ADRENAL DISORDERS

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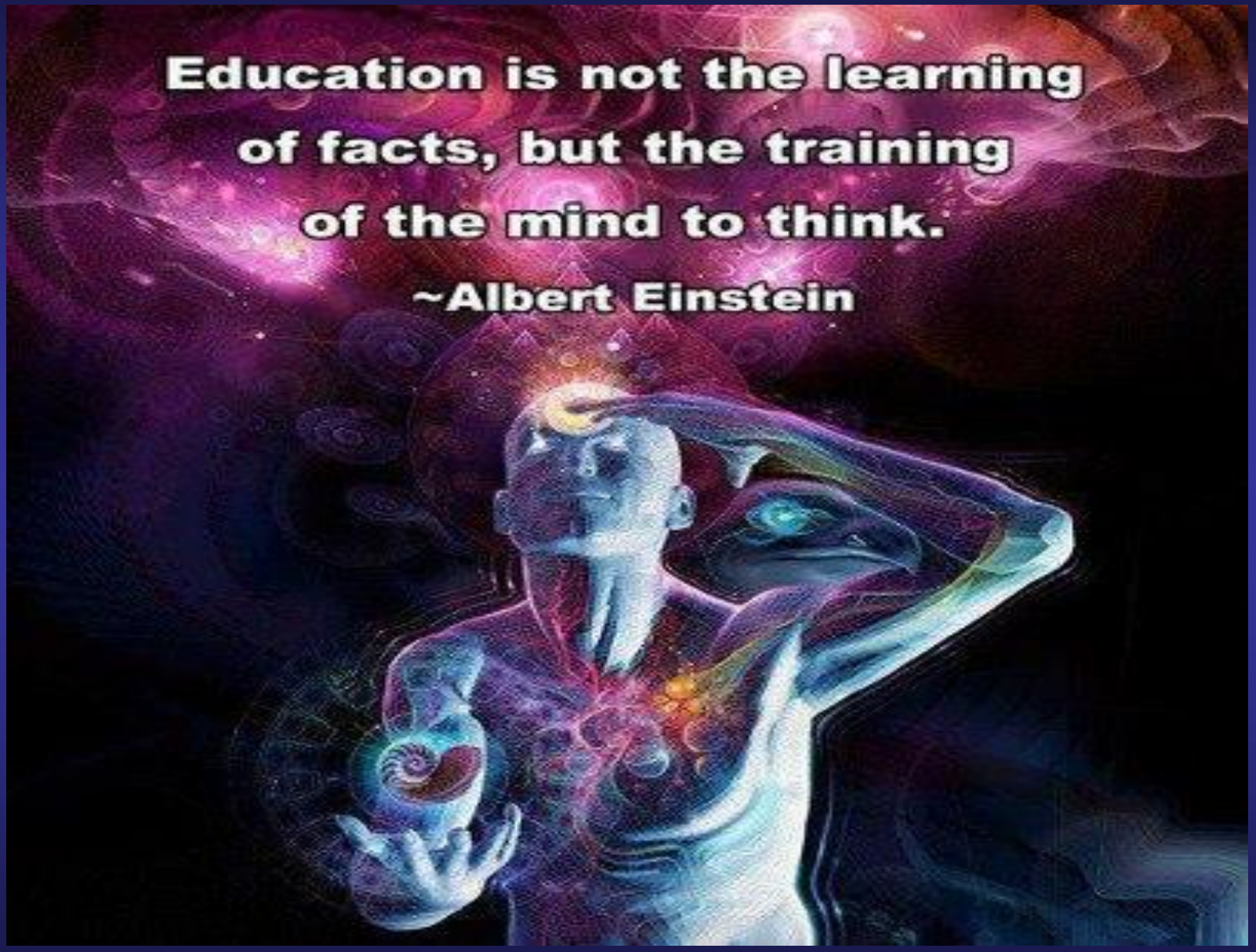
Consultant Endocrinologist


Education is not the learning
of facts, but the training
of the mind to think.
~Albert Einstein

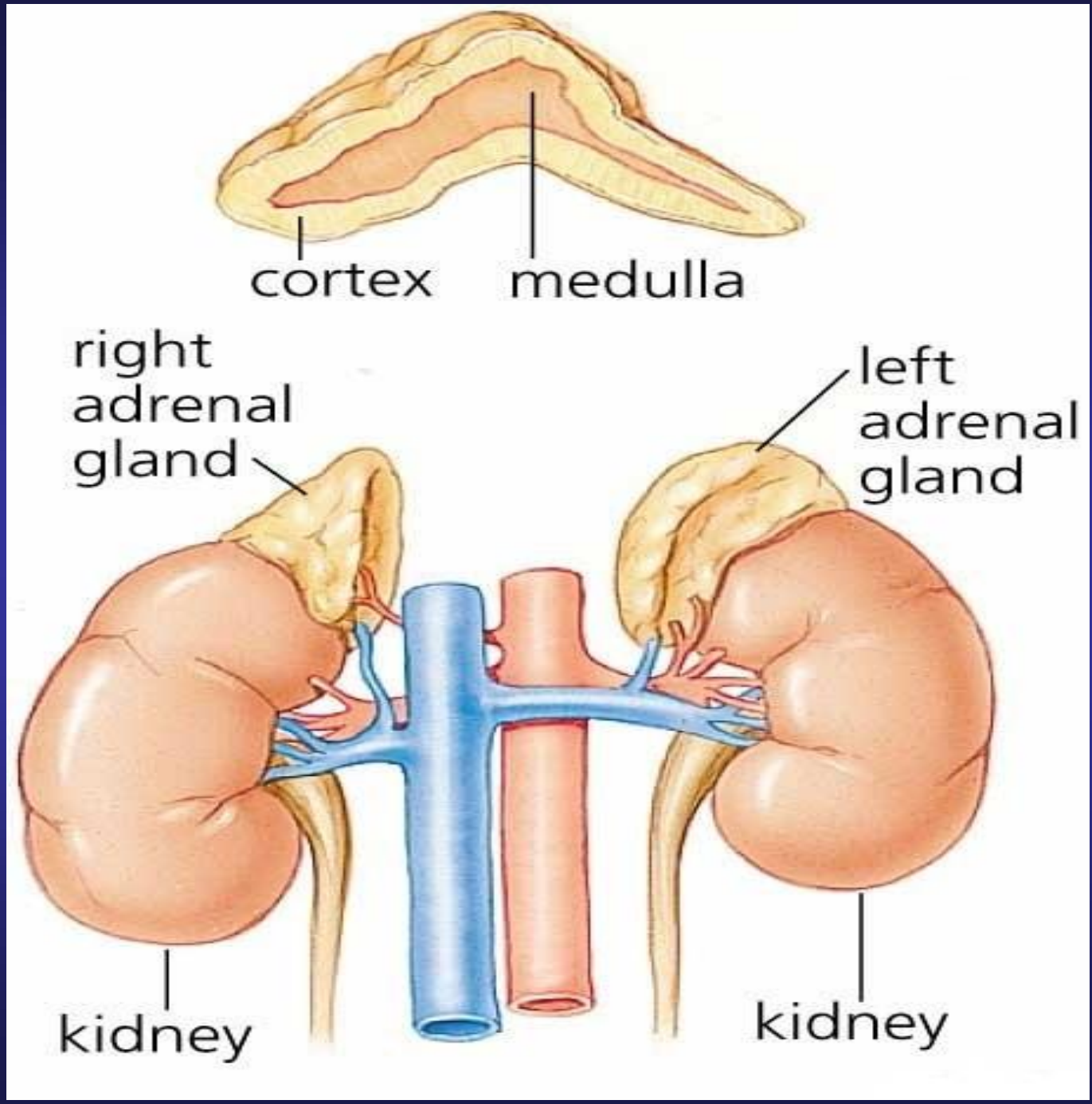
Adrenal Disorders

The adult adrenal glands weighs 8-10gm and lie in the retroperitonium above and medial to the upper poles of the kidneys. A fibrous capsule surrounds the gland. The yellowish outer cortex comprises 90% of the adrenal weight and the inner medulla about 10%.

