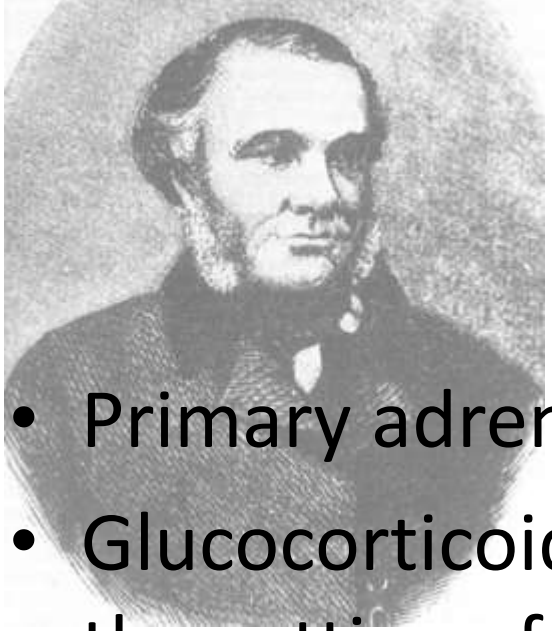
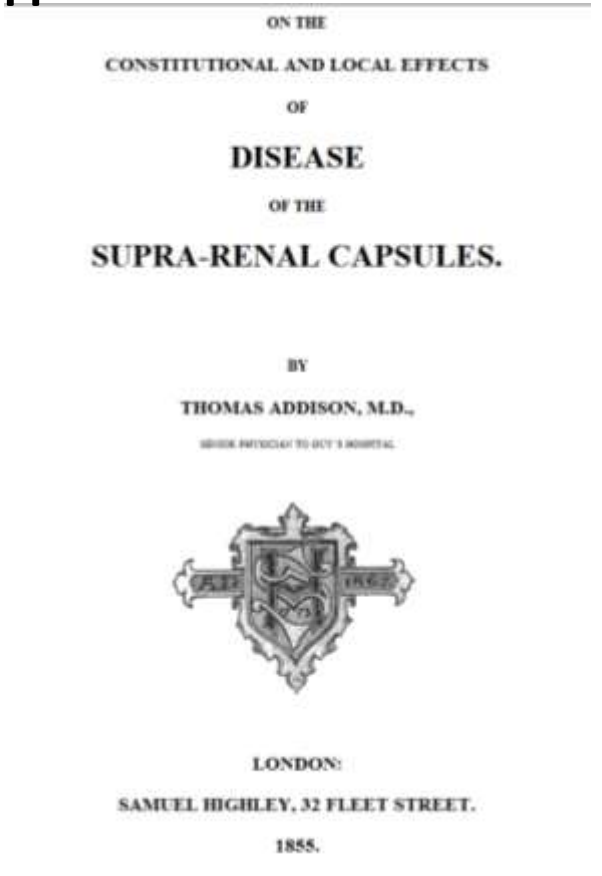
ADDISON DISEASE

Dr. Gagan Velayudhan



- Primary adrenocortical deficiency
- Glucocorticoid deficiency ocurring in the setting of adrenal disease
- Described Thomas Addison
- In 1855, *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*



ON THE

CONSTITUTIONAL AND LOCAL EFFECTS

OF

DISEASE

OF THE

SUPRA-RENAL CAPSULES.

BY

THOMAS ADDISON, M.D.,

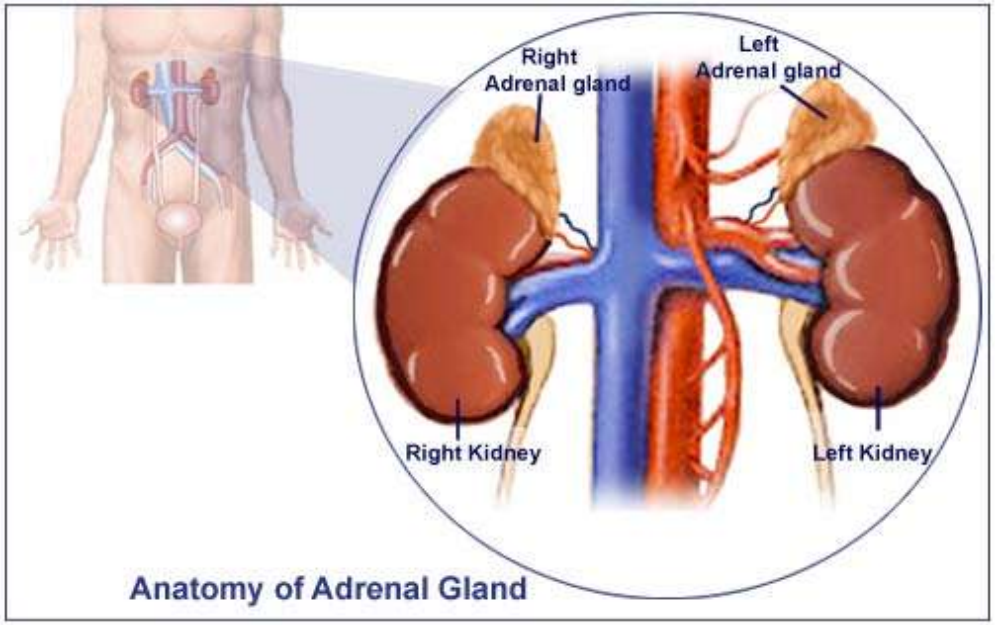
LONDON:

SAMUEL HIGHLEY, 32 FLEET STREET.

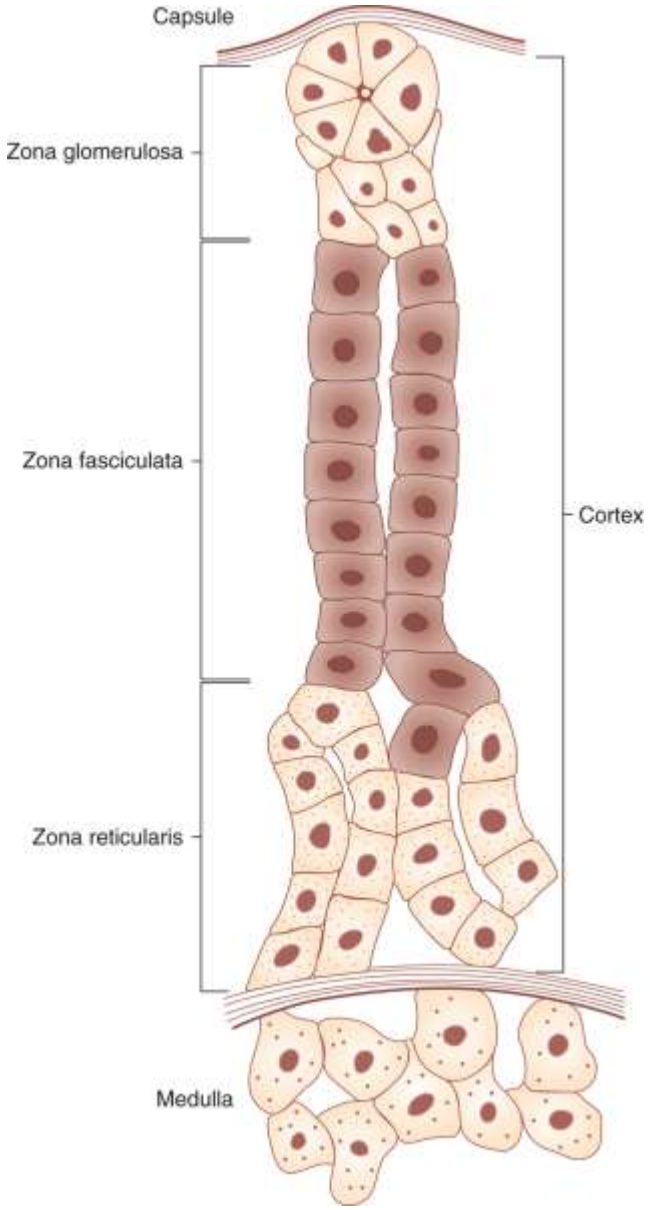
1855.

