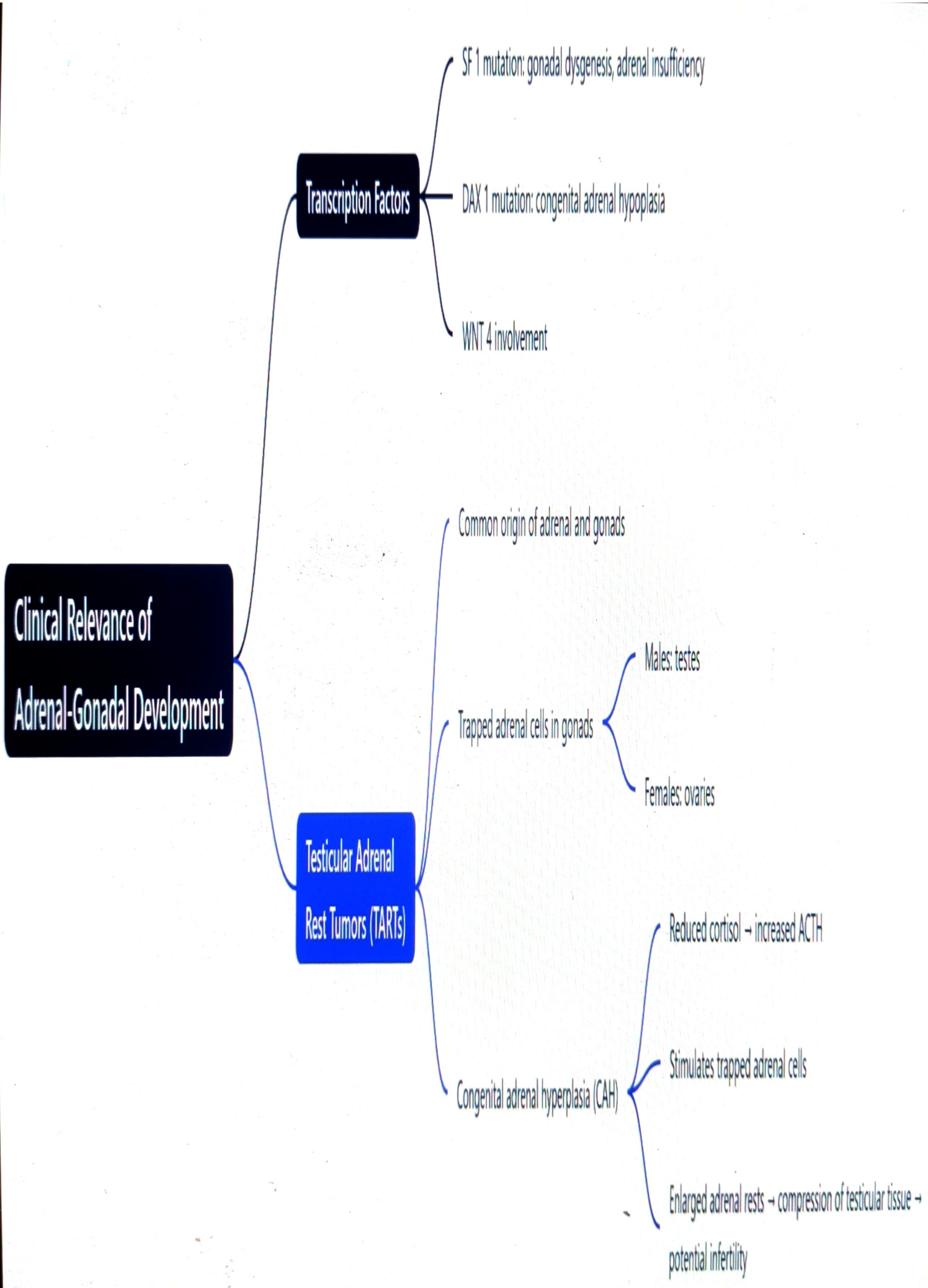
Adrenarche and Pubarche 00:16:53

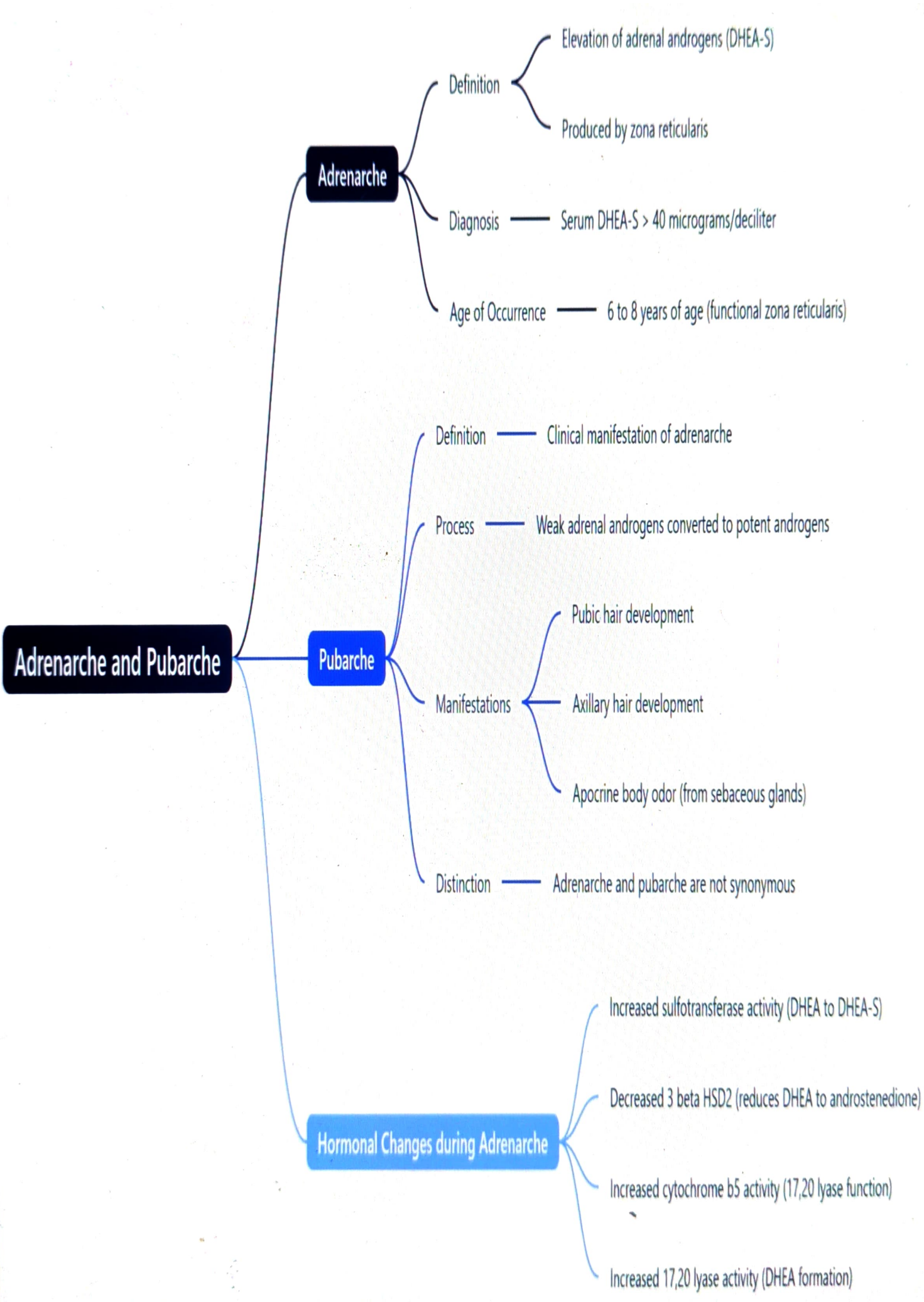
- **Adrenarche:**
  - A **biochemical finding** defined by the **elevation of adrenal androgens** (primarily DHEA-S) produced by the zona reticularis.
  - Diagnosed when serum **DHEA-S levels cross more than 40 micrograms per deciliter**.
  - Occurs by **6 to 8 years of age** when the zona reticularis becomes functional.
- **Pubarche:**
  - The **clinical manifestation of adrenarche**.
  - It occurs when the weak adrenal androgens from adrenarche are converted into more potent androgens, leading to peripheral androgenic action.
  - Manifestations include **pubic hair development, axillary hair development**, and development of apocrine body odor due to sebaceous glands.
  - Adrenarche and pubarche are **two different terminologies and should not be used synonymously**.
- **Hormonal Changes during Adrenarche (leading to increased DHEA production):**
  - **Increased sulfotransferase activity** (converts DHEA to DHEA-S).
  - **Decreased 3 beta HSD2** (reduces conversion of DHEA to androstenedione, thus favoring DHEA accumulation).
  - **Increased cytochrome b5 activity** (essential for the functioning of 17,20 lyase, which converts 17-hydroxypregnenolone to DHEA).
  - **Increased 17,20 lyase activity** (converts 17-hydroxypregnenolone to DHEA). (Decreased 17,20 lyase activity would prevent DHEA formation and is *not* a feature of adrenarche).