The outer cortex has three zones:

- Zona glomerulosa
- Zone fasiculata
- Zona reticularis

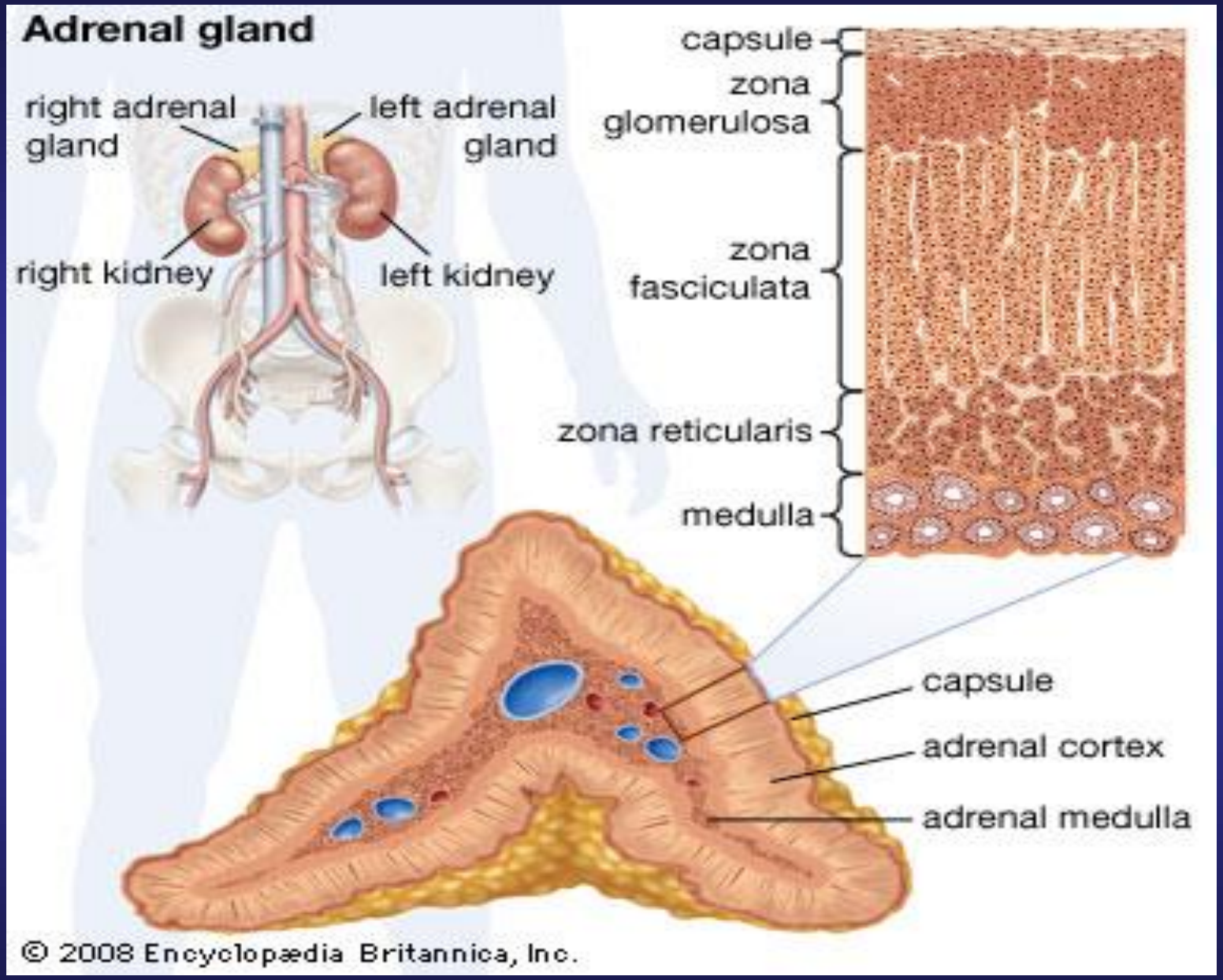
The inner two zones function as one unit, both producing cortisol and androgens while *the zona glumorulosa produces mineralocorticoids*.


cortex
medulla
right adrenal gland
left adrenal gland
kidney
kidney

Adrenal Disorders

The zona fasiculata and reticularis are regulated by ACTH

Excess or deficiency of this hormone alters the structure and function of the zones i.e. both zones atrophy when ACTH is deficient and when ACTH is present in excess, hyperplasia and hypertrophy of these zones occur.


Adrenal gland
right adrenal gland
left adrenal gland
right kidney
left kidney
capsule
zona glomerulosa
zona fasciculata
zona reticularis
medulla
capsule
adrenal cortex
adrenal medulla
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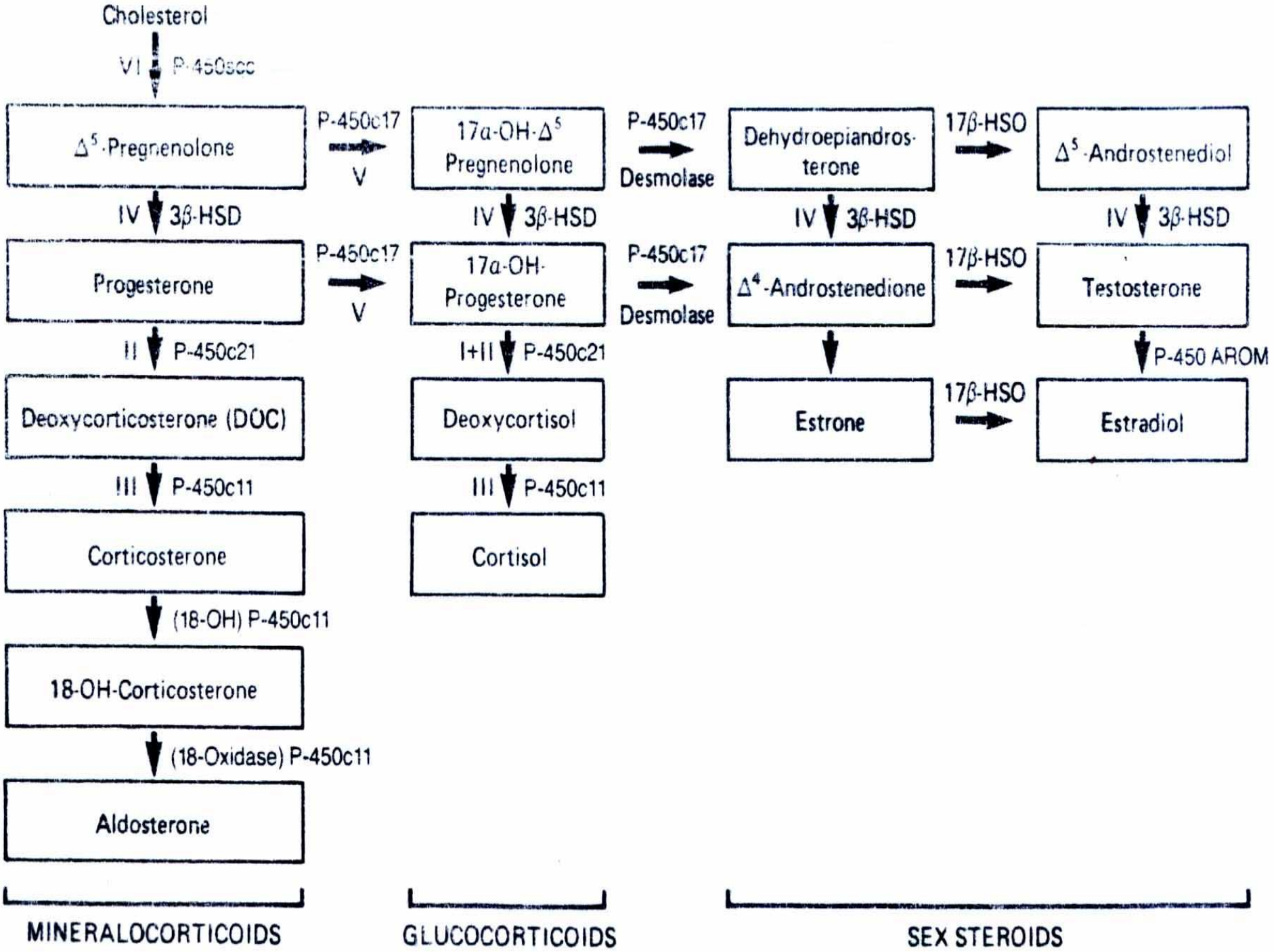

Cholesterol
VI P-450scc
Δ5-Pregnenolone
P-450c17
V
17α-OH-Δ5 Pregnenolone
P-450c17
Desmolase
Dehydroepiandros-terone
17β-HSO
Δ5-Androstenediol
IV 3β-HSD
IV 3β-HSD
IV 3β-HSD
Progesterone
P-450c17
V
17α-OH-Progesterone
P-450c17
Desmolase
Δ4-Androstenedione
17β-HSO
Testosterone
II P-450c21
I+II P-450c21
P-450 AROM
Deoxycorticosterone (DOC)
Deoxycortisol
Estrone
17β-HSO
Estradiol
III P-450c11
III P-450c11
Corticosterone
Cortisol
(18-OH) P-450c11
18-OH-Corticosterone
(18-Oxidase) P-450c11
Aldosterone
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX STEROIDS

The zona glomerulosa produces aldosterone and lacks 17 hydroxylase activity and cannot synthesize cortisol and androgens. The synthesis of aldosterone is primarily regulated by the renin angiotensin system and by potassium.

