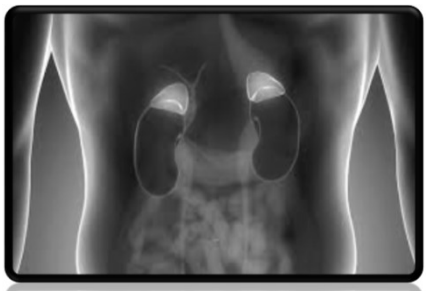
Adrenal Cortex Insufficiency & Related Lab Tests

M Reza Bakhtiari, DCLS, PhD



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Lecturer Introduction

- **Mohammad Reza Bakhtiari**
  - Doctorate in Clinical Laboratory Sciences (DCLS)
  - PhD in Medical Biotechnology
  - Faculty Member to Biotech Dept. of IROST
  - Member to IFCC Committee on Standardization of Thyroid Function Tests (C-STFT)

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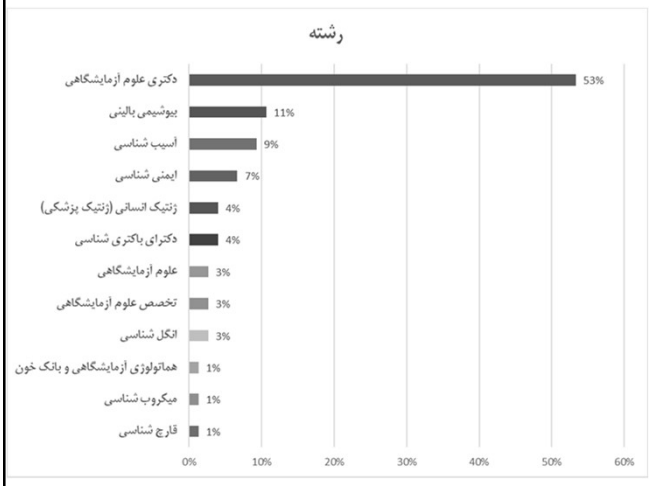
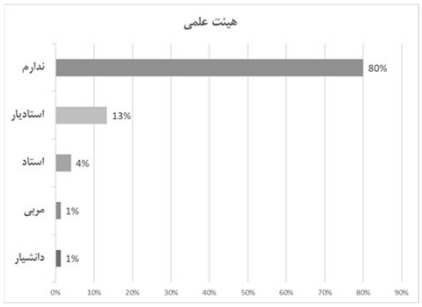
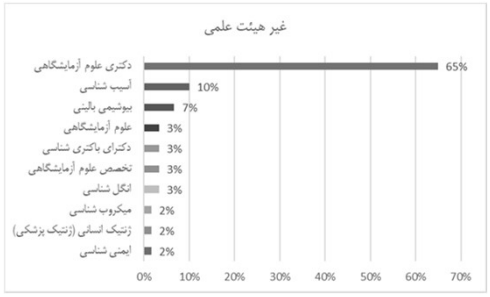
Participants







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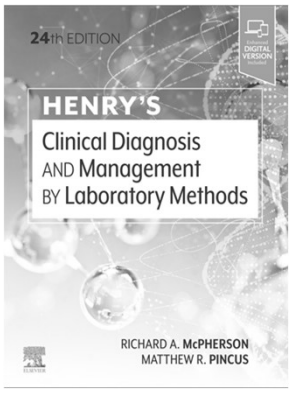
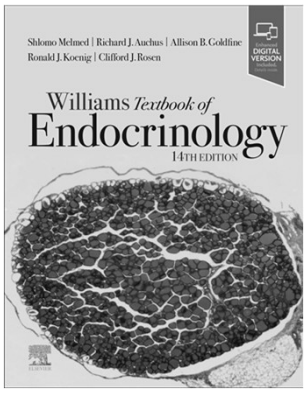
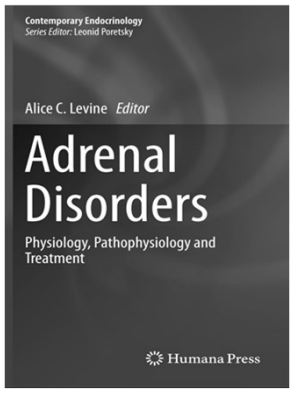
References
(Books & Papers)







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Case Presentation

A 30-year-old female patient

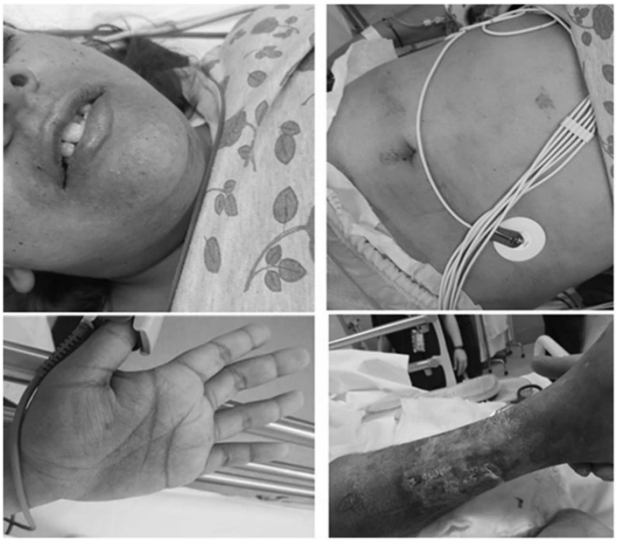
- ✓Admitted to the emergency department (ED) with fever, lethargy, hypotension, pO2 = 77 mmHg, syncopal episodes, hyperpigmented
- ✓**Lab Findings**:
  - anemia, severe electrolyte dysregulation, ↑ inflam.markers, acute renal failure, & metabolic acidosis.
- ✓Hypovolemic shock, altered mental status, (Crisis)
- ✓clinical response to glucocorticoid administration
- **PMH**
  - 2-year medical history of SLE
  - diffuse abdominal pain, general weakness, arthralgias, hyperpigmentation, nausea, vomiting, anorexia and unintentional weight loss of 48 kg over a 5-month-period.
  - She complained of watery diarrhea for 4 weeks and secondary amenorrhea for the last 3 months.

Hormones (2023). https://doi.org/10.1007/s42000-023-00463-5

Values	Results	Ref. Range
RBC	**3.38**	3.8–5.3 M/µL
HGB	**9.8**	12–16 g/dl
HCT	**29.8**	37–47%
MCV	88.1	80–99 fL
MCH	29.1	27–32 pg
MCHC	33	32–35 g/dl
D-dimer	0.33	0–0.55 mg/l
aPTT	**40.5**	25.9–36.6 s
PT	**20.5**	10.4–14 s
INR	**1.75**	0.85–1.2
Urea	**92**	17–43 mg/dl
Creatinine	**5.84**	0.55–1.02 mg/dl
Sodium	**125**	136–146 mEq/l
Potassium	**6.1**	3.5–5.1 mEq/l
Calcium (corrected)	**10.94**	8.8–10.6 mg/dl
Magnesium	**1.5**	1.9–2.5 mg/dl
Total cholesterol	**51**	< 200 mg/dl
CRP	**3.73**	< 0.5 mg/dl
ESR	**95**	1–25 mm/1st hr
Procalcitonin	**1.03**	< 0.05 ng/ml
Cortisol	**1**	3.5–19 µg/dl
Aldosterone	**21.5**	29.4–161.5 pg/ml
DHEAS	**5,7**	95.8–511.7 µg/dl
Androstenedione	**0.09**	0.25–3.44 ng/ml
17-OH-progesterone	0.48	0.13–1.67 ng/ml
Testosterone	< 0,13	0.09–1.3 ng/ml
SHBG	46	18–114 nmol/l
ANA	**1:1280 diffuse**	U/ml
Anti-ds-DNA	**22.1**	> 18 U/ml positive
Anti-β2-GP1 IgM	**39.4**	> 18 U/ml positive
Anti-β2-GP1 IgG	8.22	> 18 U/ml positive
LA	**positive**	
Direct Coombs	**positive**	
Anti-adrenal	negative	< 1:20 negative

Primary adrenal insufficiency due to bilateral adrenal hemorrhage-adrenal infarction in a patient with systemic lupus erythematosus and antiphospholipid syndrome: case presentation

- Diffuse skin hyperpigmentation more conspicuous in palmar creases and scars after laparoscopic cholecystectomy.
- An ulcer on the left lower extremity



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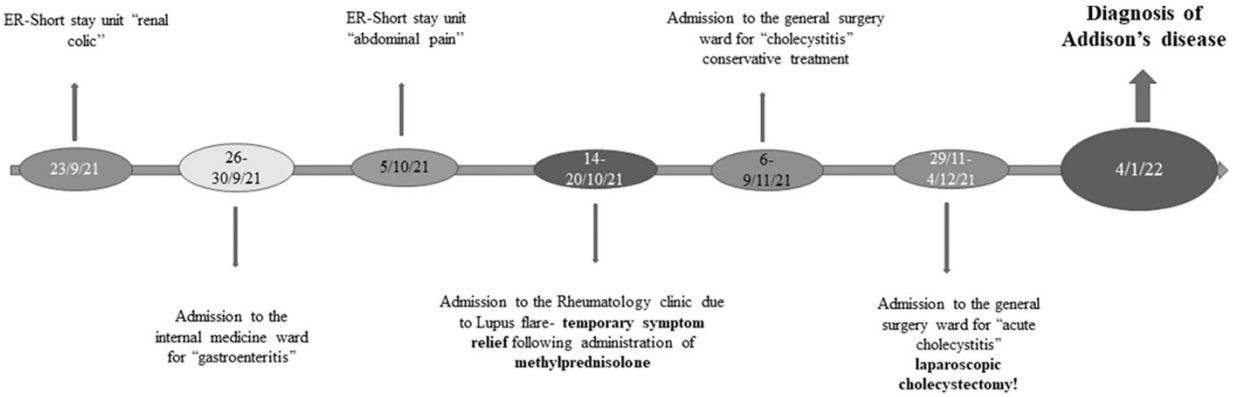