ANATOMY

- A pyramidal structure
- 6 - 11 g in weight
- 2 x 4 x 1 cm lying immediately above the kidney on its posteromedial surface.



- the zona glomerulosa constitutes approximately 15% of the cortex
- The zona fasciculata makes up 75% of the cortex;
- The innermost zona reticularis is sharply demarcated from both the zona fasciculata and adrenal medulla.



- Arterial supply is conveyed by up to 12 small arteries from the aorta, inferior phrenic, renal, and intercostal arteries.
- Subcapsular arteriolar plexus, into cortex, dense sinusoidal plexus in zona reticularis, empties into central vein
- The right adrenal vein is short, draining directly into the inferior vena cava; the longer left adrenal vein usually drains into the left renal vein.

BASIC PHYSIOLOGY

- 3 major classes of steroids:

(1) Glucocorticoids

cortisol, corticosterone

fasciculata cell layer

(2) Mineralocorticoids

aldosterone, deoxycorticosterone

Glomerulosa(outer) cell layer

(3) Adrenal androgens

mainly androgens

reticularis cell layer

‘Functional zonation’ of the Adrenal Cortex

- Glucocorticoids are secreted in relatively high amounts (cortisol 10 to 20 mg/day) from the zona fasciculata under the control of ACTH
- mineralocorticoids are secreted in low amounts (aldosterone 100 to 150 µg/day) from the zona glomerulosa under the principal control of angiotensin II

- adrenal androgens (DHEA, dehydroepiandrosterone sulfate [DHEAS], androstenedione) are the most abundant steroids secreted from the adult adrenal gland (>20 mg/day).
- The zona glomerulosa cannot synthesize cortisol because it does not express 17α-hydroxylase

Functions

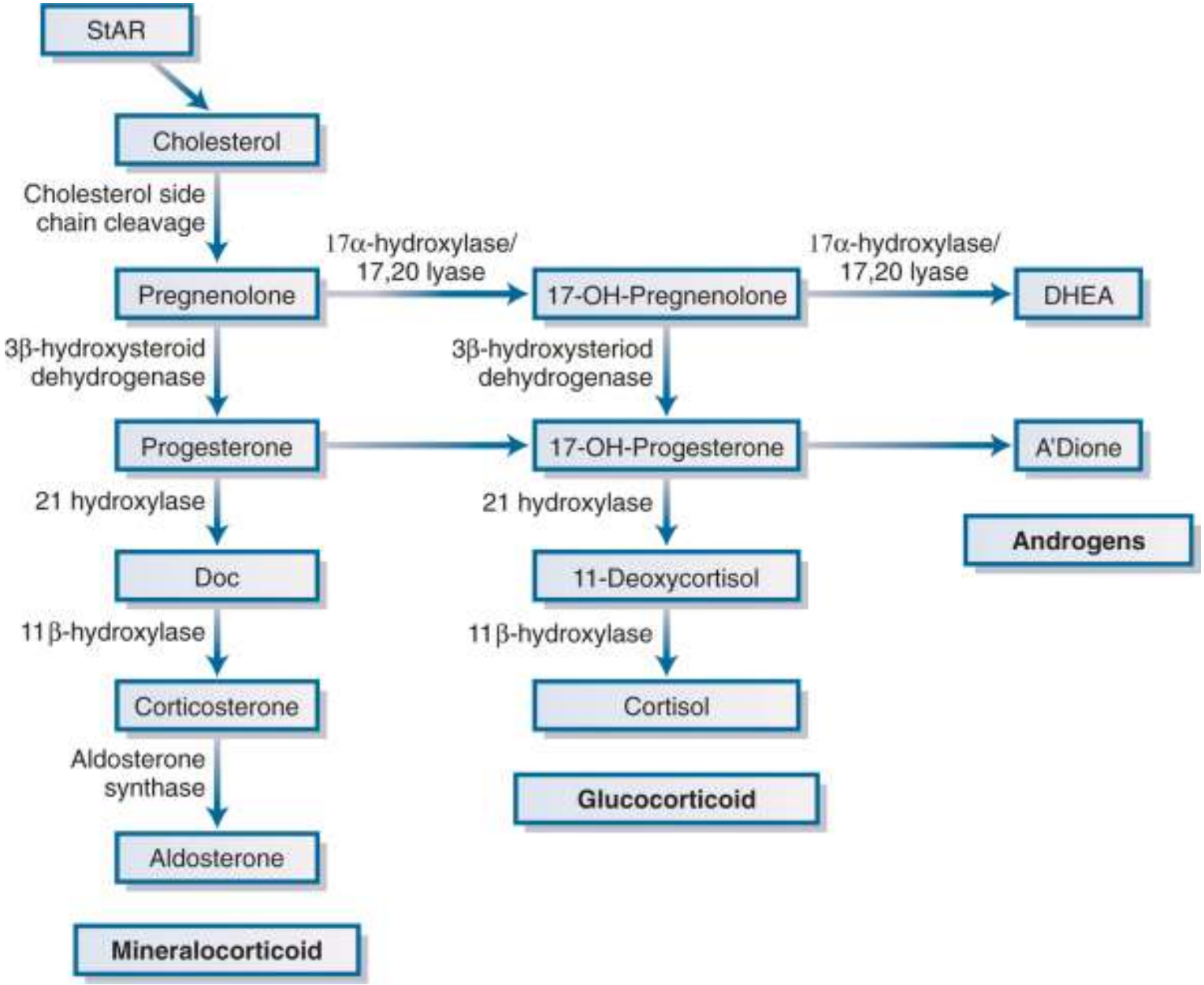
Glucocorticoids – intermediary metabolism and immune responses

Mineralocorticoids – BP ,vascular volume, electrolytes

Androgens – Secondary sexual characteristics

STEROIDOGENESIS

- Cholesterol is the precursor for all adrenal steroidogenesis.
- provided from the circulation in the form of low-density lipoprotein (LDL) cholesterol.