Adrenal Gland Development
Origin
Adrenal cortex: intermediate mesoderm
Adrenal medulla: neural crest cells (invade at 9 weeks)
Key Developmental Stages
Week 4: Intermediate mesoderm → urogenital ridge
Week 8: Urogenital ridge → adrenal gonadal primordial (splits into adrenal & gonadal primordial)
Week 9: Neural crest cells invade adrenal primordial
Essential Transcription Factors
SF1
DAX1
WNT4
Mutations → adrenal insufficiency
SF1: gonadal dysgenesis, adrenal insufficiency
DAX1: congenital adrenal hypoplasia


Fetal Adrenal Gland Anatomy and Function
Structure
Adrenal capsule present
Cortex:
Outer definitive zone
Middle transitional zone (unclear distinction)
Inner fetal zone
Size
Fetal zone has maximum volume during fetal period
Size: Four times larger than adult adrenal
Outgrows fetal kidney after 20 weeks
Maximum size at 24-28 weeks gestation
Hormone Production by Fetal Zones
Fetal Zone:
Produces sex steroids (mainly DHEA)
DHEA converted to androstenedione, then to estrogen by placenta
Definitive Zone:
Produces mineralocorticoids (enzymes not present until 24-26 weeks)
Transitional Zone:
Involved in glucocorticoid synthesis


Post-Natal Adrenal Changes
Fetal Zone Disintegration
Timeline
Disintegrates within 1-2 weeks
Completely disappears by 6 months
Definitive Zone Development
Future Adrenal Cortex
Increases in size
Zona Reticularis Development
Absence at Birth
Development Timeline
Begins at 2-3 years
Functions by 6-8 years (produces sex steroids)
Maturation completed by 16-20 years
Reaches adult DHEA levels


Clinical Relevance of Adrenal-Gonadal Development
Transcription Factors
SF 1 mutation: gonadal dysgenesis, adrenal insufficiency
DAX 1 mutation: congenital adrenal hypoplasia
WNT 4 involvement
Testicular Adrenal Rest Tumors (TARTs)
Common origin of adrenal and gonads
Trapped adrenal cells in gonads
Males: testes
Females: ovaries
Congenital adrenal hyperplasia (CAH)
Reduced cortisol → increased ACTH
Stimulates trapped adrenal cells
Enlarged adrenal rests → compression of testicular tissue → potential infertility


Adrenarche and Pubarche
Adrenarche
Definition
Elevation of adrenal androgens (DHEA-S)
Produced by zona reticularis
Diagnosis
Serum DHEA-S > 40 micrograms/deciliter
Age of Occurrence
6 to 8 years of age (functional zona reticularis)
Pubarche
Definition
Clinical manifestation of adrenarche
Process
Weak adrenal androgens converted to potent androgens
Manifestations
Pubic hair development
Axillary hair development
Apocrine body odor (from sebaceous glands)
Distinction
Adrenarche and pubarche are not synonymous
Hormonal Changes during Adrenarche
Increased sulfotransferase activity (DHEA to DHEA-S)
Decreased 3 beta HSD2 (reduces DHEA to androstenedione)
Increased cytochrome b5 activity (17,20 lyase function)
Increased 17,20 lyase activity (DHEA formation)