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Adrenal Insufficiency

Definition & Epidemiology

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Hypoadrenalism

Definition= Glucocorticoids Deficiency due to

1. Adrenal disease (Primary H.= Addison Disease) or
2. Central deficiency of ACTH (Central H.)

Addison Disease Epidemiology:

- ✓ a rare condition
  - ✓ in the developed world:
    - ✓ estimated incidence : 0.8 cases per 100,000
    - ✓ prevalence of 4 - 11 cases per 100,000
- ✓ f/m ratio (>30 y): 1.3–3.5 : 1
- ✓ significant morbidity rate
- ✓ twofold excess mortality rate
- ✓ **once the diagnosis is made it can be easily treated**

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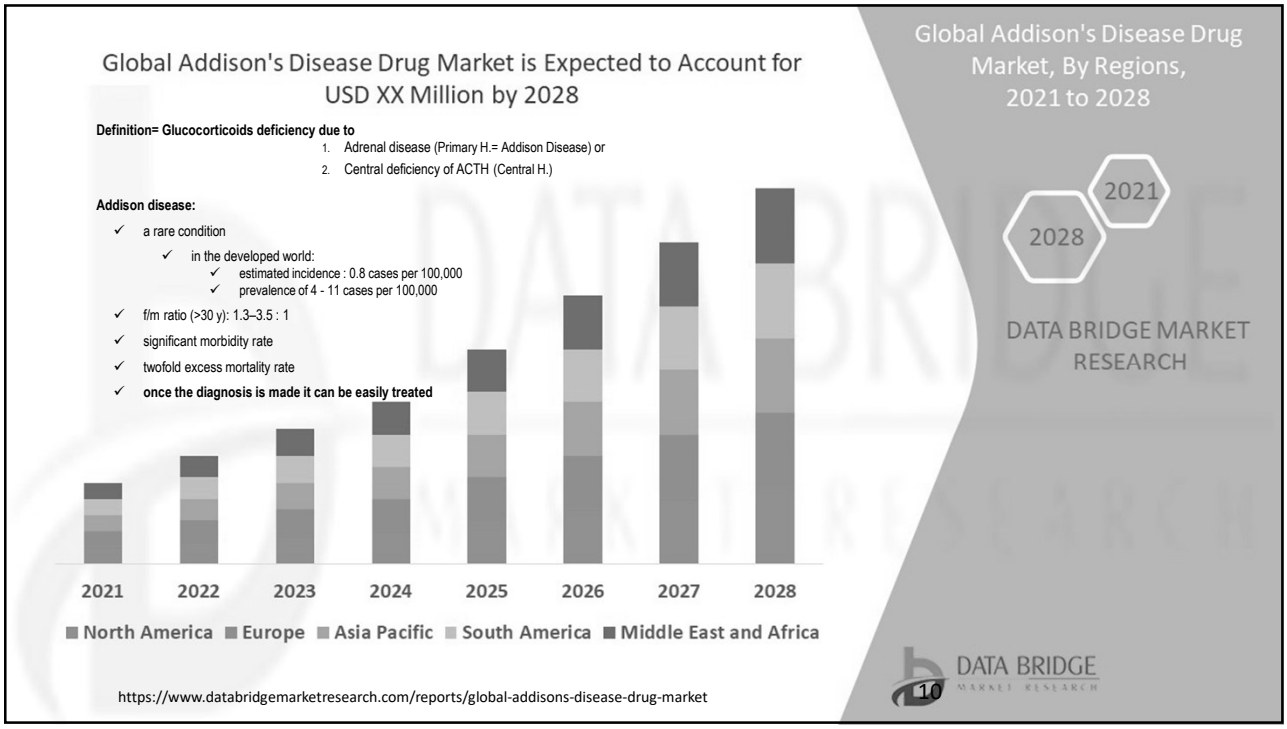
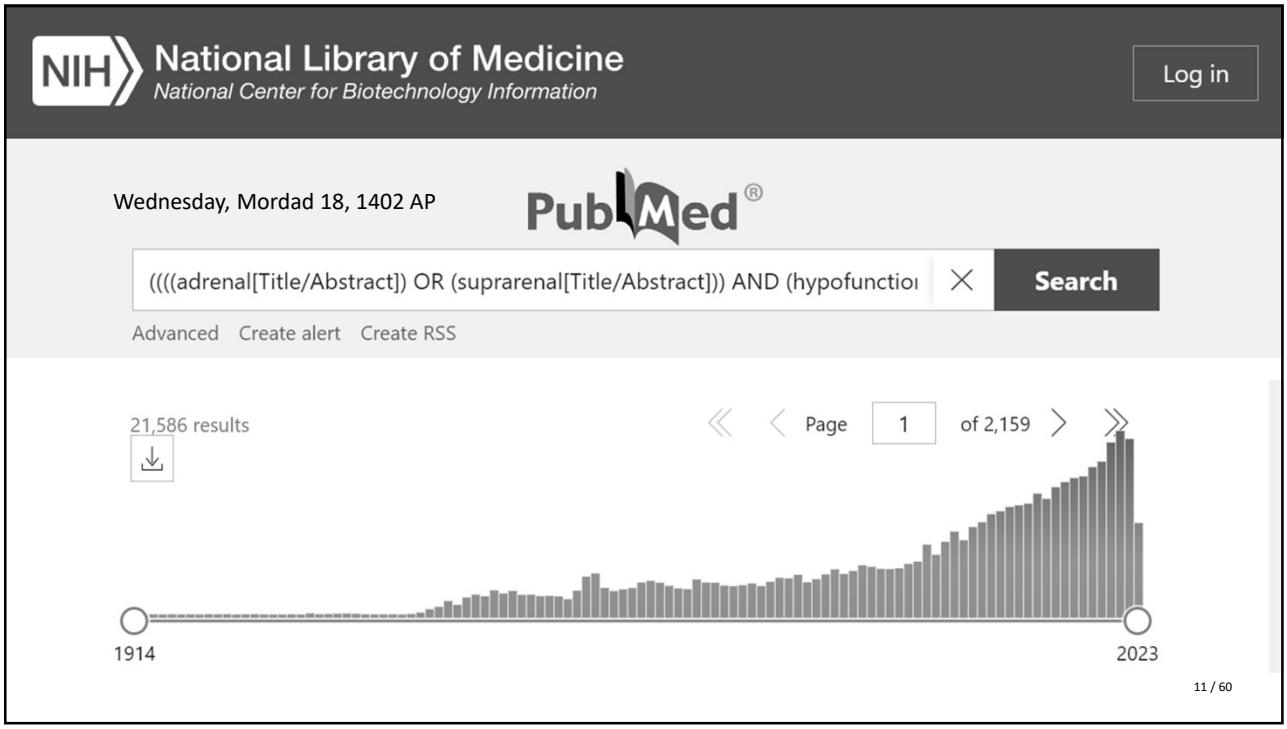
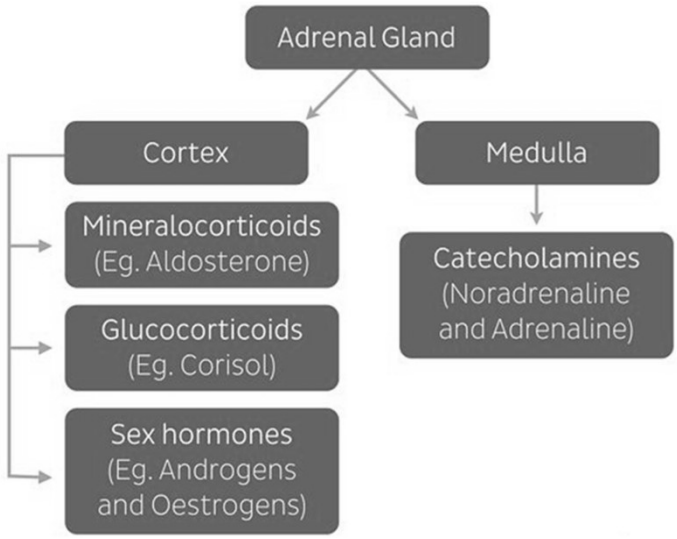