StAR
Cholesterol
Cholesterol side chain cleavage
Pregnenolone
17α-hydroxylase/ 17,20 lyase
17-OH-Pregnenolone
17α-hydroxylase/ 17,20 lyase
DHEA
3β-hydroxysteroid dehydrogenase
3β-hydroxysteriod dehydrogenase
Progesterone
17-OH-Progesterone
A'Dione
Androgens
21 hydroxylase
21 hydroxylase
Doc
11-Deoxycortisol
11β-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
Aldosterone synthase
Glucocorticoid
Aldosterone
Mineralocorticoid

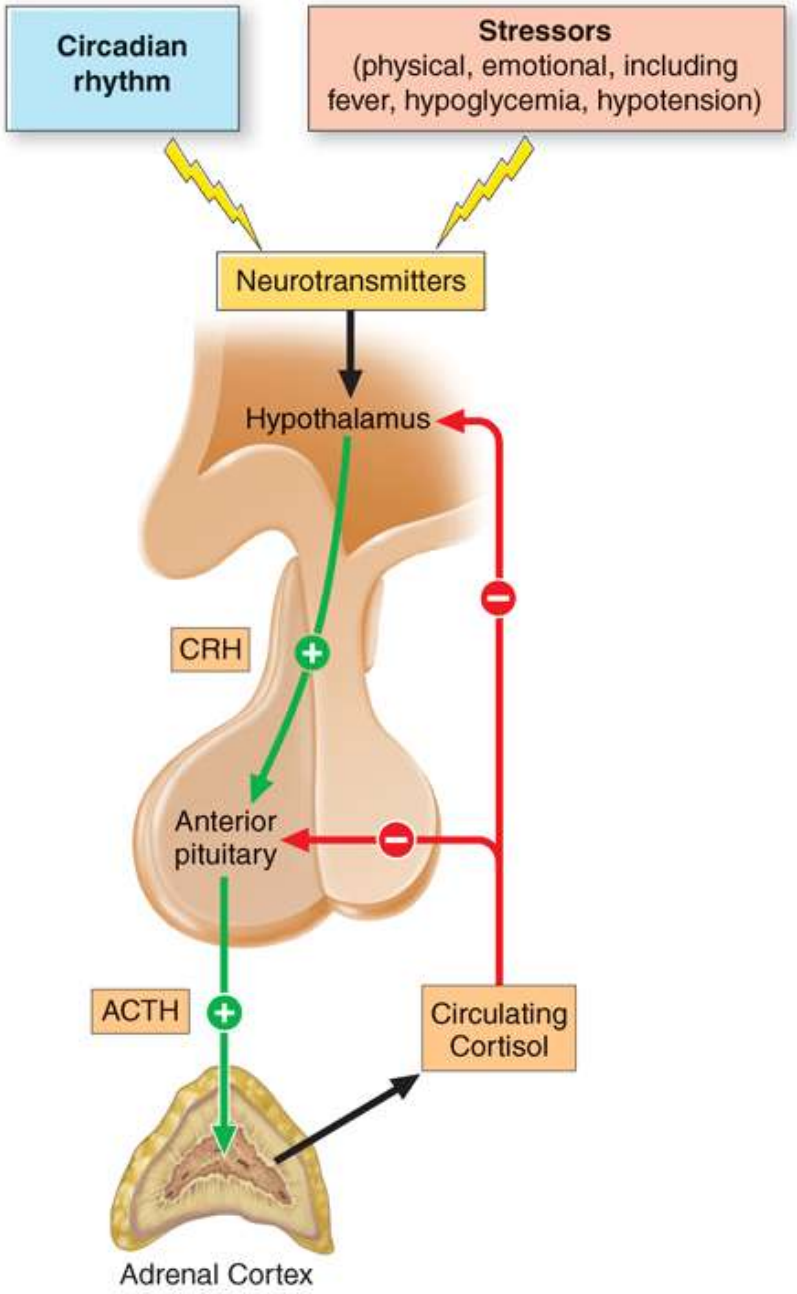
Plasma cortisol transport

Bound form

- *Alpha$_2$-globulin*:
  transcortin / cortisol-binding globulin [CBG]
- *Albumin*.

Free cortisol – (<5%)

- *Is physiologically active*
- *Only filtered at the glomerulus*


Circadian rhythm
Stressors
(physical, emotional, including fever, hypoglycemia, hypotension)
Neurotransmitters
Hypothalamus
CRH
Anterior pituitary
ACTH
Circulating Cortisol
Adrenal Cortex

ACTH

- Proopiomelanocortin (POMC)- precursor molecule

  secreted from Basophilic cells of Anterior pituitary

- Corticotropin-releasing hormone (CRH)

  Median eminence of the hypothalamus

- POMC expression within the hypothalamus and its cleavage to MSHs appear to be of crucial importance in regulating hair pigmentation and appetite control

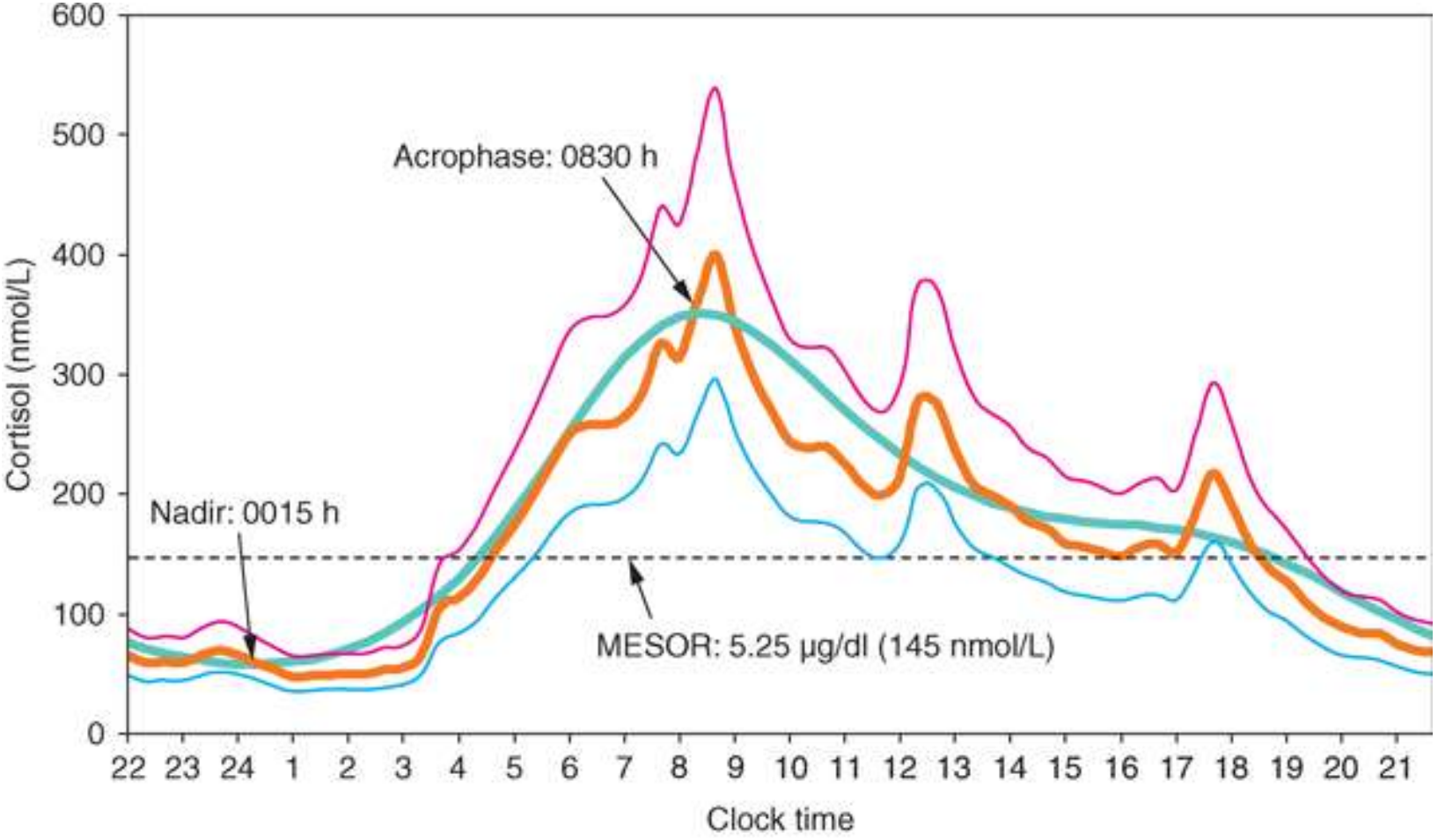
Control Of ACTH release

- CRH
- Free cortisol concentration in plasma
- Stress(e.g., pyrogens, surgery, hypoglycemia, exercise, and severe emotional trauma)
- Sleep-wake cycle