The zona fasciculata and reticularis produce cortisol, androgens and small amounts of estrogens and they do not contain the enzymatic system necessary for production of aldosterone.

Adrenal Disorders

Regulation of Secretion

- **Circadian Rhythm**

  Regulates both the magnitude and the number of CRH and ACTH secretory episodes. Cortisol secretion is low in the late evening and high in the early morning.

  This rhythm is changed by:

  1. Changes in Sleep pattern
  2. Light-dark exposure
  3. Feeding times
  4. Psychological stress
  5. CNS and pituitary disorders
  6. Cushing syndrome
  7. Liver disease
  8. Chronic renal failure
  9. Alcoholism
  10. Certain Drugs e.g. cyproheptadine

Adrenal Disorders

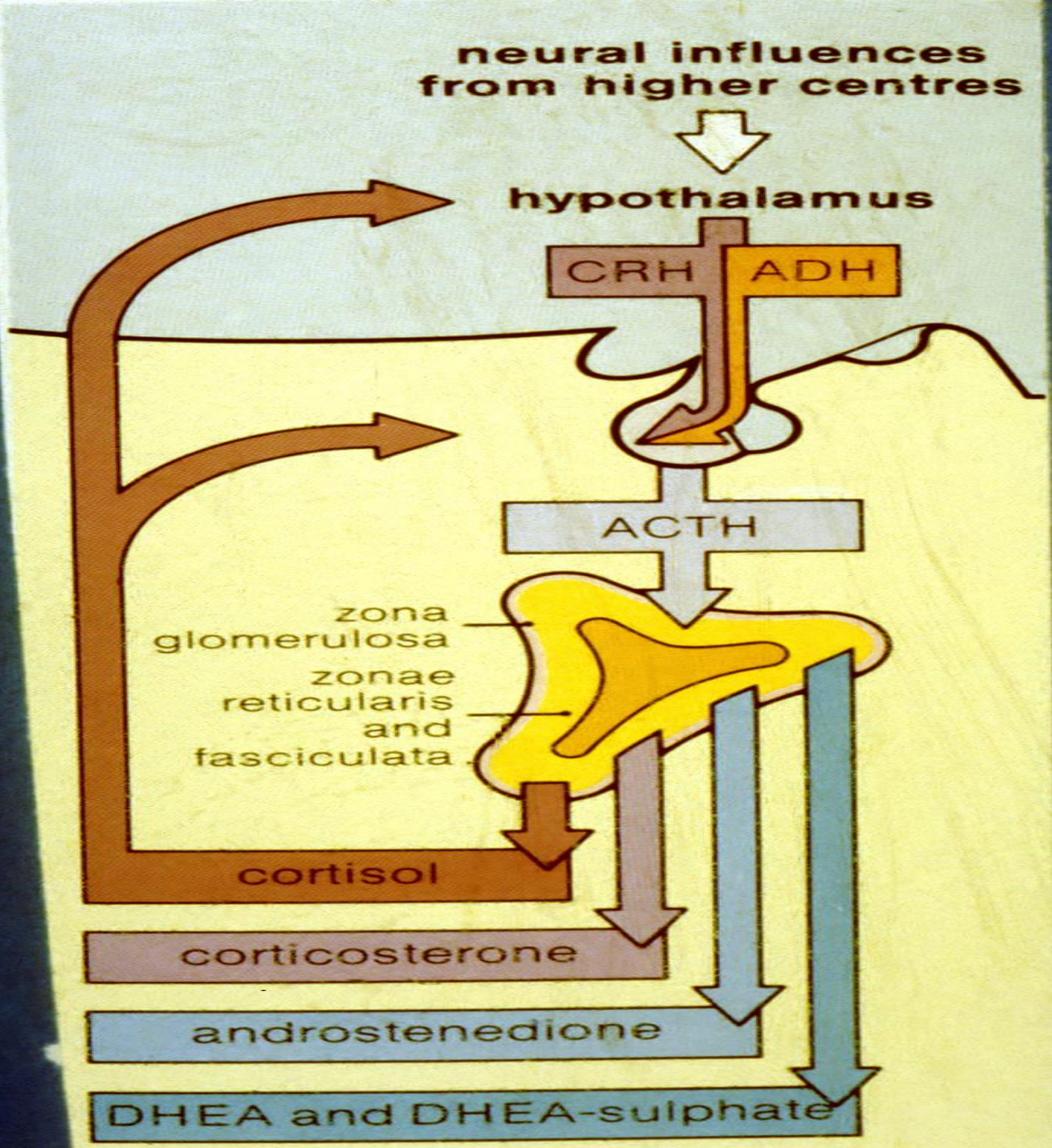
Regulation of Secretion

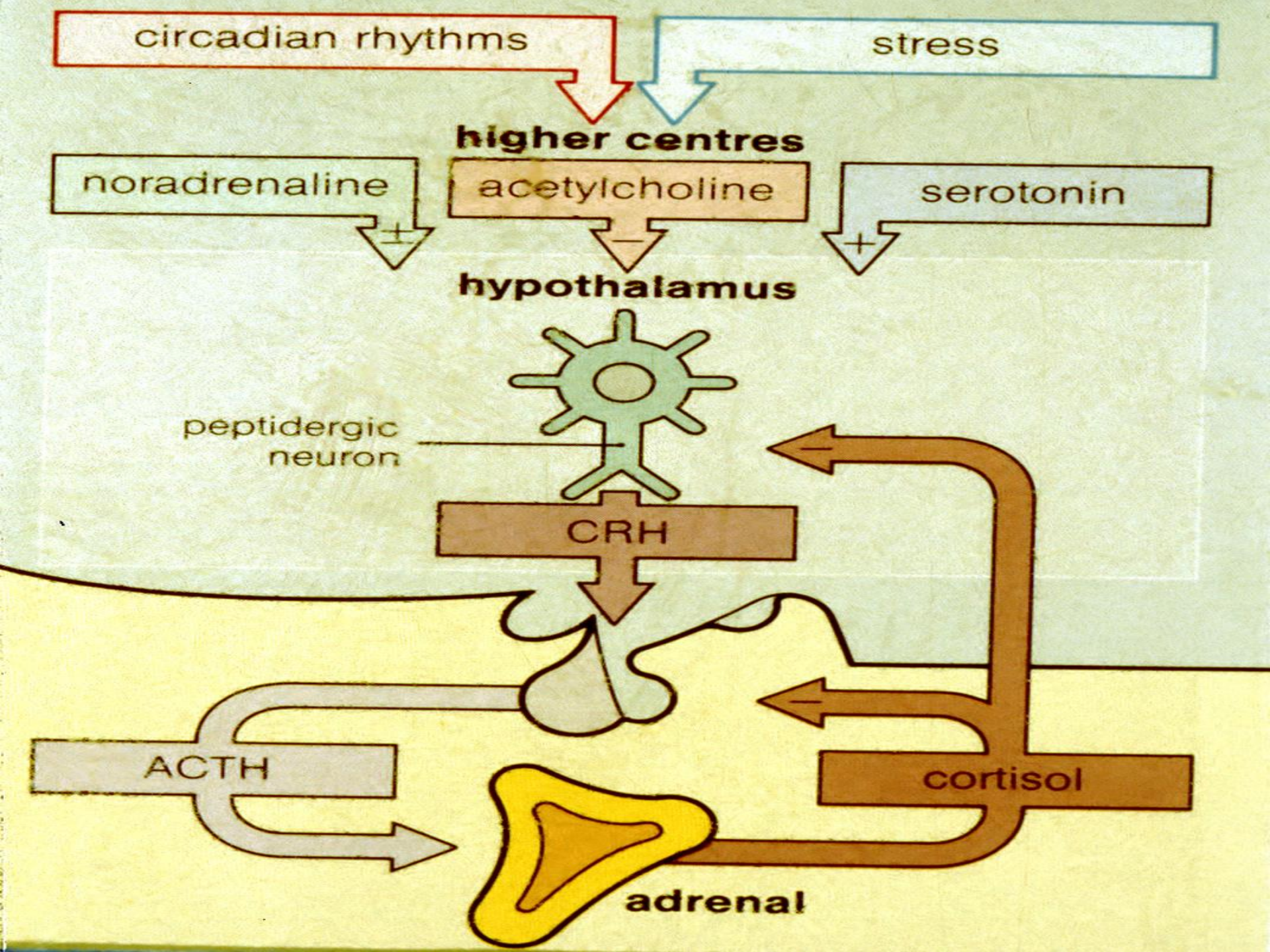
- **Stress**

  e.g. surgery and hypoglycemia. It causes ACTH and cortisol to be secreted within minutes of the onset of stress and this is mediated by inreased CRH secretion. This is abolished by prior high dose glucocorticoid administration and in Cushing's syndrome.