Healthy Adrenals

Functions of Adrenal Glands



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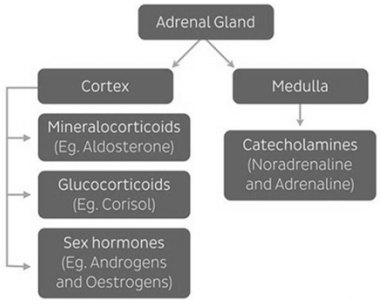
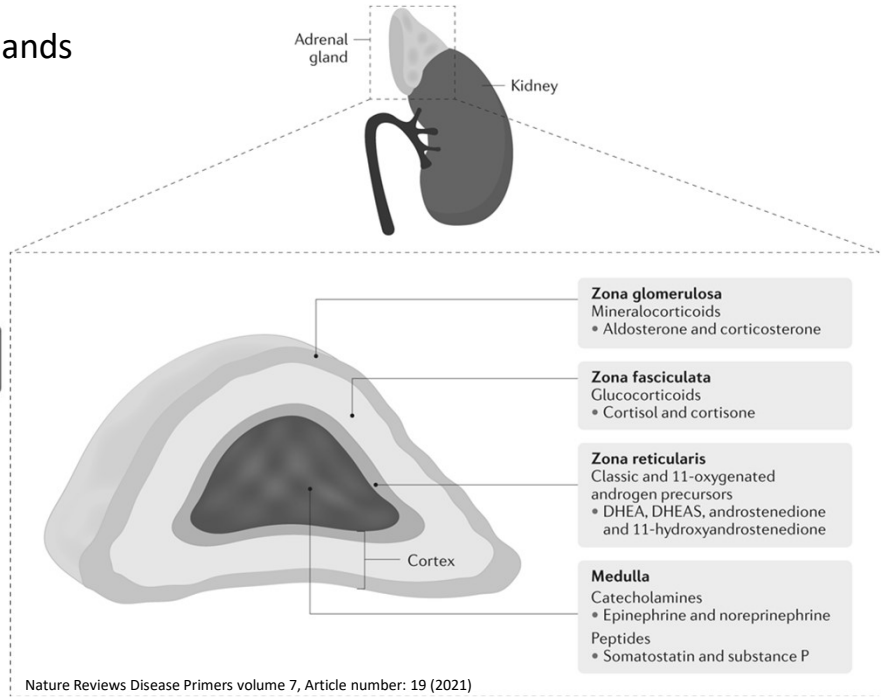
Adrenal (Suprarenal) Glands





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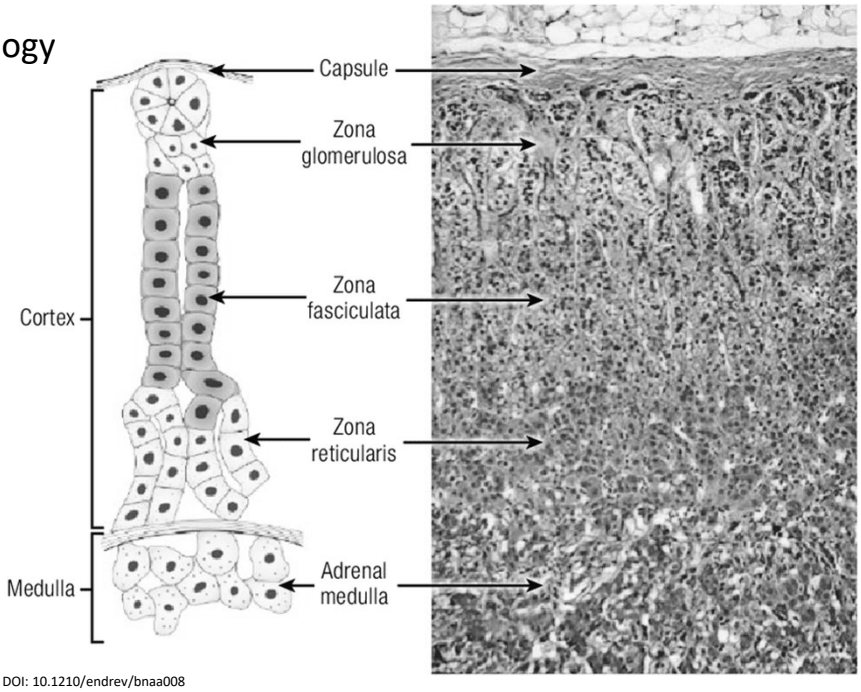
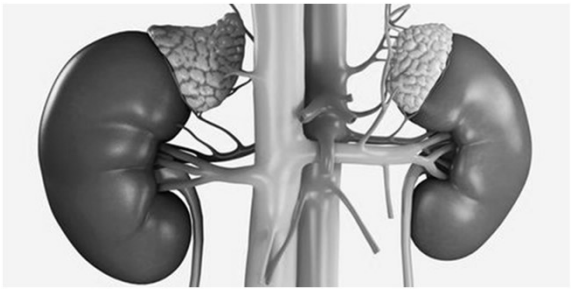
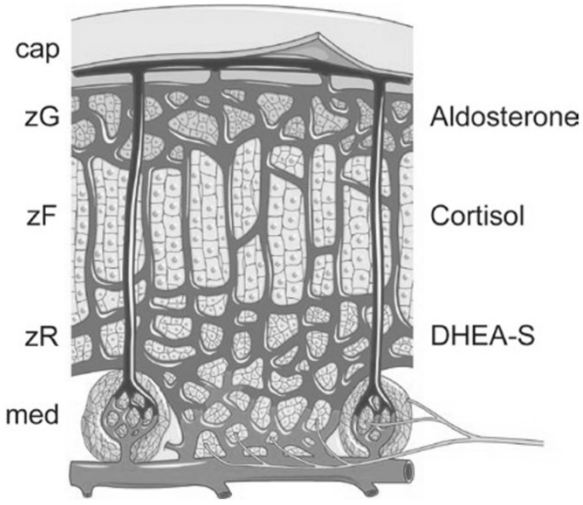
Adrenal Glands Histology



DOI: 10.1210/endrev/bnaa008

Adrenal Gland Vascularization





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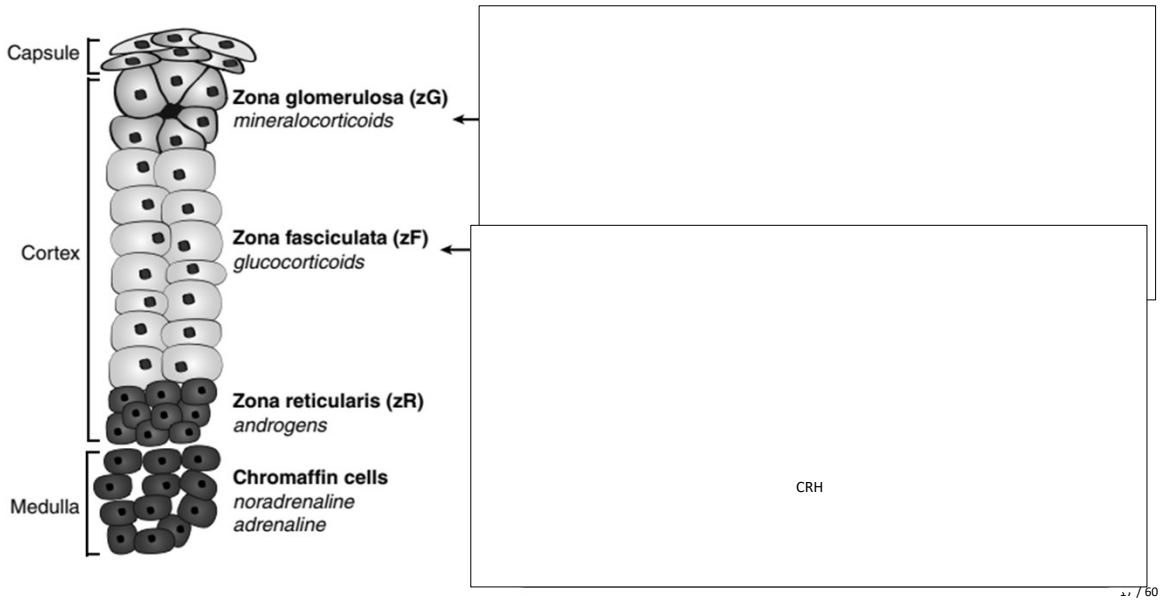
Regulation of Adrenal Cortex



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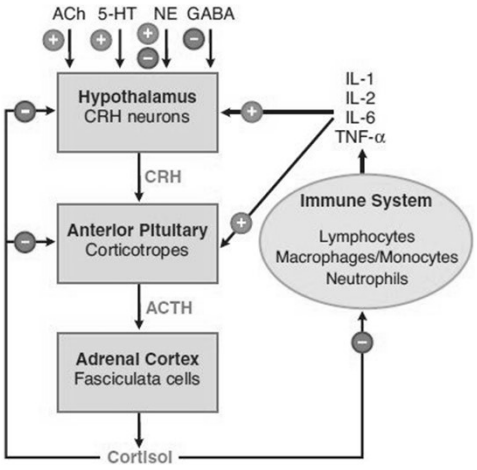
Regulation of Cortisol Secretion



	CORTISOL	ALDOSTERONE
Rate of secretion under optimal conditions	10 mg/day	0.125 mg/day
Concentration in peripheral plasma:		
8 A.M.	16 µg/100 mL	0.01 µg /100 mL
4 A.M.	4 µg/100 mL	0.01 µg/100 mL

- The hypothalamic-pituitary-adrenal (HPA) axis and the immune inflammatory network.
- Also shown are inputs from higher neuronal centers that regulate CRH secretion. + indicates a positive regulator, – indicates a negative regulator, + and – indicates a mixed effect, as for NE (norepinephrine).
- In addition, arginine vasopressin stimulates release of ACTH from corticotropes.