Circadian Rhythm

- ACTH is secreted in a pulsatile fashion
- levels are highest on waking and decline throughout the day, reaching nadir values in the evening
- pulse frequency is higher in normal adult men than in women (on average 18 pulses versus 10 pulses per 24 hours),
- the circadian ACTH rhythm appears to be mediated principally by an increased ACTH pulse amplitude between 5 and 9 AM but also by a reduction in ACTH pulse frequency between 6 and 12 PM

- Food ingestion is a further stimulus to ACTH secretion.
- Circadian rhythm is dependent upon both day-night and sleep-wake patterns and is disrupted by alternating day-night shift working patterns and by long-distance travel across time zones.It may take up to 2 weeks for circadian rhythm to reset to an altered day-night cycle


600
500
400
300
200
100
0
Cortisol (nmol/L)
Acrophase: 0830 h
Nadir: 0015 h
MESOR: 5.25 µg/dl (145 nmol/L)
22 23 24 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Clock time

Primary Adrenal Insufficiency

- Most common cause worldwide
  - Infectious
  - Tuberculous
    - Haematogenous Spread
    - Enlarged, caseation, fibrosis with calcification (50%)
  - fungal infections (histoplasmosis, cryptococcosis), cytomegalovirus

- Autoimmune adrenalitis
  - 30-40% isolated
  - 60-70% part of autoimmune polyglandular syndrome
    - APS1 (APECED) – AIRE gene, autosomal recessive
      - Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphoma
    - APS2 (HLA – DR3, CTLA – 4) polygenic
      - Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
  - Autoantibodies to 21-hydroxylase

Incidence of other endocrine and autoimmune diseases in patients with autoimmune adrenalitis

Thyroid disease	
Hypothyroidism	8
Nontoxic goiter	7
Thyrotoxicosis	7
Gonadal failure	
Ovarian	20
Testicular	2
Insulin-dependent diabetes mellitus	11
Hypoparathyroidism	10
Pernicious anemia	5
None	53

Others

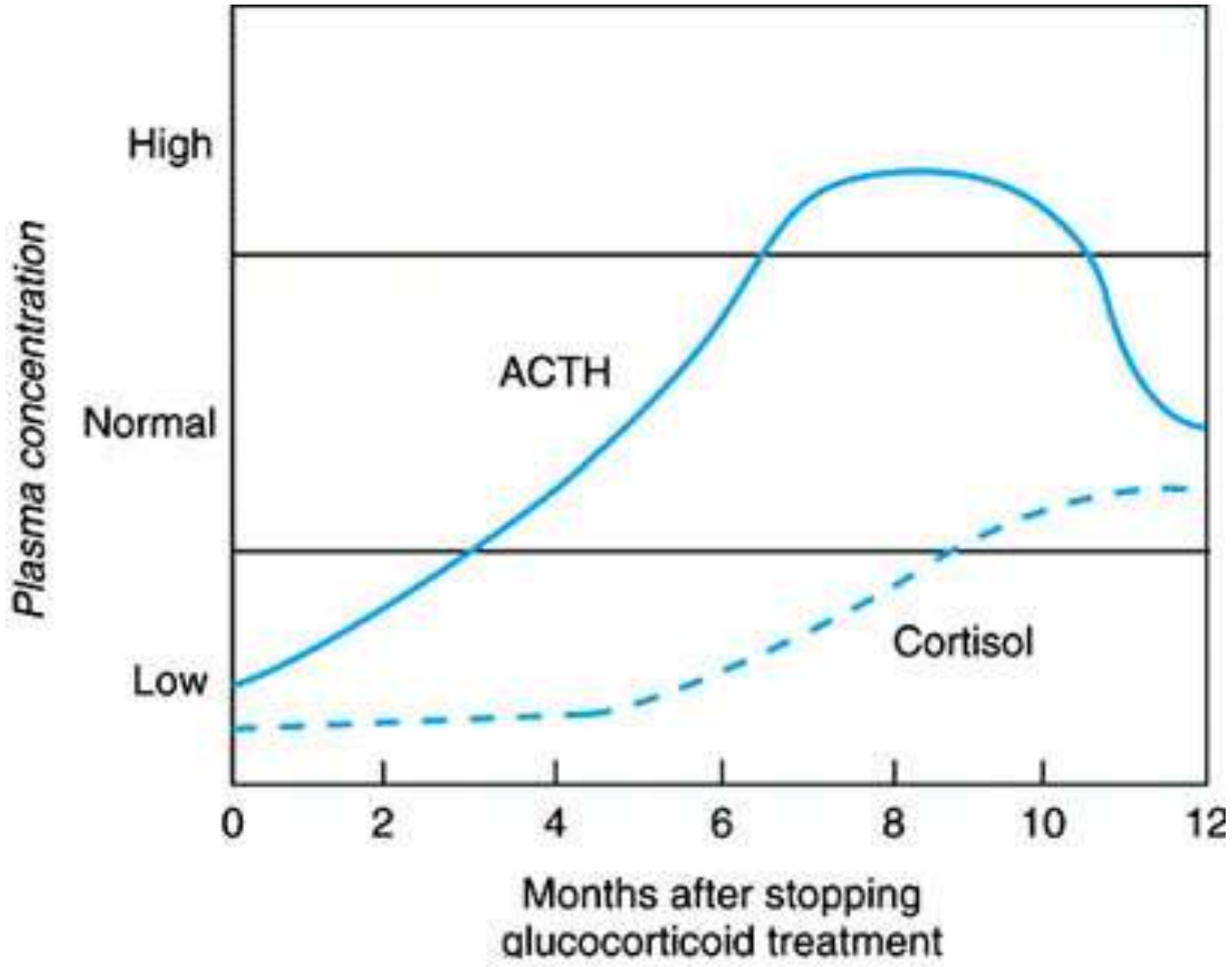
- Adrenal infiltration
  - Metastases (rare), lymphomas, sarcoidosis, amyloidosis, hemochromatosis
- Adrenal Hemorrhage
  - Meningococcal sepsis, Primary APLA
- X linked adrenoleukodystrophy
  - Accumulation of VLCFA
  - 50% cerebral ALD, 35% adrenomyeloneuropathy, rest - primary adrenal insufficiency
- Adrenal hypoplasia congenita
  - X-linked disorder (DAX-1)
  - congenital adrenal insufficiency
  - hypogonadotrophic hypogonadism
- Familial glucocorticoid deficiency
  - Rare autosomal recessive
  - Resistance to ACTH
  - MCR-2. MRAP
- Triple A or Allgroves syndrome
  - ACTH resistance, achalasia, and alacrima

- Congenital Causes
  - Congenital Adrenal Hyperplasia
  - factors regulating adrenal development and steroidogenesis (DAX-1, SF-1), cholesterol synthesis, import and cleavage (DHCR7, StAR, CYP11A1), and elements of the adrenal ACTH response pathway (MC2R, MRAP)