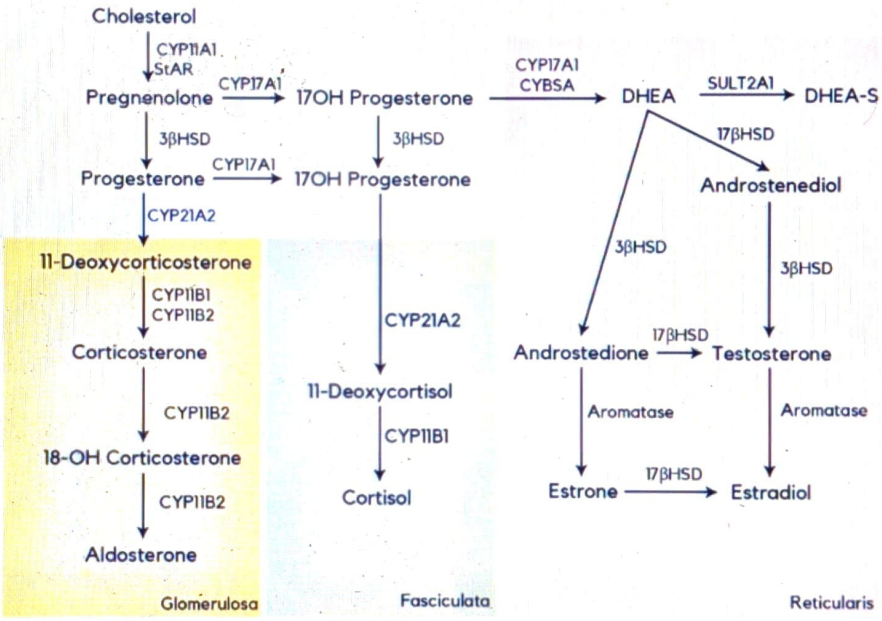
STEROIDOGENESIS-PATHWAY & REGULATION

Adrenal Steroidogenesis and Regulation 00:00:40

- Adrenal steroidogenesis is a complex process involving numerous intermediary molecules, enzymes, and cofactors. The adrenal cortex is divided into three layers, each producing specific end products:
- Zona Glomerulosa: Produces aldosterone.
- Zona Fasciculata: Produces cortisol.
- Zona Reticularis: Produces adrenal androgens (primarily androstenedione).

The steroidogenesis system requires three main components:

- Substrate: Cholesterol.
- Cofactors and Electron Donors: For enzymatic reactions.
- Enzymes: To catalyze the reactions.

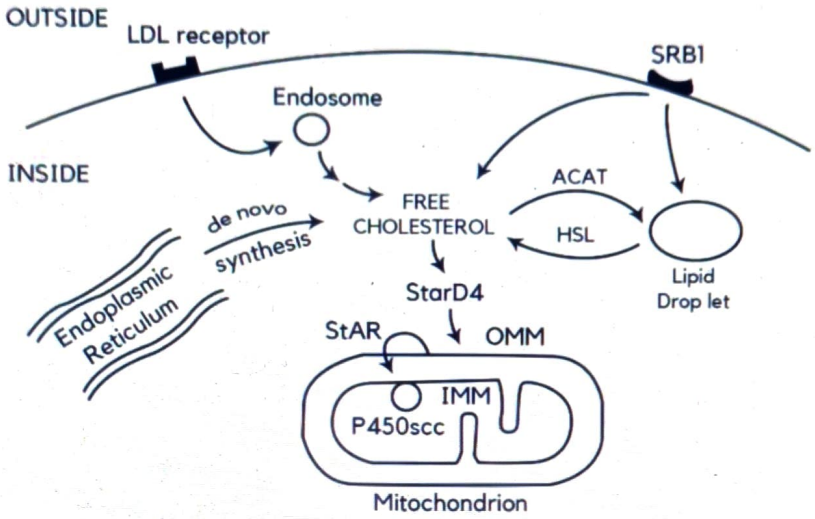


Substrate: Cholesterol 00:01:58

- Primary Substrate: Cholesterol is the essential substrate for adrenal steroidogenesis. It has 27 carbon atoms.
- Sources of Adrenal Cholesterol:
  - Circulating LDL: Historically considered the most important, taken up by LDL receptors. However, new data suggest it may not be exclusive, as patients with defective apob (e.g., abetalipoproteinemia) still have adrenal function despite very low LDL.
  - Circulating HDL: Taken up by the scavenger receptor SR-B1 on adrenal cortical cells. Validated in animals, but validation in humans is ongoing.
  - De Novo Synthesis: Adrenal cortical cells can synthesize their own cholesterol in the endoplasmic reticulum. Currently considered one of the important sources.
- Rate-Limiting Step in Cholesterol Biosynthesis: HMG-CoA reductase (inhibited by statins).