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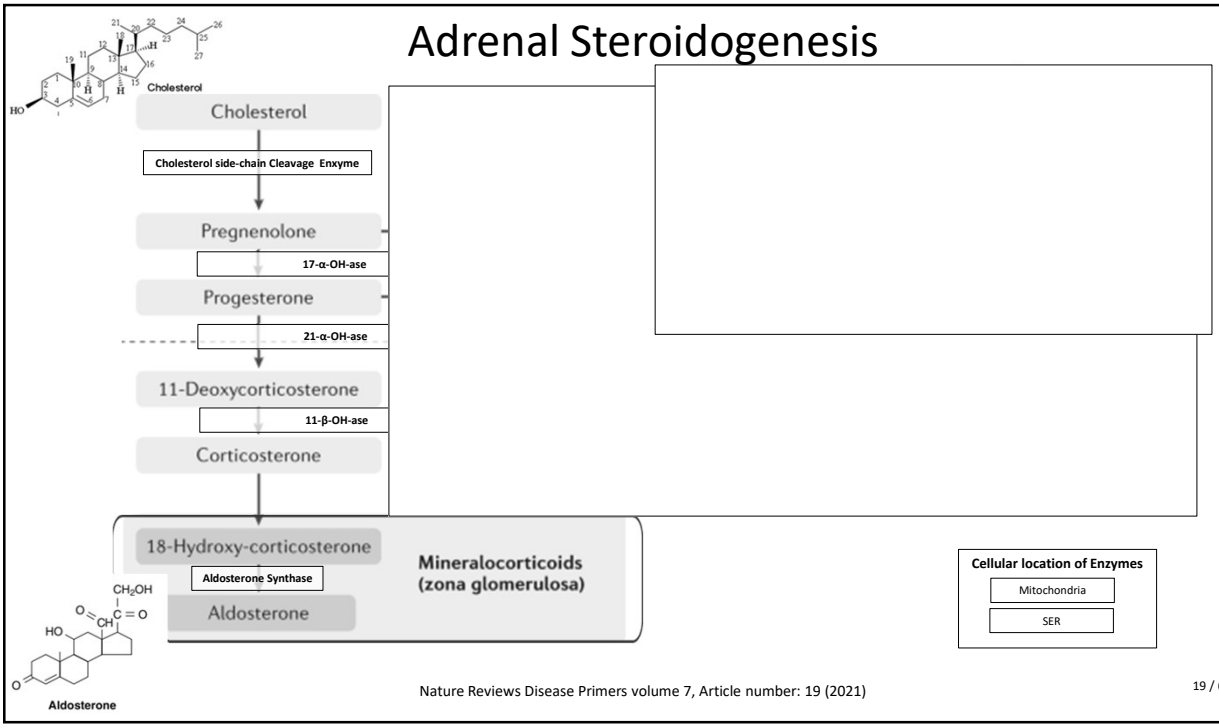
Adrenal Steroidogenesis



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Crucial roles of Adrenals in the "fight or flight" Response

- A physiological reaction to stress or danger.
- There are two main components of the adrenal gland that contribute to this response: the adrenal medulla and the adrenal cortex.
- Adrenal gland, through the combined actions of the adrenal medulla and adrenal cortex, orchestrates the fight or flight response by facilitating rapid physiological changes and maintaining energy balance in response to acute stress or danger.

1. Adrenal Medulla:
   - The adrenal medulla is responsible for the rapid response in the fight or flight mechanism.
   - When an individual perceives a threat or stress, the sympathetic nervous system is activated, leading to the release of a neurotransmitter norepinephrine.
   - The adrenal medulla then releases norepinephrine and epinephrine (adrenaline) directly into the bloodstream. These hormones have immediate effects on the body, including:
     1. ↑ HR, BP, & CO: → ↑ Blood flow to vital organs.
     2. Dilation of bronchioles: → airflow to the lungs.
     3. ↑ Glucogenolysis → ↑ Blood Glucose Levels by Epinephrine → Extra energy for the body to respond to the threat or stress
     4. ↑ Mental Alertness & Focus: Norepinephrine and epinephrine enhance brain function, sharpening attention and ↑ awareness.

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Crucial roles of Adrenals in the "fight or flight" Response

- A physiological reaction to stress or danger.
- There are two main components of the adrenal gland that contribute to this response: the adrenal medulla and the adrenal cortex.

1. Adrenal Cortex:
   - The Adrenal Cortex: plays a role in the fight or flight response, but its effects are usually slower and longer-lasting compared to the adrenal medulla.
   - The adrenal cortex produces and releases steroid hormones, glucocorticoids, primarily cortisol.
   - Cortisol has various functions in the fight or flight response, including:
     1. Modulating the immune response: Cortisol suppresses the immune system, reducing inflammation and preventing an excessive immune reaction during the stress response.
     2. Mobilizing energy reserves: Cortisol promotes the breakdown of proteins into amino acids, the conversion of amino acids into glucose, and the release of glucose into the bloodstream for energy production.
     3. Enhancing cardiovascular function: Cortisol helps regulate blood pressure and maintain adequate blood flow to vital organs.
     4. Regulating mood and emotional responses: Cortisol can influence mood, emotions, and stress perception.

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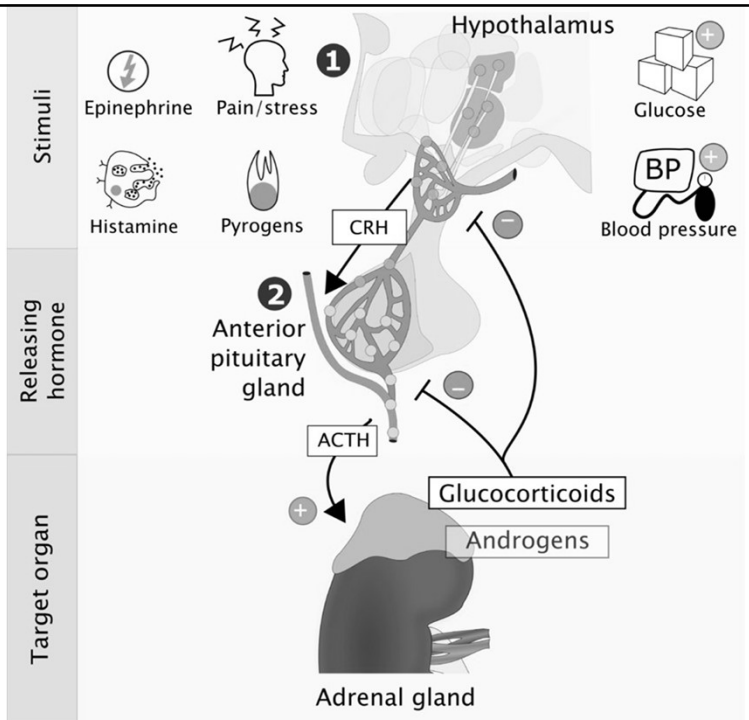

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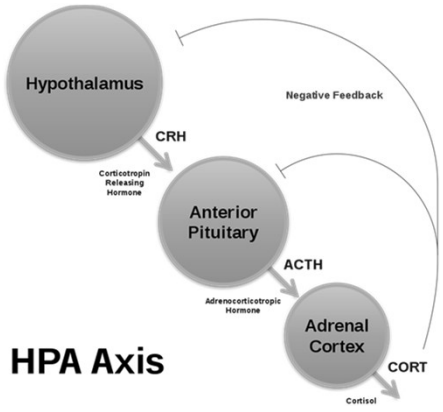
Adrenal Insufficiency

Classification of Adrenal Insufficiencies

1. Primary Hypoadrenalism = (Addison Disease)
2. Central Hypoadrenalism (ACTH deficiency)
    1. Secondary Hypoadrenalism
    2. Tertiary Hypoadrenalism



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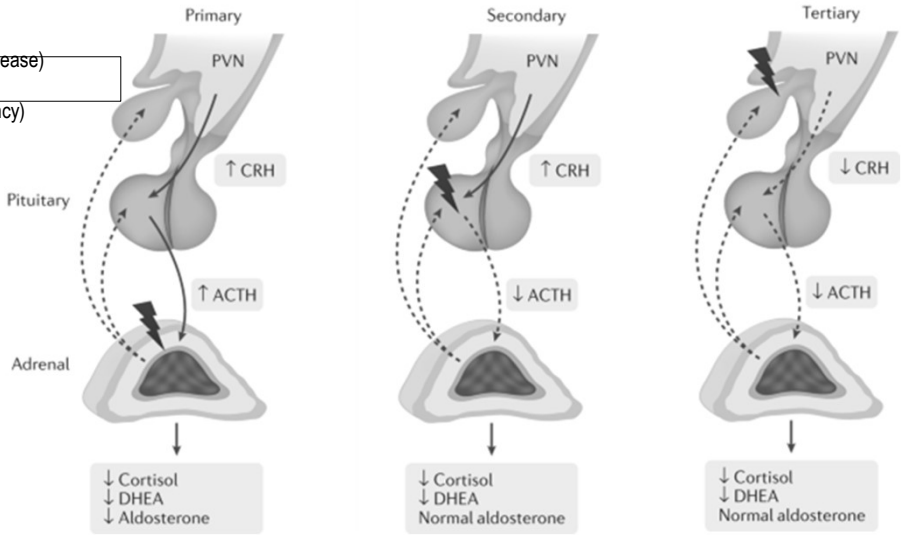

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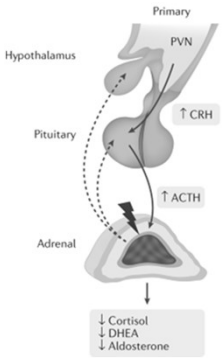

TABLE 93.1 Causes of Primary Adrenal Insufficiency

Diagnosis	Pathogenesis
Autoimmune Adrenal Insufficiency	
Infectious	
Genetic Disorders	
Familial Glucocorticoid Deficiency	