- **Feedback inhibition**

  It occurs by glucocorticoids both at the pituitary and hypothalamus inhibiting CRH and ACTH production and thus further synthesis of glucocorticoids


neural influences
from higher centres
hypothalamus
CRH
ADH
ACTH
zona
glomerulosa
zonae
reticularis
and
fasciculata
cortisol
corticosterone
androstenedione
DHEA and DHEA-sulphate


circadian rhythms
stress
higher centres
noradrenaline
acetylcholine
serotonin
+
−
+
hypothalamus
peptidergic neuron
CRH
ACTH
cortisol
adrenal

Adrenal Disorders

Circulation of Cortisol & Adrenal Androgens

Cortisol and the adrenal androgens circulate bound to plasma proteins.

The plasma half life of cortisol (70-90 min) is determined by the extent of plasma binding and by the rate of metabolic inactivation.

Cortisol binds mainly to CBG (cortisol binding globulin) or transcortin =75% and to a lesser extent to albumin=15% and about 10% of circulating cortisol is free and it is this biologically active cortisol which is regulated by ACTH

Adrenal Disorders

Circulation of Cortisol & Adrenal Androgens

CBG increases in:

1. Pregnancy
2. OCP users
3. Hyperthyroidism
4. D.M.
5. Certain hematological disorders
6. Genetic familial condition

Adrenal Disorders

Circulation of Cortisol & Adrenal Androgens

CBG decreases in:

1. Familial deficiency states
2. Hypothyroidism
3. Protein deficiency states
4. Severe liver disease
5. Nephrotic syndrome

Androgens except for testosterone bind weakly to albumin. However, testosterone is bound extensively to a specific globulin ; sex hormone binding globulin (SHBG)

Adrenal Disorders

Disorders of Adrenocortical Insufficiency

Primary adrenocortical insufficiency (Addison's disease)

Causes

Major Causes

>Autoimmune = 80%

>Tuberculosis = 20%

Rare Causes

- Adrenal hemorrhage and infarction
- Fungal infections
- Metastatic and lymphomatous replacement
- Sarcoidosis
- Amyloidosis
- Hemochromatosis
- Radiation therapy

- Surgical adrenalectomy
  Enzyme inhibitors e.g. metyrapone
- Cytotoxic drugs e.g. mitotane
- Congenital diseases e.g. enzyme defects
- Hypoplasia

Idiopathis addison's disease is frequently accompanied by other glandular failure disorders and also with a higher incidence of other immunological and autoimmune endocrine disorders e.g. hyperthyroidism, hypothyroidism, hashimoto anemia and gonadal failure.

One or more of these disorders is usually present in 40-53% of patients with idiopathic addison's disease.

Addison's disease is more common in women 2.6:1. It is usually diagonsed in the 3rd to 5th decade.

Pathophysiology & clinical features

Gradual adrenocortical destruction causes decrease adrenal reserve with normal basal steroid secretion in the initial phase but failure to respond to stress.

Acute crises can be precipitated by stresses of surgery, trauma or infection which require increased corticosteroid secretion.

With further loss of cortical tissue, even basal secretion of mineralocorticoids and glucocorticoids become deficient leading to the manifestation of chronic adrenocortical insufficiency when more than 90% of both adrenal cortices occur. About 25% of cases present with a crises or an impending one at the time of diagnosis

Pathophysiology & clinical features

The chief symptoms of chronic primary adrenocortical insufficieny are hyper-pigmentation due to secondary increase in ACTH and BLPH because of decrease negative feedback inhibition

weakness and fatigue, weight loss anorexia, and gastrointestinal disturbances.

Symptom	Percent
Weakness, fatigue, anorexia, weight loss	100%
Hyperpigmentation	92%
Hypotension	88%
G.I. disturbances	56%
Salt craving	19%
Postural symptoms	12%

Pathophysiology & clinical features

The generalized hyperpigmentation of the skin and mucous memberanes is the earliest manifestation and is increased in sun exposed areas and accentuated over pressure areas, palmar creases, nail beds, nipples, areolae, and peri-vaginal and peri-anal mucosae as well as gums and buccal mucosa. Scars formed after the onset of ACTH excess become hyper pigmented.

General weakness, fatigue, malaise, anorexia and weight loss are invariable features.

Pathophysiology & clinical features

Gastrointestinal disturbances especially nausea and vomiting occur in most patients. Diarrhoea, is less frequent. Hypotension is present in about 90% of patients and causes orthostatic symptoms. It can cause syncope and in severe cases shock.

Salt craving occurs because of sodium wasting secondary to mineralocorticoid deficiency which can also lead to dehydration, hyponatremia, hyperkalemia, and acidosis.

Pathophysiology & clinical features

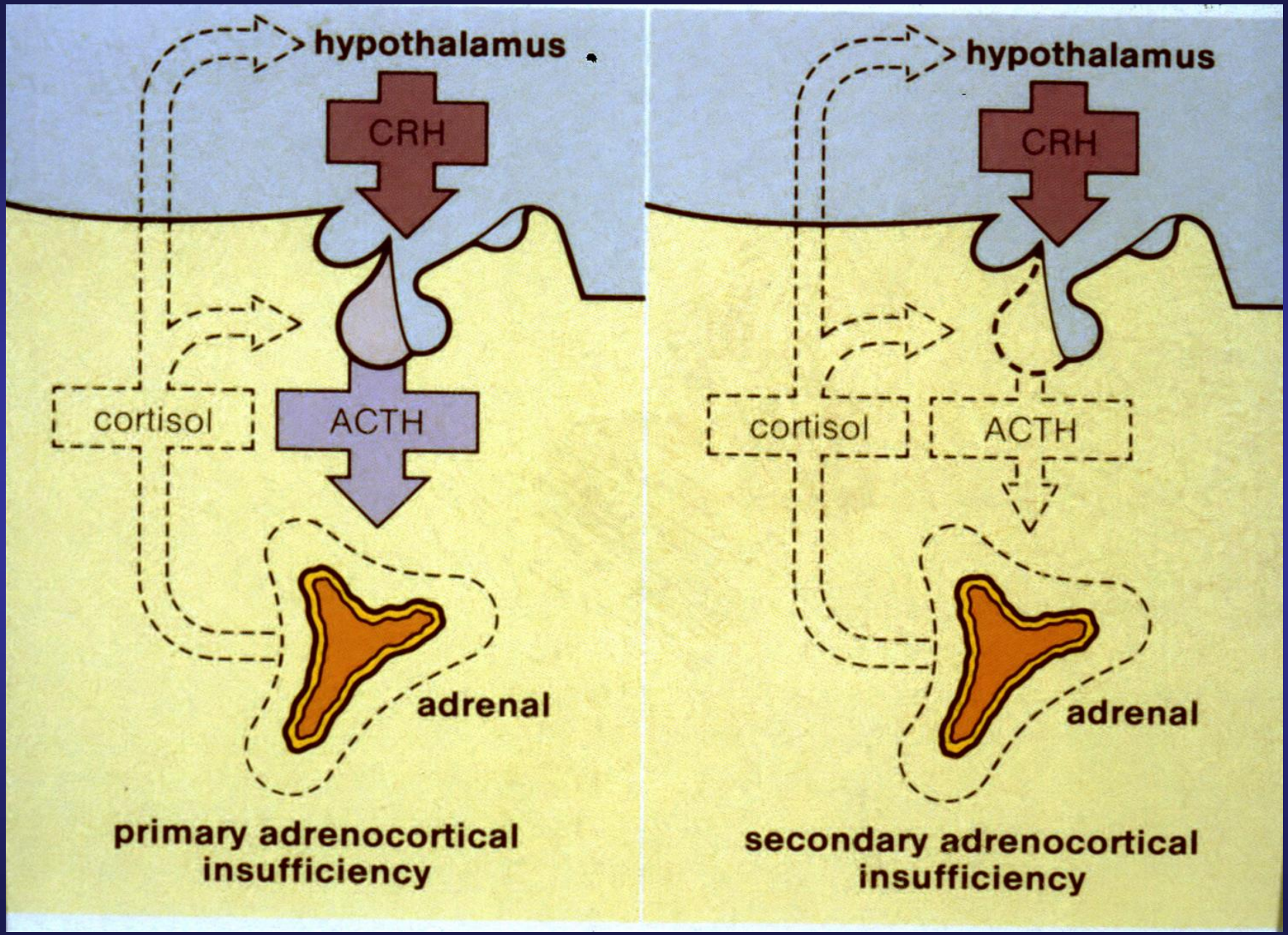
Severe hypoglycaemia is uncommon in adults but can be provoked by fasting, fever, infection or nausea and vomiting .