Autoimmune polyglandular syndrome 1 (APS1)	*AIRE*	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, rarely lymphomas
Autoimmune polyglandular syndrome 2 (APS2)	Associations with HLA-DR3, CTLA-4	Hypothyroidism, hyperthyroidism, premature ovarian failure, vitiligo, type 1 diabetes mellitus, pernicious anemia
Isolated autoimmune adrenalitis	Associations with HLA-DR3, CTLA-4	
Congenital adrenal hyperplasia (CAH)	*CYP21A2, CYP11B1, CYP17A1, HSD3B2, POR*	See Table 342-10 (see also Chap. 349)
Congenital lipoid adrenal hyperplasia (CLAH)	*StAR, CYP11A1*	46,XY DSD, gonadal failure (see also Chap. 349)
Adrenal hypoplasia congenita (AHC)	*NR0B1* (DAX-1), *NR5A1* (SF-1)	46,XY DSD, gonadal failure (see also Chap. 349)
Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN)	*X-ALD*	Demyelination of central nervous system (ALD) or spinal cord and peripheral nerves (AMN)
Familial glucocorticoid deficiency - FGD1 - FGD2 - FGD3 Triple A syndrome	*MC2R* *MRAP* ? *AAAS*	ACTH insensitivity syndromes due to mutations in the ACTH receptor MC2R and its accessory protein MRAP tall stature Alacrima, achalasia, neurologic impairment
Smith-Lemli-Opitz-Syndrome	*SLOS*	Cholesterol synthesis disorder associated with mental retardation, craniofacial malformations, growth failure
Kearns-Sayre syndrome	Mitochondrial DNA deletions	Progressive external ophthalmoplegia, pigmentary retinal degeneration, cardiac conduction defects, gonadal failure, hypoparathyroidism, type 1 diabetes
IMAGe syndrome	?	Intrauterine growth retardation, metaphyseal dysplasia, genital anomalies
Adrenal infections		Tuberculosis, HIV, CMV, cryptococcosis, histoplasmosis, coccidioidomycosis
Adrenal infiltration		Metastases, lymphomas, sarcoidosis, amyloidosis, hemochromatosis
Adrenal hemorrhage		Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome
Drug-induced		Mitotane, aminoglutethimide, arbiraterone, trilostane, etomidate, ketoconazole, suramin, RU486
Bilateral adrenalectomy		E.g., in the management of Cushing's or after bilateral nephrectomy

Secondary Adrenal Insufficiency

- Iatrogenic suppression
  - Adrenal atrophy and supression to be anticipated
  - >30mg hydrocortisone/day orally(~7.5 mg prednisolone, 0.75mg/day dexamethasone) for more than 3 weeks
  - Dosing pattern, higher dose in evening – greater supression
  - Also inadequate replacement in a patient on glucocorticoid replacement during periods of stress


High
Normal
Low
Plasma concentration
ACTH
Cortisol
0
2
4
6
8
10
12
Months after stopping
glucocorticoid treatment

- Pituitary/ Hypothalamic Tumours
  - Post surgery/radiation
- Pituitary apoplexy
  - Infarction pituitary adenoma
  - Sheehan's syndrome
- Autoimmune disease (Rare)
- Pituitary infiltration

Diagnosis	Gene	Associated Features
Pituitary tumors (endocrine active and inactive adenomas, very rare: carcinoma)		Depending on tumor size and location: visual field impairment (bilateral hemianopia), hyperprolactinemia, secondary hypothyroidism, hypogonadism, growth hormone deficiency
Other mass lesions affecting the hypothalamic-pituitary region		Craniopharyngioma, meningioma, ependymoma, metastases
Pituitary irradiation		Radiotherapy administered for pituitary tumors, brain tumors, or craniospinal irradiation in leukemia
Autoimmune hypophysitis		Often associated with pregnancy; may present with panhypopituitarism or isolated ACTH deficiency; can be associated with autoimmune thyroid disease, more rarely with vitiligo, premature ovarian failure, type 1 diabetes, pernicious anemia
Pituitary apoplexy/hemorrhage		Hemorrhagic infarction of large pituitary adenomas or pituitary infarction consequent to traumatic major blood loss (e.g., surgery or pregnancy: Sheehan's syndrome)
Pituitary infiltration		Tuberculosis, actinomycosis, sarcoidosis, histiocytosis X, granulomatosis with polyangiitis (Wegener's), metastases
Drug-induced		Chronic glucocorticoid excess (endogenous or exogenous)
Congenital isolated ACTH deficiency	*TBX19* (Tpit)	
Combined pituitary hormone deficiency (CPHD)	*PROP-1*	Progressive development of CPHD in the order GH, PRL, TSH, LH/FSH, ACTH
	HESX1	CPHD and septo-optic dysplasia
	LHX3	CPHD and limited neck rotation, sensorineural deafness
	LHX4	CPHD and cerebellar abnormalities
	SOX3	CPHD and variable mental retardation
Proopiomelanocortin (POMC) deficiency	*POMC*	Early-onset obesity, red hair pigmentation

- Hypoadrenalism during critical illness
  - Functional adrenal insufficiency
  - Previously intact HPA axis
  - Uncertain etiology, difficult to define
  - Transient
  - Inappropriate cortisol response to stress/sepsis
  - Supplemental corticosteroids

Clinical Signs and Symptoms

…..General languor and debility, feebleness of the heart's action, irritability of the stomach, and a peculiar change of the color of the skin….

Clinical Signs and Symptoms

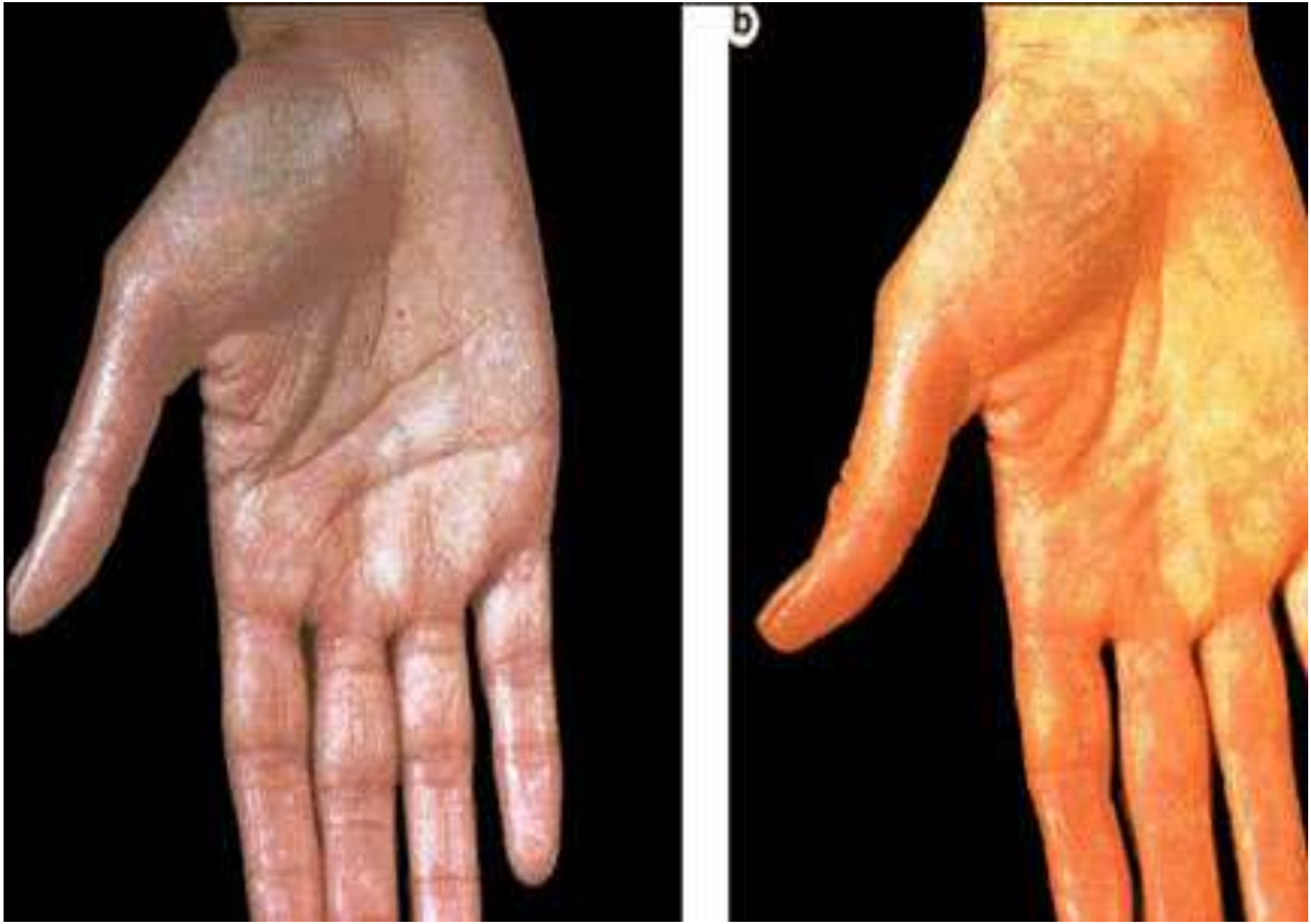
- Weakness
- Weight loss
- Pigmentation of skin & mucous membranes