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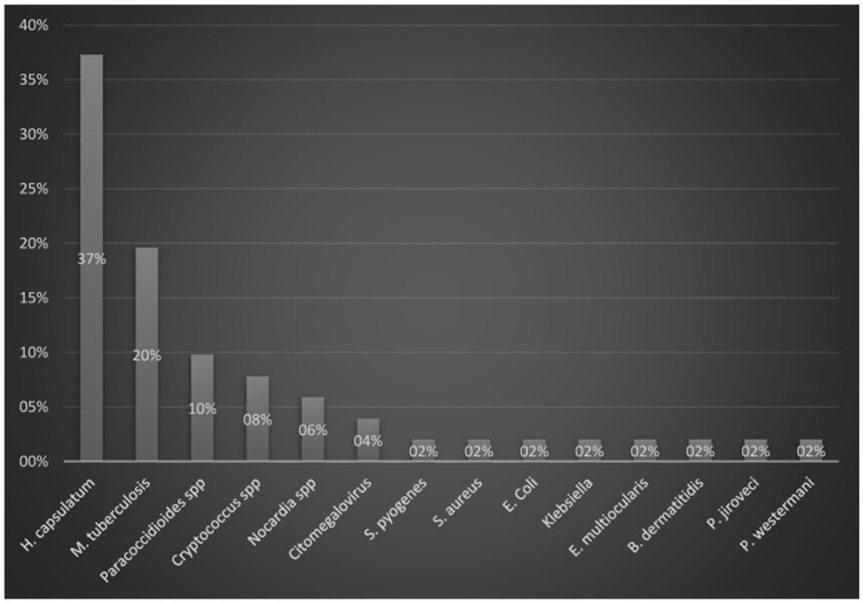
. 2023 Jul 11;12(14):4601. doi: 10.3390/jcm12144601

Isolated pathogens in adrenal biopsy samples



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Adrenal Abscesses: A Systematic Review of the Literature. J Clin Med, 2023 Jul 11;12(14):4601.

Adrenal involvement: source, location and side

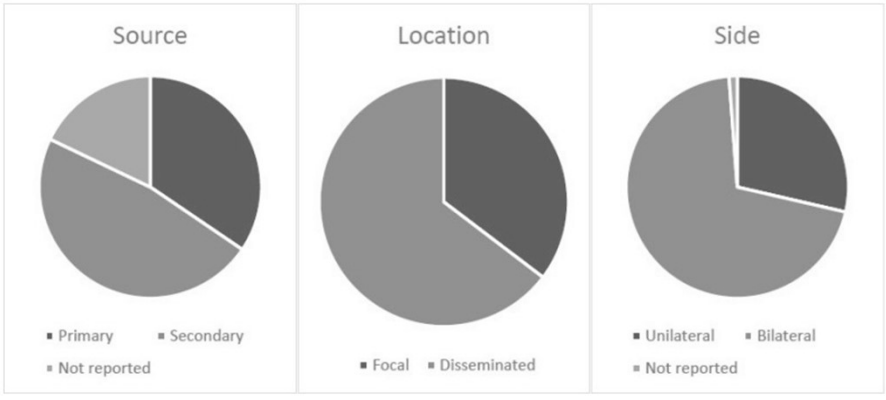

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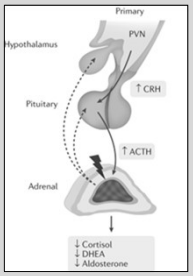
TABLE 93.2 Features of Autoimmune Polyendocrine Syndrome (APS)-I, APS-II, and X-Linked Polyendocrinopathy

Features	APS-I	APS-II	X-Linked Polyendocrinopathy Immune Dysfunction and Diarrhea
Prevalence	Rare	Common	Very rare
Time of onset	Infancy	Adulthood	Neonatal period
Genetic and inheritance	Monogenic, *AIRE*	Polygenic	*FOXP2*, X-linked
Immunodeficiency	Asplenism, susceptibility to candidiasis	None	Overwhelming autoimmunity Loss of regulatory T-cells
Adrenal insufficiency	60%–70%	40%–50%	+
Diabetes mellitus	<20%	50%–60%	80%
Autoimmune thyroid disease	10%	70%–75%	+
Premature ovarian failure		Up to 21%	
Hypoparathyroidism	80%–85%	0%–5%	–
Mucocutaneous candidiasis	70%–80%	Nil	–
Male hypogonadism	12%	Rare	–
Hypopituitarism	0%–2%	<0.1%	–
Chronic active hepatitis	+	Rare	+
Pernicious anemia	+	0.1%–10%	–
Skin manifestation	Vitiligo, alopecia 10%–15%	Vitiligo, 5%–10%	Eczema, psoriasis, or atopic dermatitis
Gastrointestinal	Diarrhea, constipation	Celiac, 4%–9%	Enteropathy, malabsorption



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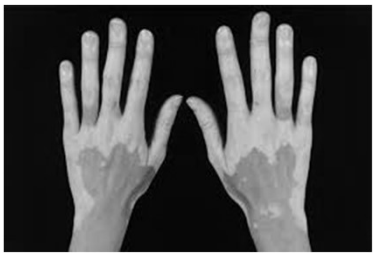
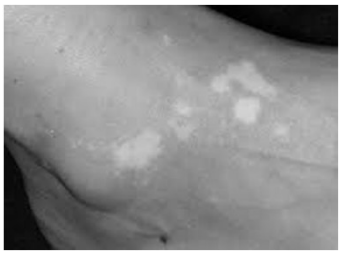
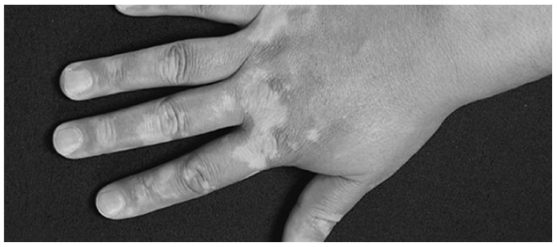
Vitiligo in Addison's Disease







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Causes of Central Adrenal Insufficiency

1. Hypothalamic-pituitary-adrenal suppression
2. Lesions of the hypothalamus or pituitary gland
3. Sarcoid
4. Head trauma
5. Isolated deficiency of ACTH

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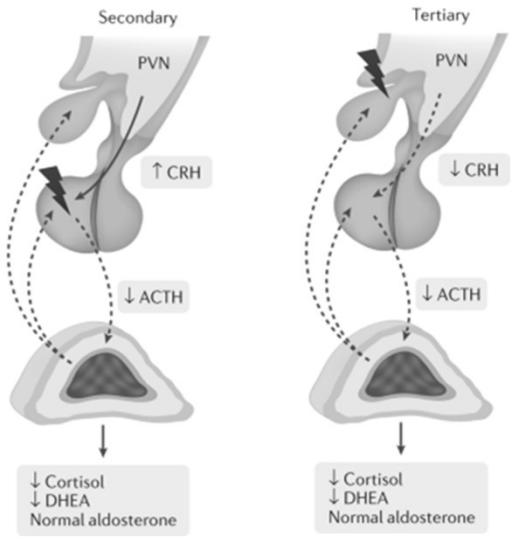

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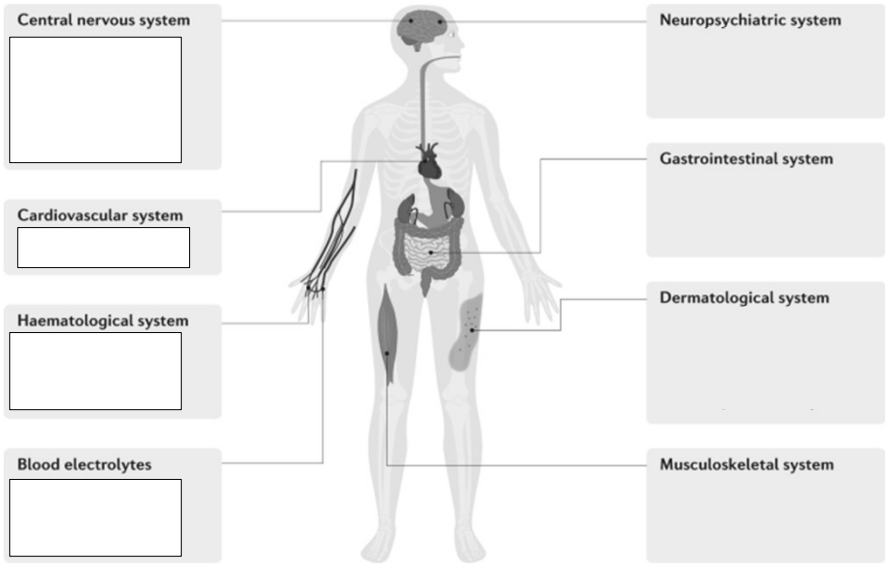
Clinical Manifestations of Adrenal Insufficiency



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Clinical & Laboratory Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13

Feature	Frequency (%)
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5

Feature	Frequency (%)
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

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Auricular calcification	5

Williams Textbook of ENDOCRINOLOGY, 14th 2020

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Mechanisms of Anemia in Adrenal Insufficiency

1. Cortisol deficiency: Cortisol has essential roles in the regulation of erythropoiesis, which is the process of red blood cell production in the bone marrow. Cortisol promotes the release of erythropoietin.