Cholesterol Transporter: StAR Protein 00:06:04

- Function: After being synthesized or taken up, free cholesterol from these three sources (LDL, HDL, de novo) must be transported from the cytoplasm into the inner mitochondrial membrane, where the early steps of steroidogenesis occur. This transport is facilitated by the StAR (Steroidogenic Acute Regulatory) protein.



- Rate-Limiting Step in Adrenal Steroidogenesis: The transport of cholesterol by StAR is considered the rate-limiting step in adrenal steroidogenesis.
- StAR Deficiency:
  - Causes Congenital Lipoid Adrenal Hyperplasia (CLAH).
  - "Lipoid" refers to the accumulation of excess free cholesterol in the cytoplasm because it cannot be transported into the mitochondria for steroid synthesis.
  - "Adrenal Hyperplasia" results from the massive enlargement of adrenal cortical cells due to this cholesterol accumulation.
- Two-Hit Hypothesis in StAR Deficiency:
  - First Hit: In the neonatal period, decreased steroid synthesis (cortisol and aldosterone) leads to a salt wasting crisis.
  - Temporary Improvement: Other inactive, StAR-independent transporters can temporarily take over cholesterol transport, causing a temporary relief of adrenal insufficiency symptoms.
  - Second Hit: By 2-3 months of age, the massive free cholesterol deposition leads to the destruction of adrenal cortical cells, causing a permanent deficiency of cortisol and aldosterone and a second salt wasting crisis.

Enzymes 00:12:32

- Adrenal steroidogenic enzymes are classified by their location:
- Mitochondrial Enzymes (Type 1):
  - Side-chain cleavage enzyme (desmolase).
  - 11-beta-hydroxylase (CYP11B1, cortisol-producing enzyme).
  - Aldosterone synthase (CYP11B2).

- Endoplasmic Reticulum Enzymes (Type 2):
  - 21-hydroxylase (most common deficiency in CAH).
  - 17-hydroxylase.
  - Aromatase (converts androgens to estrogens).
- Enzyme Present in Both Mitochondria and Endoplasmic Reticulum:
  - 3-beta-hydroxysteroid dehydrogenase type 2 (3-beta-HSD2).

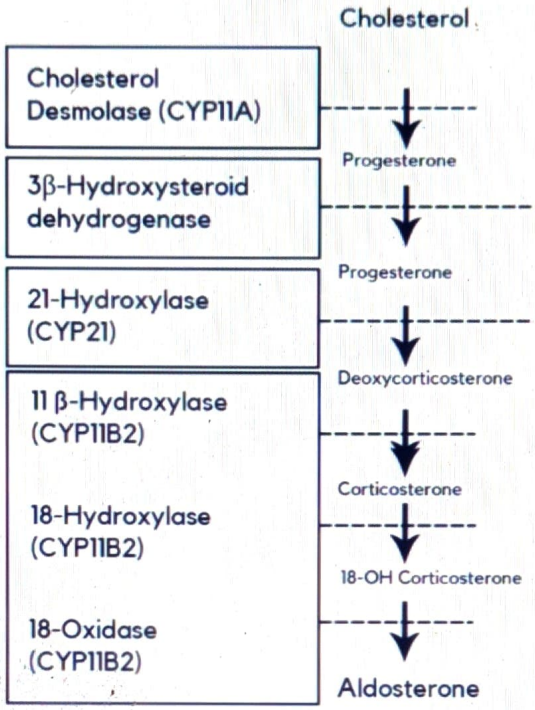
Electron Donors 00:15:05

- Electron donors are required to catalyze the conversion of metabolites:
- For Mitochondrial Enzymes: Adrenodoxin (also known as ferredoxin).
- For Endoplasmic Reticulum Enzymes: P450 oxidoreductase.
  - P450 oxidoreductase acts as an electron donor for 21-hydroxylase, 17-hydroxylase, and aromatase.
  - P450 oxidoreductase deficiency can cause a clinical syndrome with features mimicking deficiencies of all three of these enzymes, leading to a form of congenital adrenal hyperplasia (CAH).