Amenorrhoea is common and can be due to weight loss and chronic illness or associated ovarian failure. Loss of body hair can occur secondary to deficient adrenal androgens secretion.

Laboratory Findings

- Hyponatremia and hyperkalaemia are classical in primary adrenal insufficiency
- There might be normocytic anaemia, neutropenia, eosinophilia and relative lymphocytosis
- Azotaemia and increased serum creatinine is due to volume depletion and dehydration.
- Mild acidosis is frequently present
- Mild to moderate hypercalcemia

Abdominal radiograph reveal adrenal calcification in half the patients with tuberculosis adrenilitis and in some patients with other invasive or hemorrhagic causes of adrenal insufficiency


hypothalamus
CRH
cortisol
ACTH
adrenal
primary adrenocortical insufficiency
hypothalamus
CRH
cortisol
ACTH
adrenal
secondary adrenocortical insufficiency

Diagnostic Tests

Since basal levels of adrenocorticol steroids may be normal in partial adrenal insufficiency, test of adrenocortical reserves are necessary to establish the diagnosis.

Rapid ACTH stimulation test:

After a baseline cortisol sample is obtained a synthetic ACTH called Tetracosactrin is given in a dose of 0.25mg IM. Or IV. and additional cortisol samples are obtained at 30 and 60 min following the injection.

Plasma ACTH Levels

It differentiates between primary and secondary states being high in the primary form and low normal or low in secondary forms.

Secondary Adrenocorticol Insufficiency

The commonest cause of ACTH deficiency is exogenous glucocorticoid administration.

Pituitary/hypothalamic tumors are the most common causes of naturally occurring pituitary ACTH hyposecretion.

Secondary Adrenocorticol Insufficiency

ACTH deficiency is the primary event and leads to decrease cortisol and adrenal androgen secretion. Aldosterone secretion remains normal except in few cases.

Basal ACTH and cortisol may be normal but ACTH reserve is impaired and the response to stress is subnormal.

With chronicity there is atrophy of zona fasciculate and reticularis and therefore basal cortisol secretion is decreased.

At this stage, the pituitary adrenal axis is impaired and will not respond to stress and to exogenous ACTH.

Secondary Adrenocorticol Insufficiency

The clinical features may be non-specific initially unless an acute crisis occur in an undiagnosed patient.

The hyper-pigmentation is absent because of deficient ACTH and BLPH and the mineralocorticoid secretion is usually normal. Otherwise the symptoms may be similar to primary electrolytes abnormalities are usually absent and hypotension is usually not present except in acute presentations.

Hyponatremia may occur because of water retention and inability to excrete a water load with no hyperkalaemia. Hypoglycemia is occasionally the presenting feature.

Treatment of Adrenocorticol Insufficiency

Patients with Addison's disease require life long therapy usually with both glucocorticoids and mineralo-corticoids.

Hydrocortisone is the preparation used in a dose of 25-30 mg/d. It is usually given as twice per day but can be given once daily or three times daily as suitable for the well being and normal energy level for each patient.

Fluorocortisone is the mineralocorticoid of choice given in 0.05-0.1 mg/day dose in the morning. In secondary hypoadrenalism fluorocortisone is rarely required.

Acute Adrenal Crisis

A state of acute adrenocortical insufficiency occuring in patients with Addison's disease who are exposed to the stress of infection trauma surgery or dehydration.

Clinical Features

- Hypotension and shock
- Fever
- Dehydration and voluem depletion,
- Nausea, vomiting, anorexia
- Weakness, apathy, depressed mentation
- Abdominal Pain
- Hypoglycemia
- Fever

Shock and coma may rapidly lead to death in untreated patients

Treatment

It should be started as soon as possible once diagnosis suspected.

- Parenteral cortisol is commonly used and it has sufficient mineralocorticoid activity so additional treatment is not required.
- The dose is 100 mg every 6 hrs, and the dose is gradually tapered when condition is stable.
- Maintenance therapy with oral cortisol with or without a mineralcorticoid is then given.

Treatment

- Intravenous fluids including glucose and saline are required to correct volume depletion, hypotension and hypoglycemia as well as the acidosis and hyperkalaemia but the shock may not respond to vasopressors unless glucocorticoids are administered.

  Adrenal crisis can be prevented in an already diagnosed patient by proper education on dosage of drugs during illness.

Treatment

The patient should be informed about life-long therapy and the need to increase the dose of steroids during illness(it should be at least doubled for minor illnesses) and if symptoms continue, a physician should be called.

If oral therapy cannot be taken because of vomiting or diarrhoea, then medical assistance should be sought for parenteral therapy

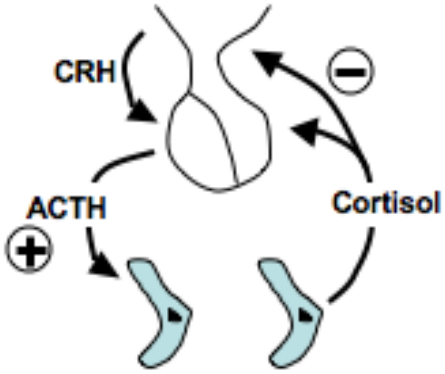
Cushing's Syndrome

Chronic gulcocorticoid excess whatever the cause leads to a constellation of symptoms and physical features known as Cushing's syndrome.

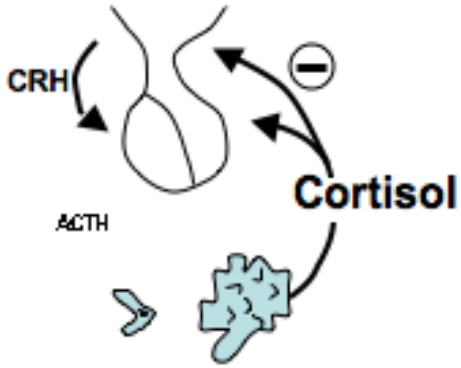
The most common cause is iatrogenic i.e. secondary to chronic steroid ingestion.