2. Iron deficiency: Adrenal insufficiency can be associated with gastrointestinal symptoms such as nausea, vomiting, and diarrhea, which can contribute to poor nutrient absorption and, consequently, iron deficiency.

3. Autoimmune destruction:
   - Hemolytic Anemia in Addison's disease?
   - Autoimmune process can also affect the bone marrow, leading to decreased red blood cell production and anemia.

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Causes of Simultaneous Hyperkalemia and Hyponatremia

1. Adrenal Insufficiency / Addison's disease:
2. Acute Renal Failure:
3. Medications: Some Diuretics
4. Acid-base disorders: Some acid-base imbalances, such as metabolic acidosis,
5. Kidney diseases: Certain kidney conditions, like chronic kidney disease or polycystic kidney disease, can impair the kidneys' ability to maintain the proper potassium and sodium levels
6. Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

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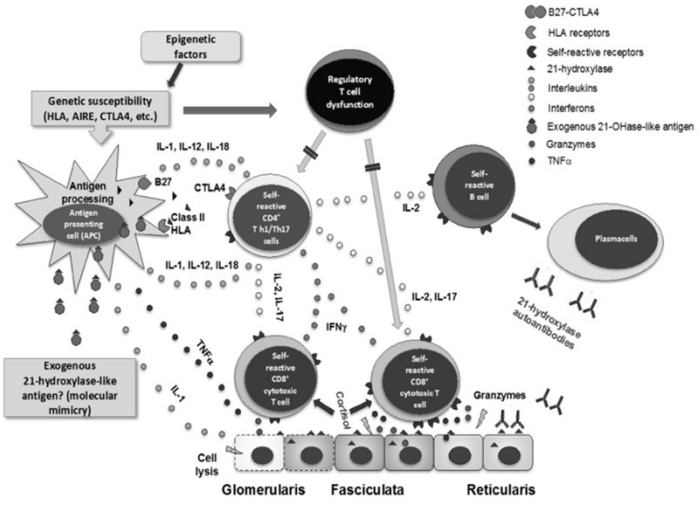
Mechanisms of Autoimmune Adrenalitis

1. Unknown exogenous Ags (viruses, bacteria, chemicals) cross reactive with 21-hydroxylase may activate Ag Presenting Cells.
2. APCs process and present 21-OH-like Ags to Th1 / Th17.
3. T-helper cells promote activation and clonal expansion of cytotoxic T-lymphocytes to exogenous Ag, also of autoreactive cytotoxic CD8+ T-cells and autoreactive B cells which release self-destructive cytokines and steroid 21-OH autoantibodies (21-OHAbs), respectively.
4. This self-reactive process might be allowed by possible deficiency in T-regulatory (T-reg) cells.
5. The progressive destruction of glomerular, fascicular, and reticular cells of adrenal cortex is mediated by cytotoxic T cells through local production of cytokines.
6. Invitro: 21-OHAbs may also activate the complement system and antibody-dependent cellular cytotoxicity.
7. Local release of cortisol by zona fasciculata may hamper or delay this process



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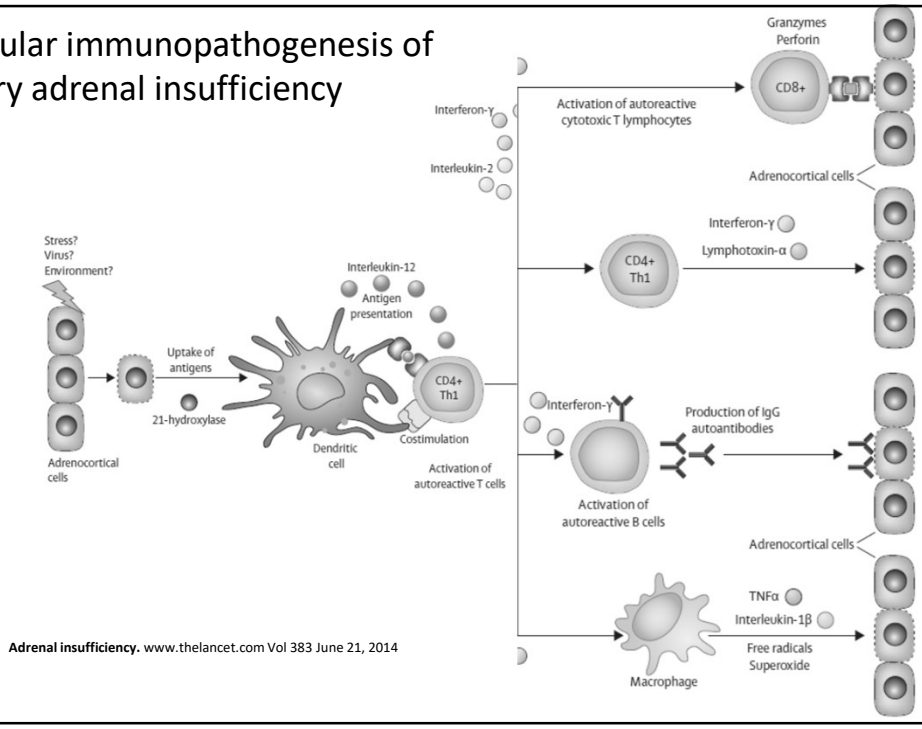
Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. Journal of Endocrinological Investigation. 2019

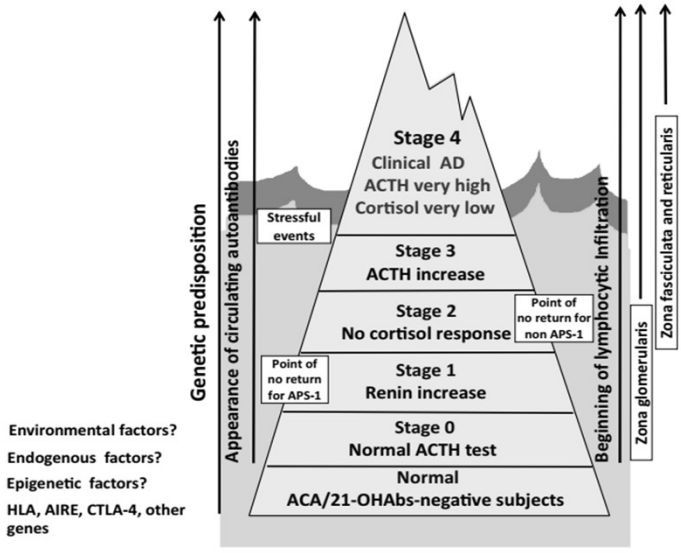
Molecular immunopathogenesis of primary adrenal insufficiency



Adrenal insufficiency. www.thelancet.com Vol 383 June 21, 2014

The natural history of autoimmune Addison's disease in adults

(From subclinical to clinically overt stage)



Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. Journal of Endocrinological Investigation. 2019

Stages of Adrenal Dysfunction in the History of AAD

Autoimmune Addison's disease	Stage	ACA and/or 21-OHAbs	Symptoms	Plasma renin	Plasma aldosterone	Plasma ACTH	Plasma cortisol	Plasma cortisol after i.v. ACTH (250 µg)
Potential	0	+	Absent	N	N	N	N	N

*Below 500 nmol/L. N, normal range.

The natural history of autoimmune Addison's disease from the detection of autoantibodies to development of the disease: a long-term follow-up study on 143 patients. Eur J Endo, 2019

Adrenal Insufficiency

Laboratory Diagnosis

Stages of Loss of Adrenal Function in Anti-Adrenal Ab^{+} Patients

Stage	Laboratory findings
0	Adrenal autoantibodies
1	Increased renin with low or normal aldosterone
2	Decreased response to ACTH stimulation
3	Persistently elevated ACTH
4	Low cortisol

Addison's Disease in Evolution: An Illustrative Case and Literature-ENDOCRINE PRACTICE Vol 20 No. 9 September 2014

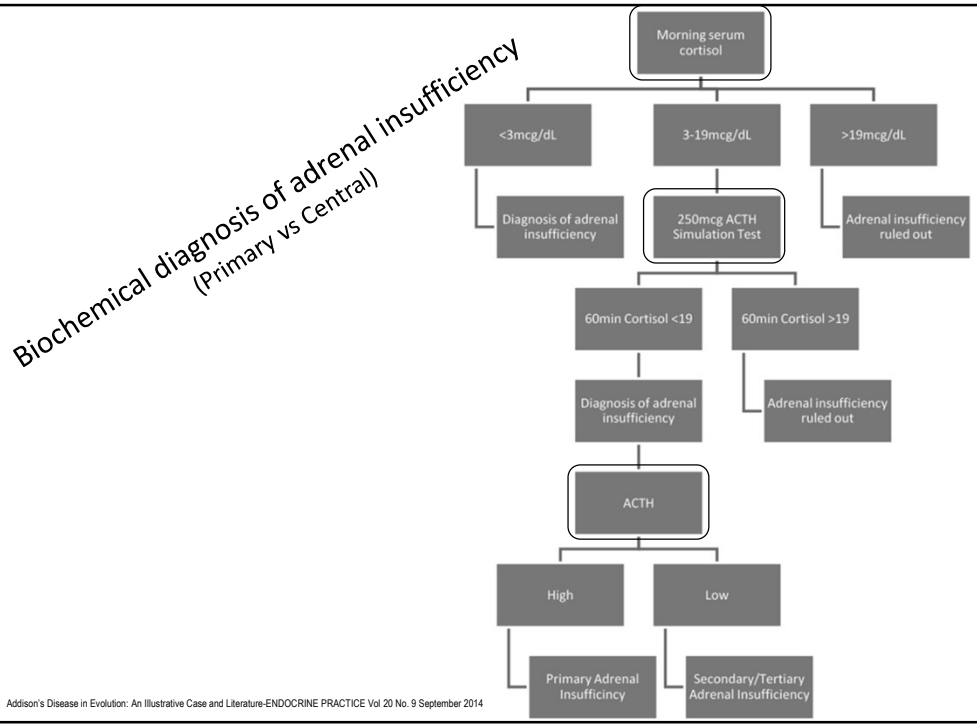
Consensus statement on the diagnosis, treatment and follow-up of patients with Primary Adrenal Insufficiency