  Elbows, creases of the hand

  Areas that normally are pigmented like areolae & nipples

  Tanning following sun exposure may be persistent.

  Irregular areas of vitiligo may paradoxically be present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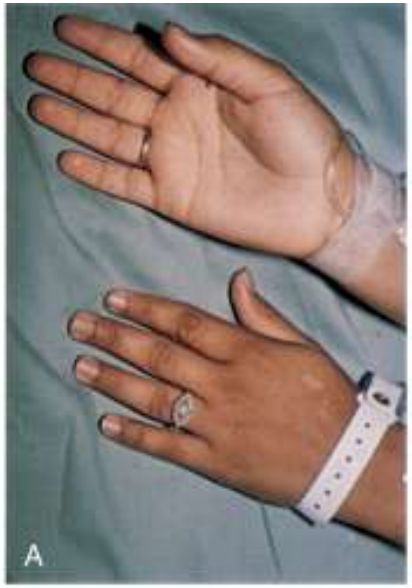
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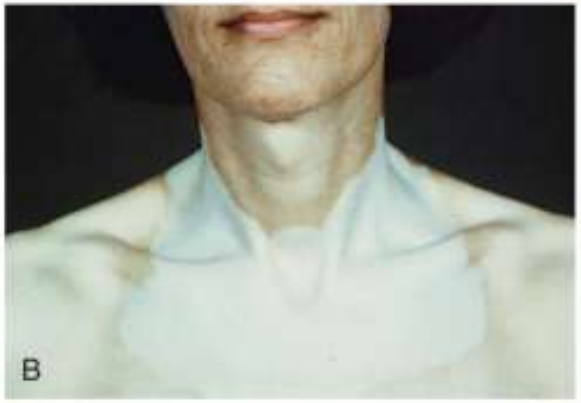
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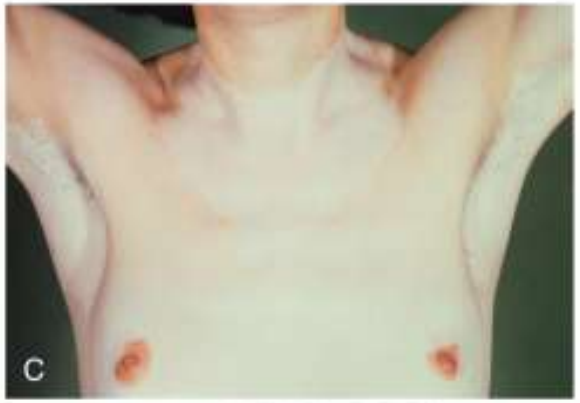
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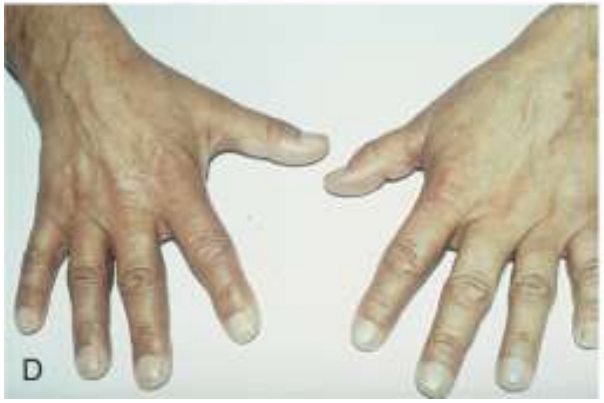
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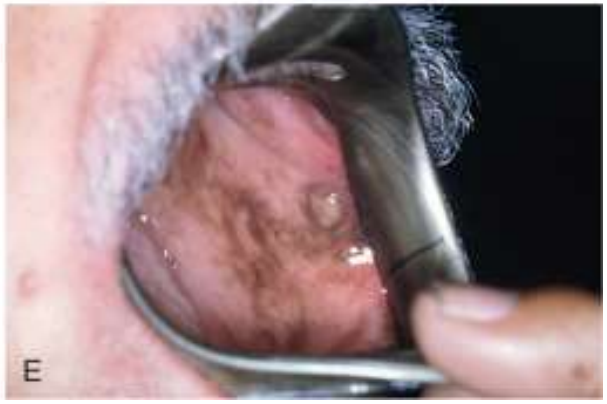
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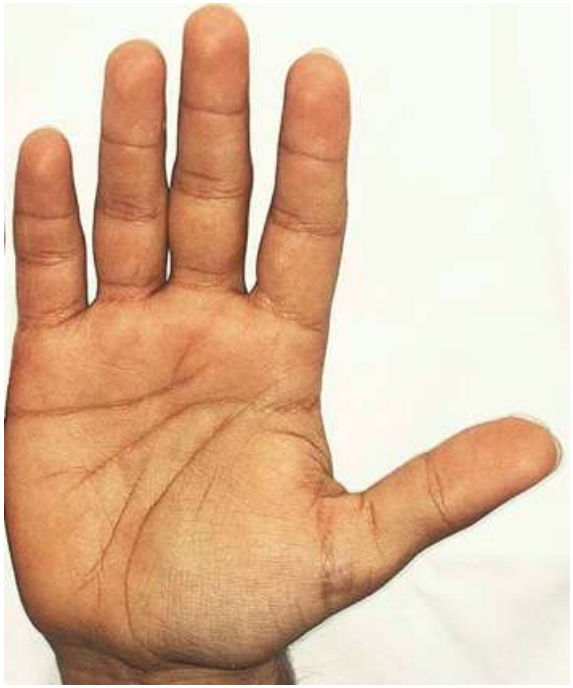
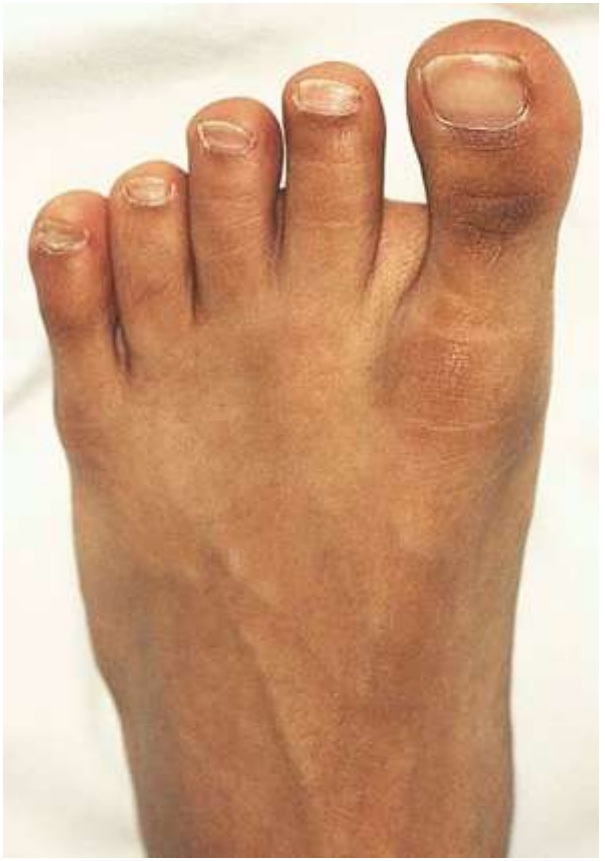
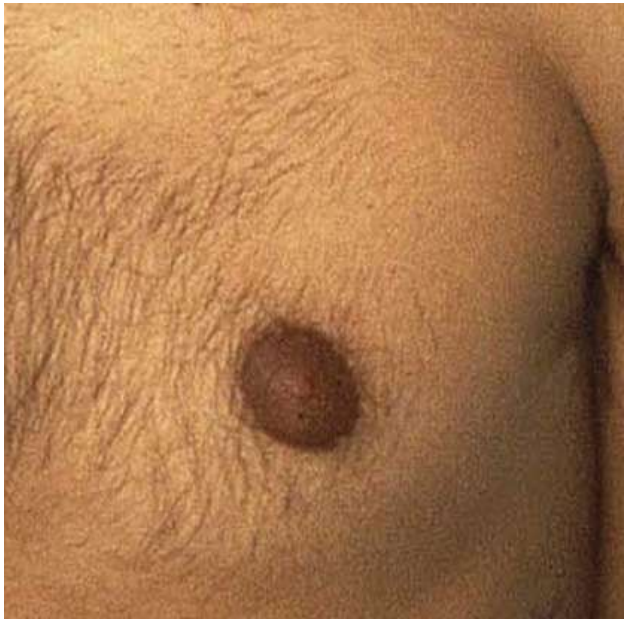