Aldosterone Synthesis (Zona Glomerulosa) 00:17:40

- Pathway:
  - Cholesterol is transported into mitochondria by StAR.
  - Cholesterol is converted to Pregnenolone by cholesterol desmolase (side-chain cleavage enzyme). (This step is common to all three adrenal cortical zones).
  - Pregnenolone is converted to Progesterone by 3-beta-HSD2.
  - Progesterone is converted to Deoxycorticosterone by 21-hydroxylase.
  - Deoxycorticosterone is converted to Aldosterone by CYP11B2 (aldosterone synthase).
- Key Enzyme Not Involved: 17-hydroxylase is not required for aldosterone synthesis, and its expression is absent in the zona glomerulosa.
  - Clinical Implication: In 17-hydroxylase deficiency (a form of CAH), there is no salt wasting crisis because aldosterone production is intact; in fact, there is an overproduction of aldosterone, leading to hypertension.
- Actions of CYP11B2 (Aldosterone Synthase): It has three actions:
  - 11-beta-hydroxylation.
  - 18-hydroxylation.
  - 18-oxidation.
- Mineralocorticoid Activity of Precursors:
  - Deoxycorticosterone (DOC) and subsequent metabolites have mineralocorticoid action.
  - Progesterone has an anti-mineralocorticoid action.
  - Aldosterone is the primary mineralocorticoid because a higher percentage of it is in the free, biologically active form (50% free) compared to DOC (>90% bound, <10% free).
- Basic Facts about Aldosterone:
  - Circulating Concentration: Expressed in nanograms/dl, about 1000 times lower than cortisol.
  - Daily Production: 100-150 micrograms/day.

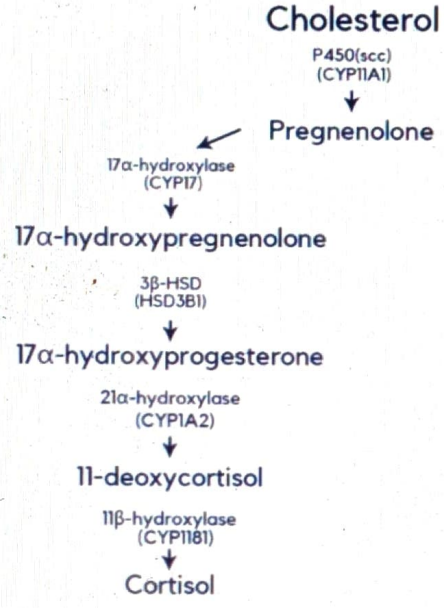
- Half-Life: 10-20 minutes.
- Binding: 50% free; bound to cortisol-binding globulin (CBG) or albumin.

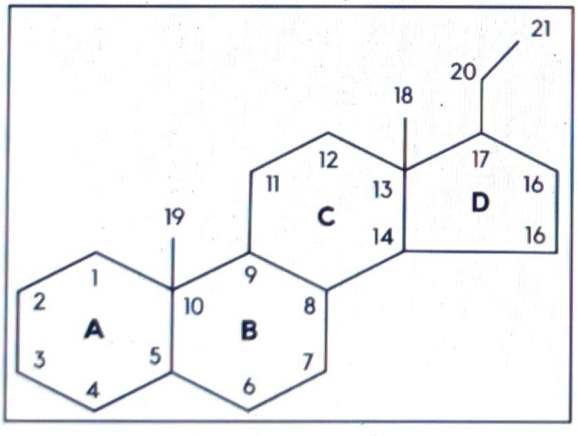


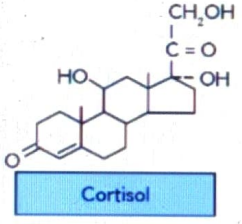
Cortisol Synthesis (Zona Fasciculata) 00:27:28