Table 1 *Summary of recommendations*

Area	No	Recommendation*
Diagnosis	1	The diagnosis of PAI should be considered in all patients presenting with unexplained collapse, hypotension, vomiting or diarrhoea. Hyperpigmentation, hyponatraemia, hyperkalaemia, acidosis and hypoglycaemia increase clinical suspicion of PAI
	2	Treatment of suspected acute adrenal insufficiency should never be delayed by diagnostic procedures
	3	The diagnostic test for primary PAI should be paired measurement of serum cortisol and plasma ACTH. In equivocal cases, a synacthen (tetracosactide) stimulated (0.25 mg im or iv) peak serum cortisol <500 nmol L^{-1} is diagnostic of PAI
	4	S-cortisol <250 nmol L^{-1} and increased ACTH in the presence of acute illness (suspected acute adrenal insufficiency) is diagnostic of primary PAI. S-cortisol <400 nmol L^{-1} and increased ACTH in the presence of acute illness raises a strong suspicion of PAI

Consensus statement on the diagnosis, treatment ad follow-up of patients with primary adrenal insufficiency. Journal of Internal Medicine, 2013
(European Consortium& the Endocrine Society Clinical Practice Guideline)

Biochemical diagnosis of adrenal insufficiency (Primary vs Central)



Addison's Disease in Evolution: An Illustrative Case and Literature-ENDOCRINE PRACTICE Vol 20 No. 9 September 2014

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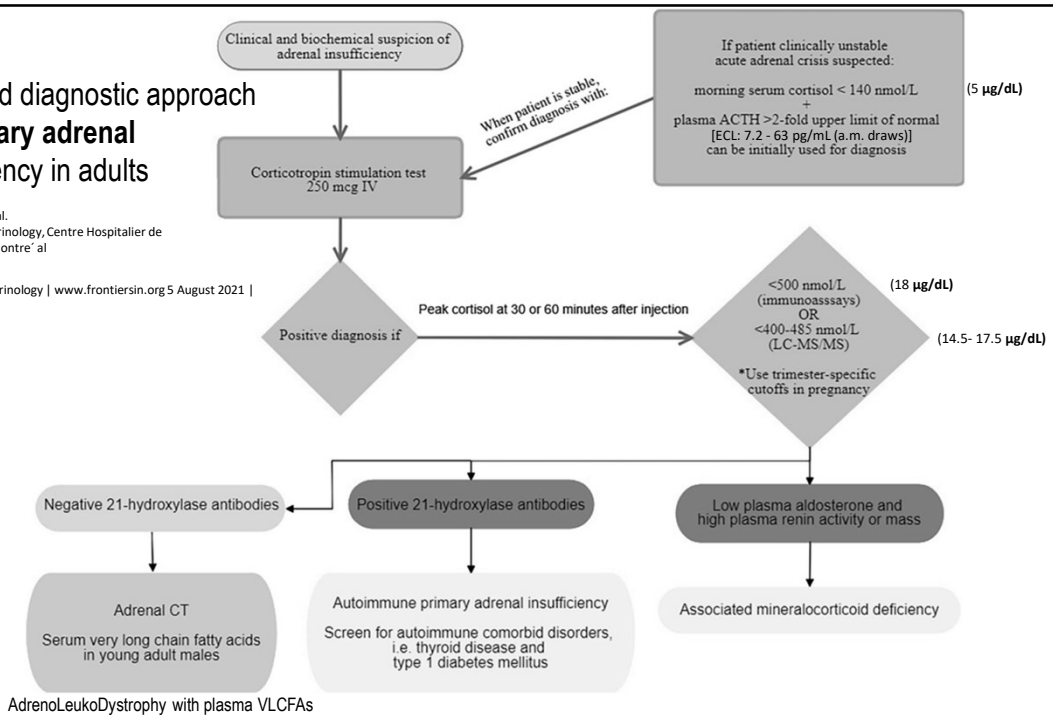
Proposed diagnostic approach for **primary adrenal** insufficiency in adults

Andre Lacroix et al.
Division of Endocrinology, Centre Hospitalier de l'Universite´ de Montre´al
QC, Canada

Frontiers in Endocrinology | www.frontiersin.org 5 August 2021 |



AdrenoLeukoDystrophy with plasma VLCFAs

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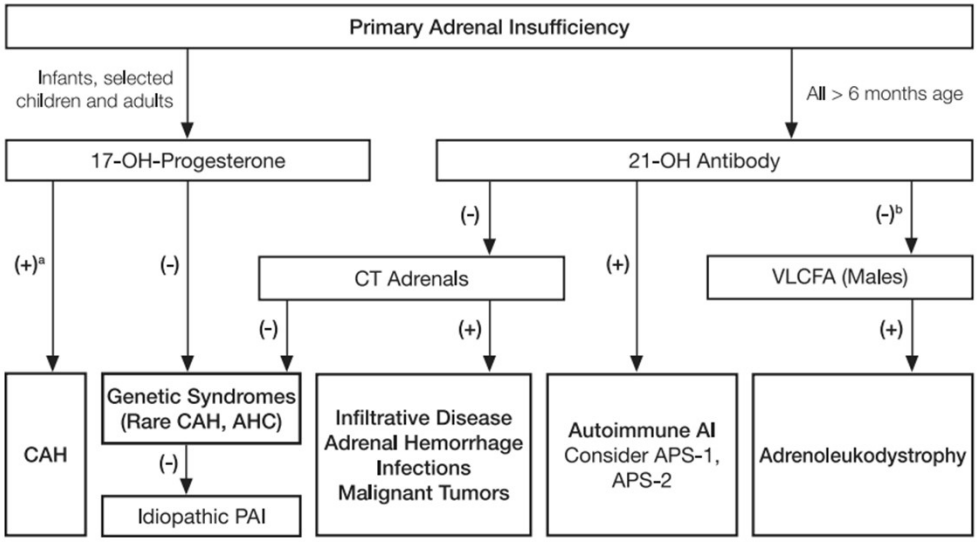
Lab Tests for Differential Diagnosis of Adrenal Insufficiencies

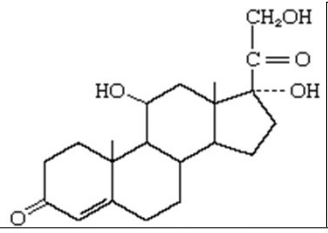
	Lab Tests				
Adrenal Insufficiency	**Cortisol 8 am**	**ACTH**	**Cortisol after ACTH**	**Cortisol after CRH**	**ACTH after CRH**
Primary	Low	High	No Response	No Response	Highly Rise
Secondary	Low	Low	Rise	No Response	No Response
Tertiary	Low	Low	Rise	Rise	Rise

Diagnosis & Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline



J Clin Endocrinol Metab, Feb. 2016, 101(2):364–389

Cortisol Molecule & Assays



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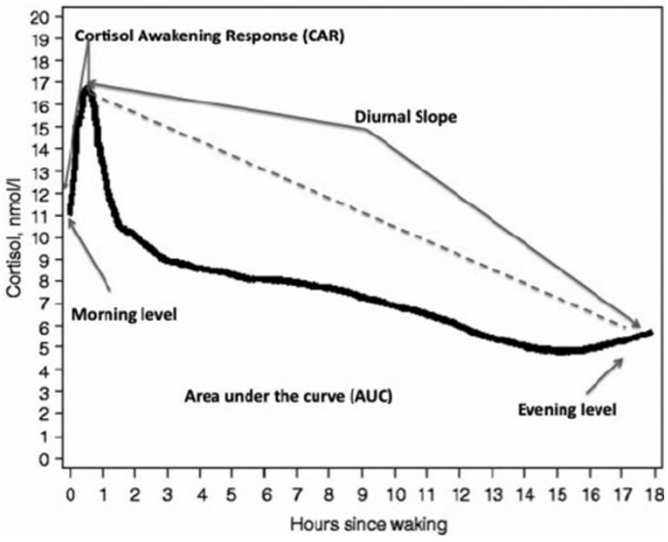
Cortisol Diurnal Variation



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Reference Values

FREE CORTISOL

6 - 10:30 a.m. Collection: 0.121 - 1.065 µ /dL

TOTAL CORTISOL

5 - 25 µ/dL (a.m.)
2 - 14 µ /dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.
Reference Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

SPECIMEN STABILITY INFORMATION

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	28 days	

MayoClinic-2023

		Biological Variation			Desirable specification		
Sample	Analyte	CV_g	CV_i	II	I(%)	B(%)	TE(%)
Serum	**Cortisol**	15.2	38.1	0.4	7.6	10.26	22.8
Plasma	ACTH						
Serum	17-HydroxyProgesterone	19.6	50.4	0.38	9.8	13.5	29.7

https://www.westgard.com/biodatabase1.htm-2023

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Method comparison results and Bland-Altman plots of the Cortisol II assay vs. LC-MS/MS in serum

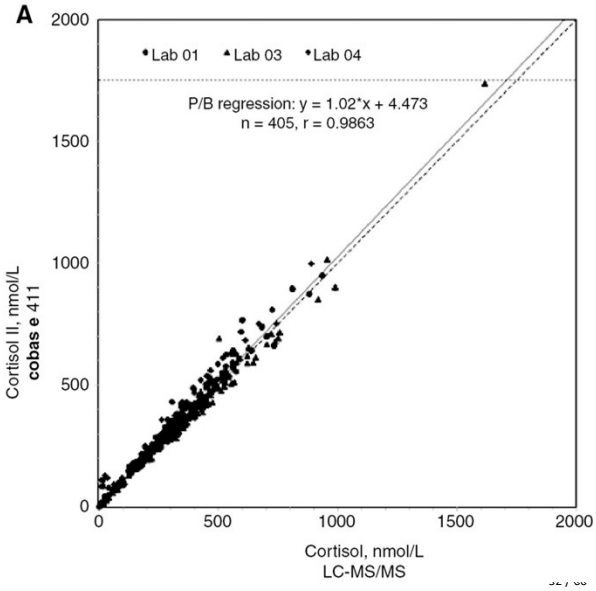
Vogeser, Michael, et. Al. ..