Clinical Signs and Symptoms

- Anorexia, nausea, and vomiting, diarrhea
- Abdominal pain
- Salt craving

Clinical Signs and Symptoms

- Hypotension (<110/70) with postural accentuation is frequent
- Syncope
- Axillary and pubic hair may be decreased in women due to loss of adrenal androgens

Laboratory Findings

- Early phase

No demonstrable abnormalities in the routine laboratory parameters

Basal steroid output may be normal. Adrenal stimulation with ACTH uncovers abnormalities

It elicit a subnormal increase of cortisol levels or no increase at all

Laboratory Findings

- serum sodium, chloride, and bicarbonate levels are reduced
- Serum potassium level is elevated
- Mild to moderate hypercalcemia occurs in 10–20%
- normocytic anemia, relative lymphocytosis, moderate eosinophilia.

Diagnosis

- Made with ACTH stimulation testing
  - Synacthen
  - Cosyntropin
- Assess adrenal reserve capacity for steroid production
- The test can be performed at any time of the day.

- The ACTH stimulation test involves intramuscular or intravenous administration of 250 µg of tetracosactrin (Synacthen).
- Plasma cortisol levels are measured at 0 and 30 minutes after ACTH, and a normal response is defined by a peak plasma cortisol level greater than 525 nmol/L (19 µg/dL).

- Cosyntropin ($ACTH_{1-24}$) stimulation test
- 250 µg administered
- At 30 to 60 mins, plasma cortisol should be atleast 20 µg/dl
- Patients on hydrocortisone, to be avoided atleast 8 hrs prior to assay
- Other steroids eg:prednisone, dexamethasone do not interfere

Distinguishing primary and secondary adrenal insufficiency

In primary adrenal insufficiency,

plasma ACTH and associated peptides (beta-Lipotrophin) are elevated.

Subnormal increase in aldosterone

In secondary adrenal insufficiency,

plasma ACTH values are low or "inappropriately" normal

Aldosterone increment will be normal (5 ng/dL)

Symptom, Sign, or Laboratory Finding	*Frequency (%)*
Symptom	
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	6–13

Sign

Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88–94
Vitiligo	10–20
Auricular calcification	5