Others causes are:

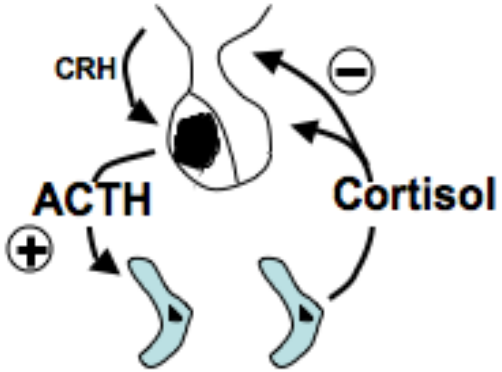
- ACTH dependent:
  - Cushing's disease 68
  - Ectopic ACTH syndrome 15
- ACTH independent:
  - Adrenal adenoma 9
  - Adrenal carcinom 8



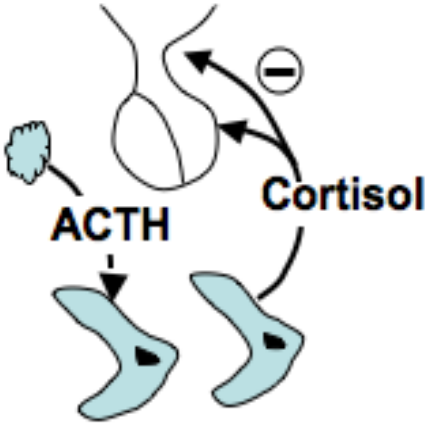
Normal



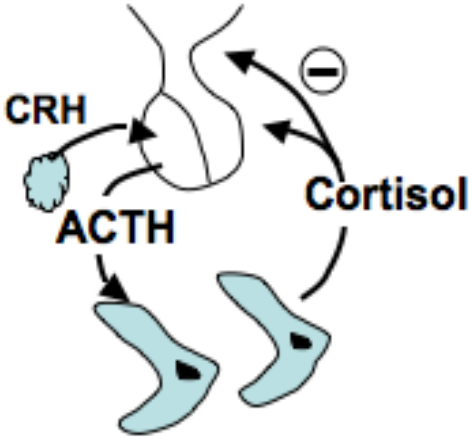
ACTH - Independent Cushing's Syndrome
(Benign or Malignant Adrenal Tumor) (19%)



Cushing's Disease
(67%)



Ectopic ACTH
(12%)



Ectopic CRH
(<1%)

ACTH Dependent Cushing's Syndrome

Cushing's Syndrome

Cushing's disease is defined as the specific type of cushing's syndrome due to excessive pituitary ACTH secretion

(commonly secondary to an adenoma).

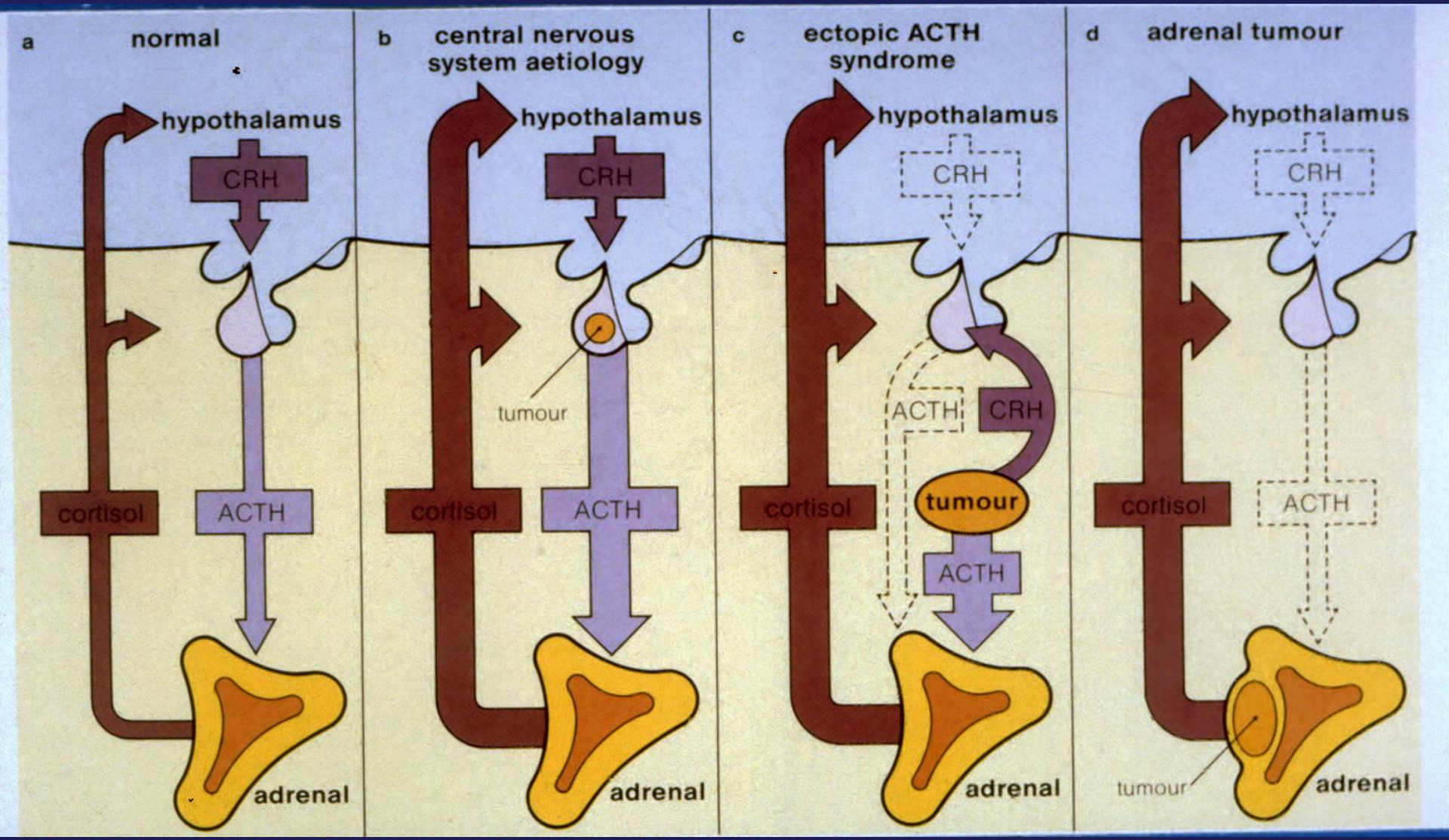
Women to men ratio is 8:1 and the age of diagnosis is usually between 20-40 yrs.

Cushing's Syndrome

In the ectopic ACTH syndrome, non-pituitary tumors secrete biologically active ACTH.

It is more common in men, female to male ratio is 1:3 with the peak incidence at the age of 40-60 years. It is most common with oat-cell carcinoma of the lung (50% of the cases) but other tumors, e.g. pancreatic cell tumors, carcinoid tumors, etc. can cause it.

Glucocorticoid producing adrenal adenomas and carcinomas arise spontaneously and they are autonomous and not under pituitary hypothalamic control.


a
normal
hypothalamus
CRH
cortisol
ACTH
adrenal
b
central nervous system aetiology
hypothalamus
CRH
tumour
cortisol
ACTH
adrenal
c
ectopic ACTH syndrome
hypothalamus
CRH
ACTH
CRH
cortisol
tumour
ACTH
adrenal
d
adrenal tumour
hypothalamus
CRH
cortisol
ACTH
tumour
adrenal

Clinical Features

1. Obesity

   The most common manifestation and is classically central affecting mainly the face (moonfaced), neck, trunk, and abdomen with relative sparing of the extremities.

2. Skin Changes

   There is thinning of the skin because of atrophy of the epidermis and underlying connective tissue and facial plethora.

   They also have striae which are classically red to purple and are due to loss of connective tissue support as well as easy bruising.

   Minor wound heal slowly and they have frequent mucocutaneous fungal infections.

   Hyperpigmentation is common in the ectopic ACTH.