Institute of Laboratory Medicine, Hospital of the University of Munich (LMU), Munich, Germany

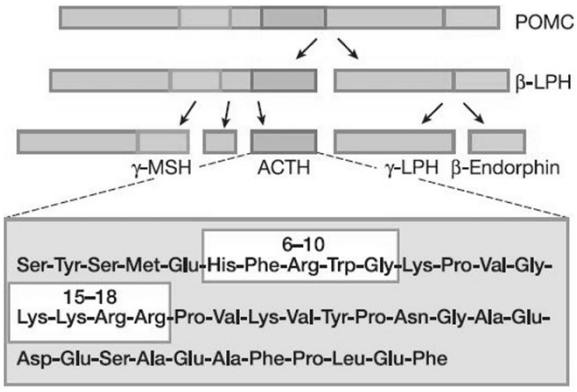
"**Multicenter performance evaluation of a second generation cortisol assay**"

Clinical Chemistry and Laboratory Medicine (CCLM), vol. 55, no. 6, 2017, pp. 826-835. https://doi.org/10.1515/cclm-2016-0400

The Elecsys ACTH assay employs two monoclonal antibodies specific for ACTH (9-12) and for the C-terminal region (ACTH 36-39).



Processing of ProOpioMelanoCortin (POMC) to ACTH



- POMC is converted to ACTH (39 aa) and other peptides in the anterior pituitary.
- The boxes within the ACTH structure indicate regions important for steroidogenic activity (residues 6-10) and binding to the ACTH receptor (15-18).
- α-Melanocyte-stimulating hormone also derives from the POMC precursor and contains the first 13 residues of ACTH.
- LPH, lipotropin;
- MSH, melanocyte-stimulating hormone.

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Reference Values

ACTH

7.2 - 63 pg/mL (a.m. draws)

No established reference values for p.m. draws
Pediatric reference values are the same as adults, as confirmed by peer reviewed literature

Preferred Method: ECL

SPECIMEN STABILITY INFORMATION

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Frozen (preferred)	28 days	
	Refrigerated	3 hours	
	Ambient	2 hours	

MayoClinic-2023

		Biological Variation			Desirable specification		
Sample	Analyte	CV_g	CV_i	II	I(%)	B(%)	TE(%)
Serum	Cortisol	15.2	38.1	0.4	7.6	10.26	22.8
Plasma	**ACTH**						
Serum	17-HydroxyProgesterone	19.6	50.4	0.38	9.8	13.5	29.7

https://www.westgard.com/biodatabase1.htm-2023

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ACTH assay Collection Instructions:

1. Morning (6 a.m.-10:30 a.m.) specimen is desirable.
2. Collect with a pre-chilled lavender top (EDTA) tube and transport to the laboratory on ice.
3. Centrifuge at refrigerated temperature within 2 hours and immediately separate plasma from cells.
4. Immediately freeze plasma

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Reference Values

17-Hydroxyprogesterone

Males: <220 ng/dL

Females Follicular: <80 ng/dL Luteal: <285 ng/dL Postmenopausal: <51 ng/dL

Reference Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

SPECIMEN STABILITY INFORMATION

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	28 days	
	Frozen	28 days	
	Ambient	7 days	

MayoClinic-2023

		Biological Variation			Desirable specification		
Sample	Analyte	CV_g	CV_i	II	I(%)	B(%)	TE(%)
Serum	Cortisol	15.2	38.1	0.4	7.6	10.26	22.8
Plasma	ACTH						
Serum	**17-HydroxyProgesterone**	19.6	50.4	0.38	9.8	13.5	29.7

https://www.westgard.com/biodatabase1.htm-2023

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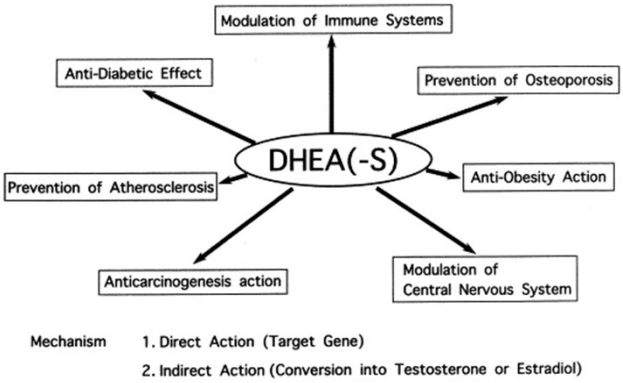
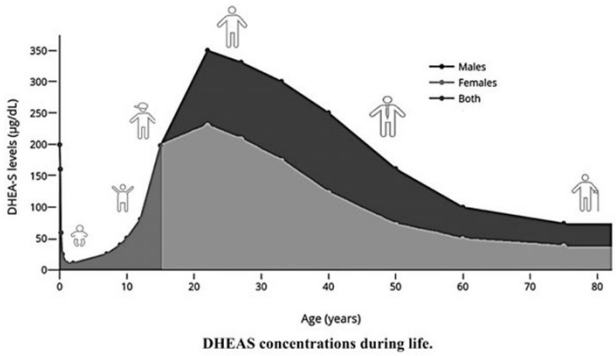
DHEA, Chronic Fatigue Syndrome and Adrenal Imbalance



Mechanism 1. Direct Action (Target Gene)
2. Indirect Action (Conversion into Testosterone or Estradiol)



DHEAS concentrations during life.

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DHEA, Chronic Fatigue Syndrome and Adrenal Imbalance

- High levels of plasma circulating DHEA are suggested as a marker of human longevity,
- Various pathophysiological conditions lead to a decreased DHEA level, including
  - adrenal insufficiency,
  - severe systemic diseases,
  - acute stress, and
  - anorexia.
- More recent studies have established the importance of DHEA in (CNS).
- A Neuro-Steroid with potential activities as
  - potential neuroprotective,
  - pro-cognitive,
  - anxiolytic, and
  - antidepressant effects.

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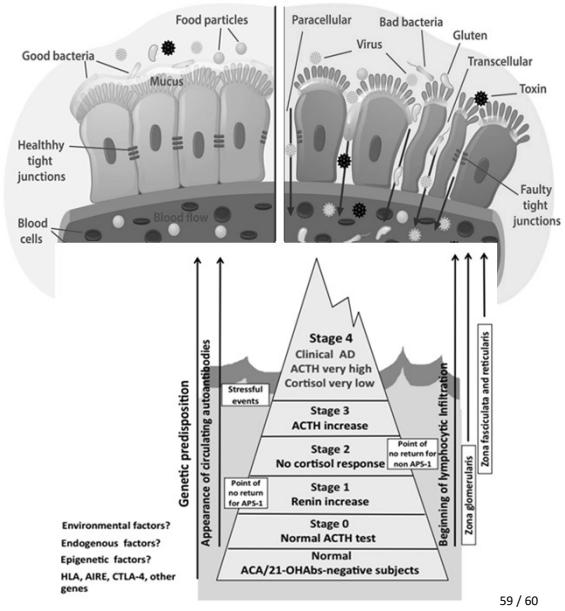
Leaky Gut Syndrome

Five steps of healing the gut

1. **Remove**
   - Elimination diet to get rid of the most triggering foods.
   - Treat any signs of infection or overgrowth of bacteria in the gut.
2. **Replace**
   - Our bodies need adequate gastric-acid digestive enzymes to break down our food. If there are signs of deficiency, we replace what is missing.
   - Medications such as proton pump inhibitors create an acid deficiency in the stomach and drive the inflammatory process in the gut.
3. **Repair**
   - The damaged gut needs nutrients to repair itself. We use natural, plant-based juices and glutamine-based supplements to expedite this process.
   - Patients notice a significant improvement in about two weeks under optimal conditions.
4. **Re-inoculate**
   - The microbiome of the gut outnumbers our body's cells 100:1. We need a diversity of bacteria and yeast to support the processes in the gut.
   - By using probiotics, prebiotics, and fermented foods, like kefir, kimchi, and sauerkraut.
5. **Rebalance**
   - Recall a time when stress has led to an overactive gastrointestinal tract.
   - It's necessary to reduce stress, slow down, and transition to a calmer state to maintain progress.



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Thank You for Your Attention

Adrenal Insufficiency

dr.bakhtiari.academy

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