- Pathway:
  - Cholesterol is transported by StAR and converted to Pregnenolone by desmolase.
  - Pregnenolone is acted upon by 17-alpha-hydroxylase to produce 17-hydroxypregnenolone.
  - 17-hydroxypregnenolone is converted to 17-hydroxyprogesterone by 3-beta-HSD2.
    - 17-hydroxyprogesterone (17-OHP) is a crucial screening tool for 21-hydroxylase deficiency, as its concentration increases when the enzyme is deficient.
  - 17-hydroxyprogesterone is converted to 11-deoxycortisol by 21-alpha-hydroxylase.
  - 11-deoxycortisol is converted to Cortisol by 11-beta-hydroxylase (CYP11B1).
- Basic Facts about Cortisol:
  - Production: 10-20 mg/day or 6-8 mg/m² per day. Cortisol is the most abundantly produced steroid by the adrenal gland.
  - Half-Life: Approximately 60 minutes (1 hour).
  - Binding:
    - 80-85% bound to CBG.
    - 5-10% bound to albumin.
    - 5-10% is in free form, which is the biologically active fraction.
  - Clinical Importance of Binding: In conditions that reduce CBG and albumin (e.g., liver disease, nephrotic syndrome), total cortisol levels decrease, but the free cortisol fraction remains normal. In such cases, free cortisol (salivary or urine cortisol) should be measured, rather than serum total cortisol, which can be erroneously low.

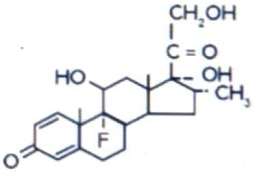
- Cortisol Structure and Analogs:
  - Cortisol has 21 carbon atoms and a four-ring structure (A, B, C, D) called cyclopenta-perhydrophenanthrene.
  - Hydrocortisone: Exogenous hydrocortisone is structurally identical to endogenous cortisol.
  - Prednisolone: Differs from hydrocortisone by an additional double bond between C1 and C2. This structural similarity means prednisolone has strong cross-reactivity with cortisol assays.
  - Dexamethasone: Has two main structural changes: an additional double bond, a fluorine atom, and a methyl group at the 16 position. The fluorine atom makes its structure entirely different, so dexamethasone has no cross-reactivity with cortisol assays.
  - Fluorinated glucocorticoids: Dexamethasone, fludrocortisone, fluticasone.
  - Chlorinated glucocorticoid: Clobetasol.



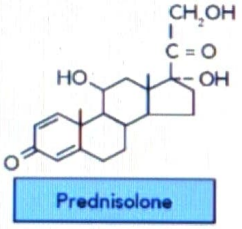




Cortisol



Dexamethasone



Prednisolone

Adrenal Androgen Synthesis (Zona Reticularis) 00:38:30

- Major Adrenal Androgens: DHEA, DHEA-S, and androstenedione.
  - The conversion of androstenedione to testosterone, and testosterone to estradiol, primarily occurs in the periphery (e.g., adipose tissue, testes, ovaries), not predominantly in the adrenal gland itself.

- Pathway:
  - Cholesterol is converted to Pregnenolone by desmolase.
  - Pregnenolone is acted upon by 17-hydroxylase to produce 17-hydroxypregnenolone.
  - 17-hydroxypregnenolone is acted upon by 17,20-lyase to generate DHEA.
    - 17,20-lyase activity is part of the CYP17A1 enzyme (which also has 17-alpha-hydroxylase activity).
    - The 17,20-lyase function is specific and exclusive to the zona reticularis.
  - DHEA can be converted to DHEA-S by the enzyme sulfotransferase.
    - The sulfotransferase enzyme is present only in the adrenal gland. Therefore, elevated DHEA-S is diagnostic of adrenal pathology.
  - DHEA can also be converted to androstenedione by 3-beta-HSD2.
    - Elevated DHEA or androstenedione can originate from either the adrenal or gonads.
- Adrenal Testosterone Production:
  - While androstenedione is the main end product, a small amount (~5%) of testosterone can be produced in the adrenal gland by 17-beta-HSD5. This isoform is less efficient than the 17-beta-HSD3 found predominantly in the testes.
  - Thus, the statement that adrenal glands cannot synthesize testosterone is factually incorrect, even though it's not a major physiological contributor.
- Cytochrome b5 Reductase:
  - This is a cofactor essential for the proper functioning of the 17,20-lyase enzyme.
  - Deficiency in cytochrome b5 reductase mimics 17,20-lyase deficiency, reducing androgen biosynthesis.
  - It is also known as methemoglobin reductase because it reduces methemoglobin.
  - Cytochrome b5 reductase deficiency can lead to disorders of sex differentiation (DSD) along with methemoglobinemia.