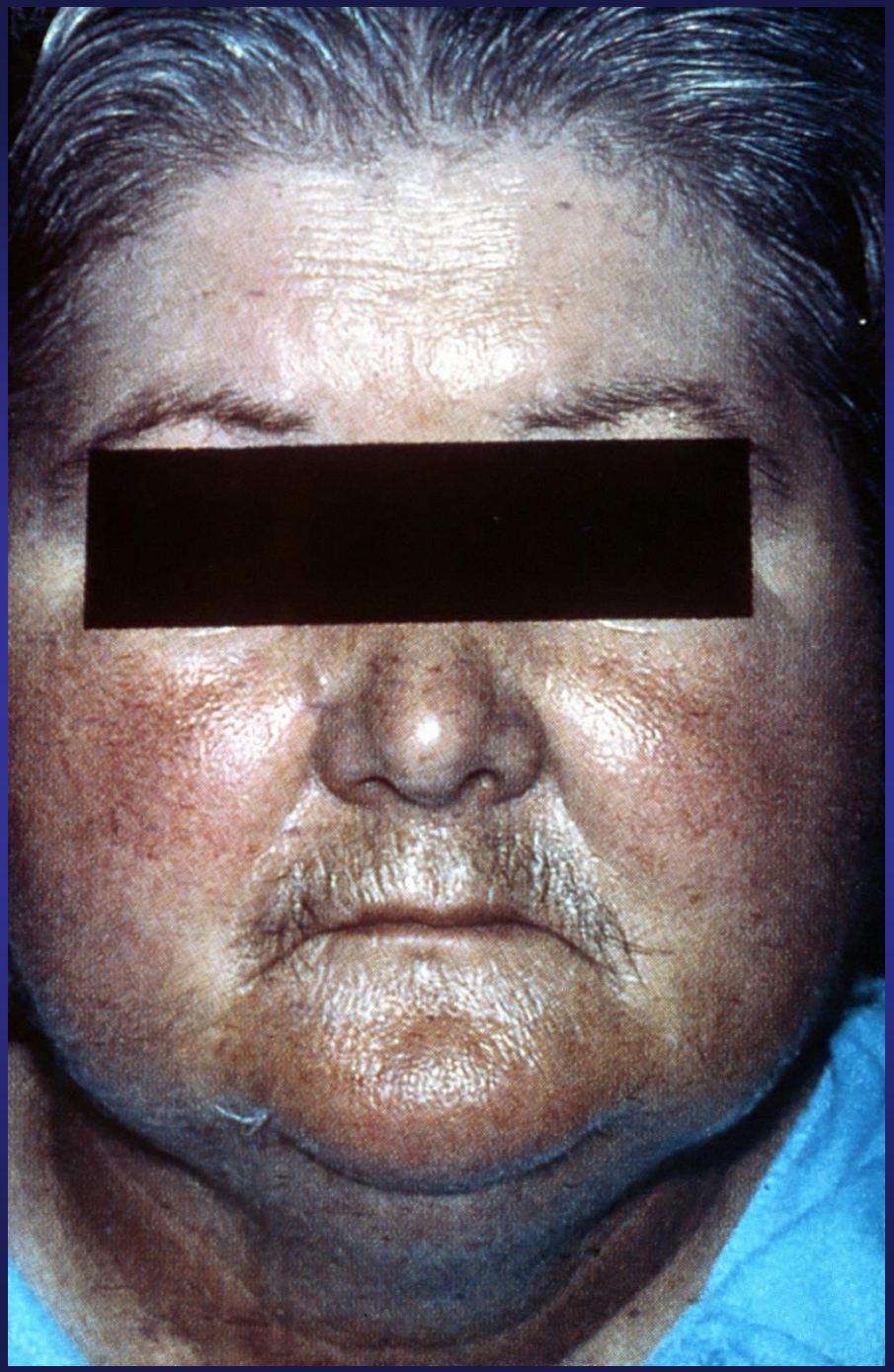
Clinical Features

3. Hirsutism

   Facial hirsutism is most common but it can occur anywhere in the body. It is due to the hyper secretion of adrenal androgens. Acne and seborrhea usually accompany the hirsutism. Virilism is rare and occur in adrenal carcinoma.

4. Hypertension

   It is a classical feature in Cushing's syndrome and its complications contribute greatly to the morbidity and mortality in the disease.



Clinical Features

5. Gonadal Dysfunction

   This is very common as a result of elevated androgens and cortisol, e.g. amenorrhoea, infertility, decreased libido.

6. Psychological Distrubances

   Symptoms range from mild irritability to anxiety, depression, poor memory and concentration to euphoria and mania as well as sleep disorders.

   Sever depression and psychosis as well as hallucinations and paranoia can occur.

Clinical Features

7. Muscle Weakness

   Commonly proximal and more prominent in the lower limbs.

8. Osteoporosis

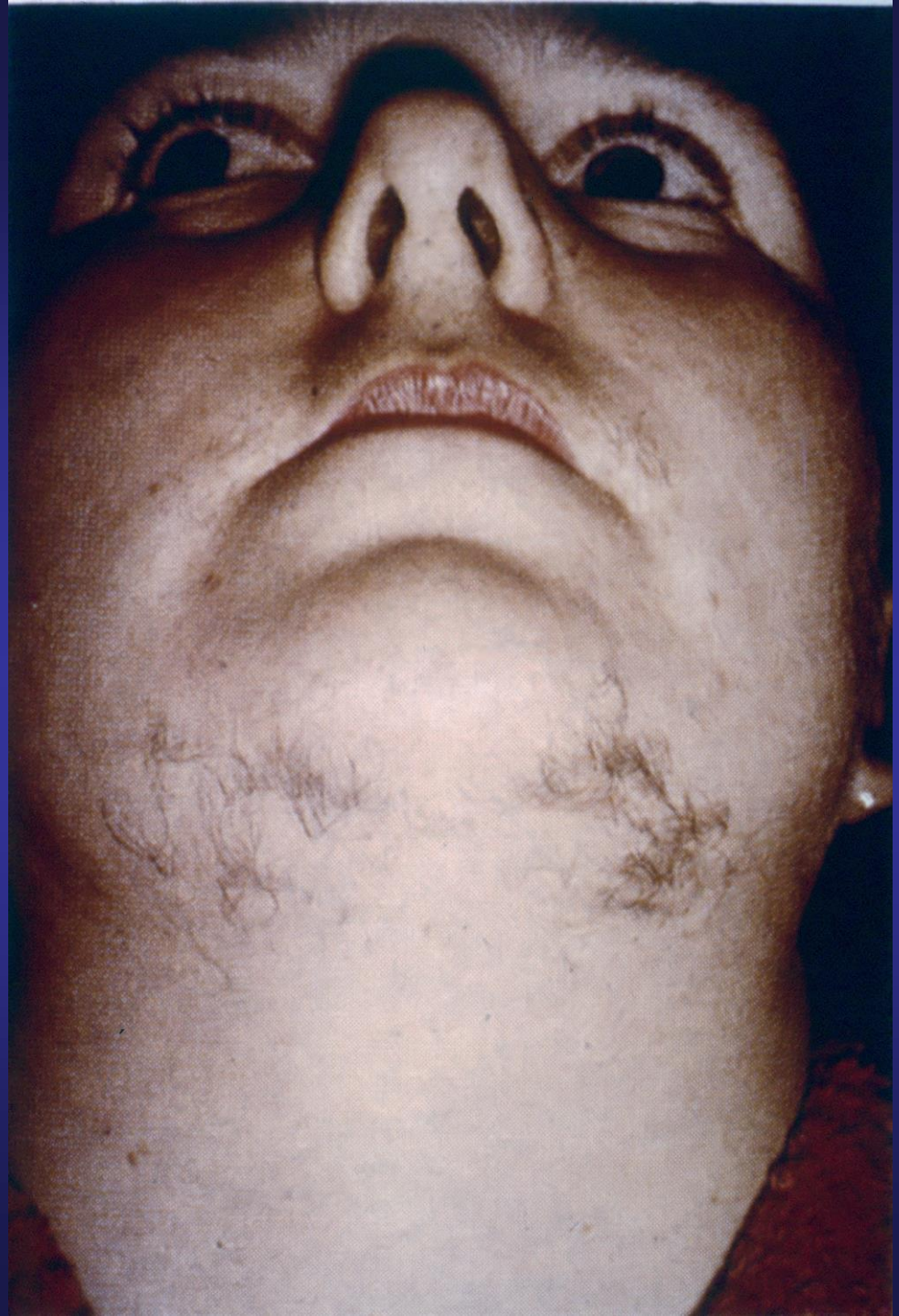
   A common complication presenting with backpain, and pathological fractures can occur in severe cases.