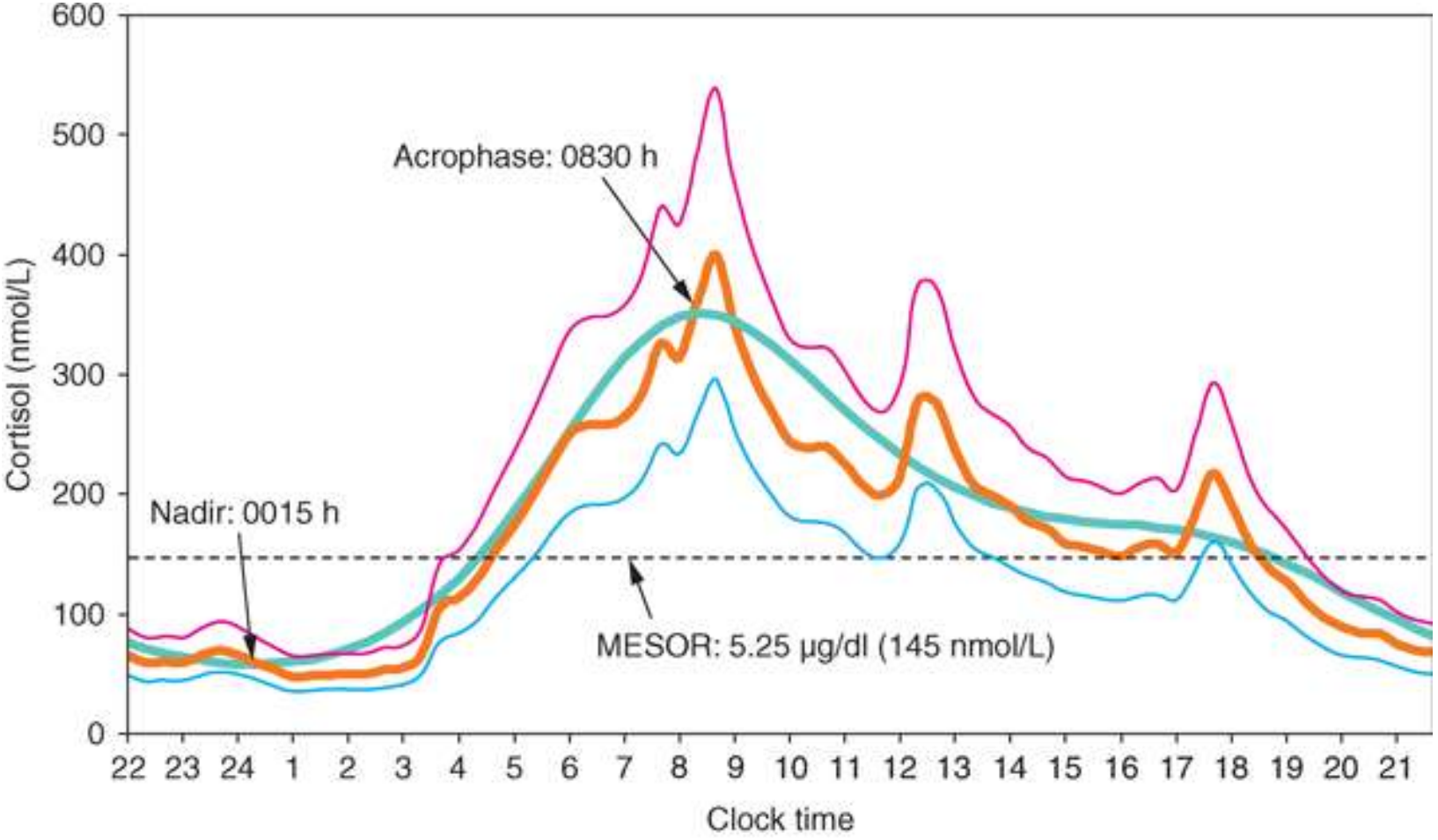
Laboratory Finding

Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

TREATMENT

- Hydrocortisone (cortisol)
- Dose is 20–30 mg/d. with meals /with milk / an antacid
- to prevent increase gastric acidity &direct toxic effects on the gastric mucosa.
- Two-thirds of the dose in morning,

one-third in late afternoon – to stimulate normal diurnal rythm


600
500
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Cortisol (nmol/L)
Acrophase: 0830 h
Nadir: 0015 h
MESOR: 5.25 µg/dl (145 nmol/L)
22 23 24 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Clock time

- <30 mg/day sufficient
- Bone mineral density reduction >30 mg/day
- End points – weight gain, sense of well being, blood pressure
- Objective assesment – cortisol curves with ACTH measurement
- smaller doses in hypertension and diabetes mellitus.

- Increased dosages in Obese individuals and those on anticonvulsive medications

- Mineralocorticoid supplementation

  0.05–0.1 mg fludrocortisone per day PO.
- Maintain an ample intake of sodium (3–4 g/d).
- Plasma sodium, supine and erect blood pressure, plasma renin activity to assess adequacy
- Mineralocorticoid supplementation usually neglected
- In female patients androgen levels are also low.

  Daily replacement with 25–50 mg of DHEA PO may improve quality of life and bone mineral density

Complications

- Gastritis
- hypokalemia,
- sodium retention lead to hypertension, cardiac enlargement, and even congestive heart failure

So Periodic measurements of body weight, serum potassium level, and blood pressure

Special Therapeutic Problems

- During intercurrent illness, esp in fever, the dose of hydrocortisone should be doubled
- increase the dose of fludrocortisone and to add salt in strenuous exercise with sweating, extremely hot weather, gastrointestinal upsets such as diarrhea

- Severe stress/trauma
  - Immediate 4mg Dexamethasone
- Illness/surgery in hospital
  - Moderate illness – hydrocortisone – 50 mg BD PO/IV
  - Taper to maintenance dose while pt recovers
- Severe illness
  - Hydrocortisone – 100 mg/q8h
  - Taper by half dose to bring to maintanence level

- Minor procedures
  - No extra supplementation
- Moderate stress
  - Endoscopy, andiography
  - Single dose 100 mg hydrocortisone prior to procedure
- Major Surgery
  - Hydrocortisone 100 mg just before induction and continue every q8h for first 24 hrs, then taper by half/day to maintanence

Secondary Adrenocortical Insufficiency

- MC following prolonged administration of excess glucocorticoids
- Panhypopituitarism

DIFF WITH PRIMARY

- Not hyperpigmented

  ACTH and related peptide levels are low
- Manifestations of multiple hormone deficiencies in total pitutary insufficiency
- Severe dehydration, hyponatremia, and hyperkalemia not seen

Patients receiving long-term steroid therapy

- have two deficits

1. adrenal atrophy secondary to the loss of endogenous ACTH

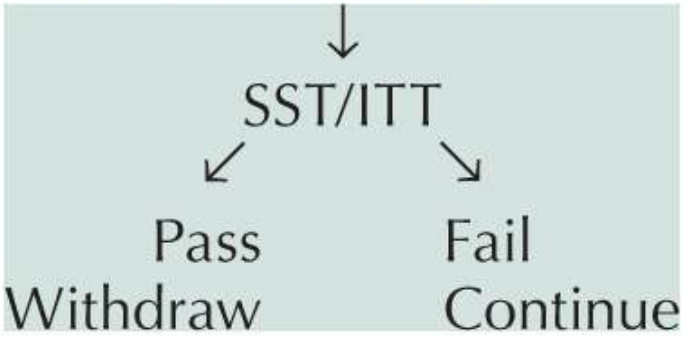
2. failure of pituitary ACTH release

Have low blood cortisol, ACTH levels, and abnormal ACTH stimulation test

Treatment

- Do not differ from that for the primary insufficiency.
- Mineralocorticoid therapy is usually not necessary
- Most patients recover, but take days to months

Plan for steroid withdrawal in a patient on chronic steroids

	Duration of Glucocorticoid Treatment			
Dose (mg pred/day)	**≤3 wk** [*]		**>3 wk**	
≥7.5 mg	Can stop	Reduce rapidly e.g., 2.5 mg every 3-4 days		
		THEN		
5-7.5 mg	Can stop	Reduce by 1 mg every 2-4 wk	OR	Convert 5 mg pred to HC 20 mg and
		THEN		↓ by 2.5 mg/wk to 10 mg for 2-3 mo
<5 mg	Can stop	Reduce by 1 mg every 2-4 wk		

Adrenal crisis

- Dehydration, hypotension, or shock out of proportion to severity of current illness
- Nausea and vomiting with a history of weight lost and anorexia
- Abdominal pain, so-called acute abdomen
- Unexplained hypoglycemia
- Unexplained fever
- Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
- Hyperpigmentation or vitiligo
- Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal

Adrenal Crisis: Treatment

AIM - Repletion of circulating glucocorticoids and replacement of the sodium and water deficits.

1. IV infusion of 5% glucose in normal saline solution
2. bolus IV infusion of 100 mg hydrocortisone
3. continuous infusion of hydrocortisone at a rate of 10 mg/h. An alternative is 100-mg bolus of hydrocortisone IV every 6 h.

- Maintain BP by IV saline and vasopressors
- Broad spectrum antibiotics

- Following improvement, the steroid dosage is tapered by 1 to 3 days and mineralocorticoid therapy is reinstituted

Differential diagnoses

- Shock – hypovolemic, cardiogenic, septic
- Hyponatremia
  - Diarrhoea, CCF, severe illness, hypothyroidism
- Hyperkalemia
  - GI bleed, rhabdomyolysis, Drugs – ACE, spironolactone
- Acute abdomen
  - Neutrophilia is seen, whereas addisonian crisis relative lymphocytosis and eosinophilia
- 90% cortisol protein bound, hence total cortisol may be low in severely ill patients. Free cortisol usually normal

—THANK YOU