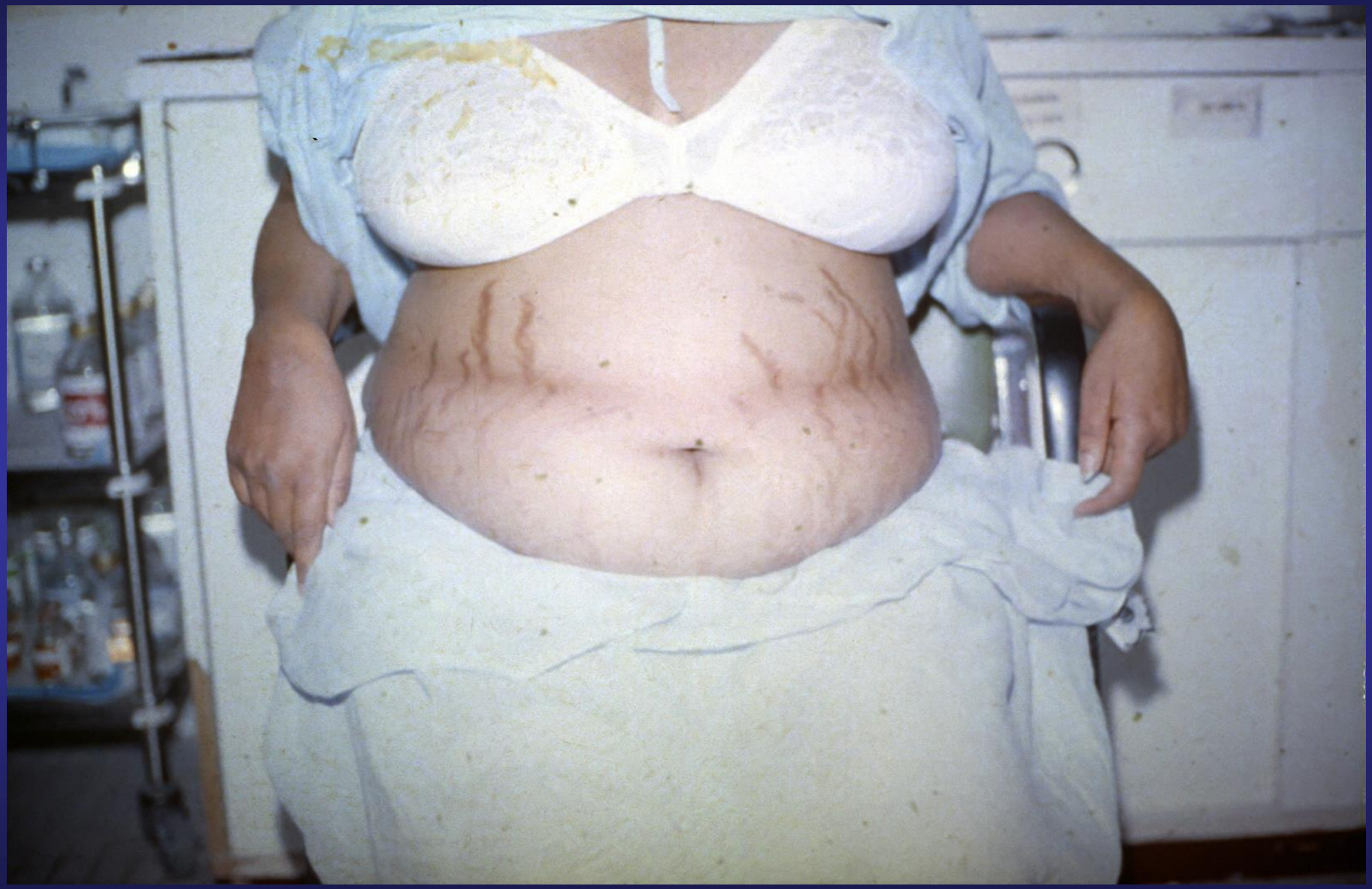
9. Renal Calculi

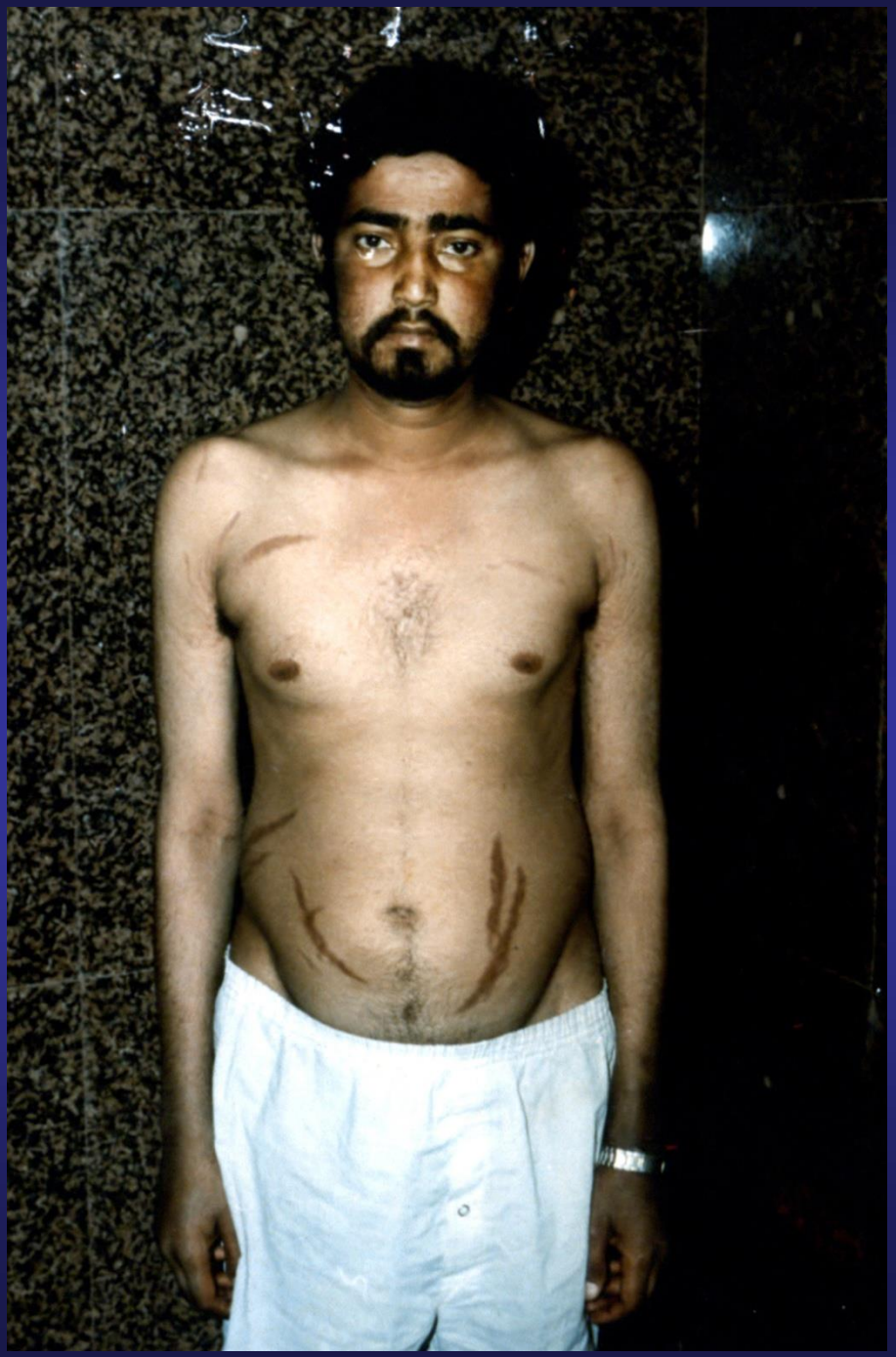
   Occur secondary to hypercalcuria and renal colic may occasionally be a presenting complaint.

10. Thirst and Polyuria

    Occur secondary to development of diabetes mellitus but asymptomatic glucose intolerance is much more common.







Laboratory & Radiological Findings

High normal hemoglobin and hematocrit are usual with lymphocytopenia and depressed eosinophils count.

Hypokalemic alkalosis may occur in the setting of ectopic ACTH production.

Most patients have secondary

Hyperinsulinism and abnormal glucose tolerance tests while some have fasting hyperglycemia or clinical diabetes mellitus .

Laboratory & Radiological Findings

There is hypersecretion of cortisol which is random and episodic with loss of normal circadian rhythm, therefore plasma cortisol (and ACTH in the ACTH dependent types) remain elevated throughout the day.

The 24- hour urinary free cortisol is an excellent method for diagnosis of Cushing's syndrome and in differentiating it from other forms of hypercortisolism, e.g. obesity.

In Cushing's disease, ACTH is normal or modestly elevated while in the ectopic syndrome, it is markedly elevated.

In adrenal tumors, ACTH is undetectable.

Dexamethasone Suppression Tests

Establish the presence of a Cushing's syndrome regardless of the cause.

It assesses feedback inhibition of the hypothalamic pituitary adrenal axis which is abnormal in Cushing's syndrome.

Dexamethasone Suppression Tests

A. OVERNIGHT 1 MG DEXAMETHASONE SUPPRESSION TEST

   A screening test .

   If the test is positive in the absence of conditions causing false positive results. e.g. alcoholism, depression, and drugs, then the diagnosis should be confirmed by other tests.

B. TWO-DAY LOW DOSE TEST

   Dexamethasone 0.5 mg is given every 6 hours for two days. Plasma cortisol level should suppress after the last dose .

Dexamethasone Suppression Tests

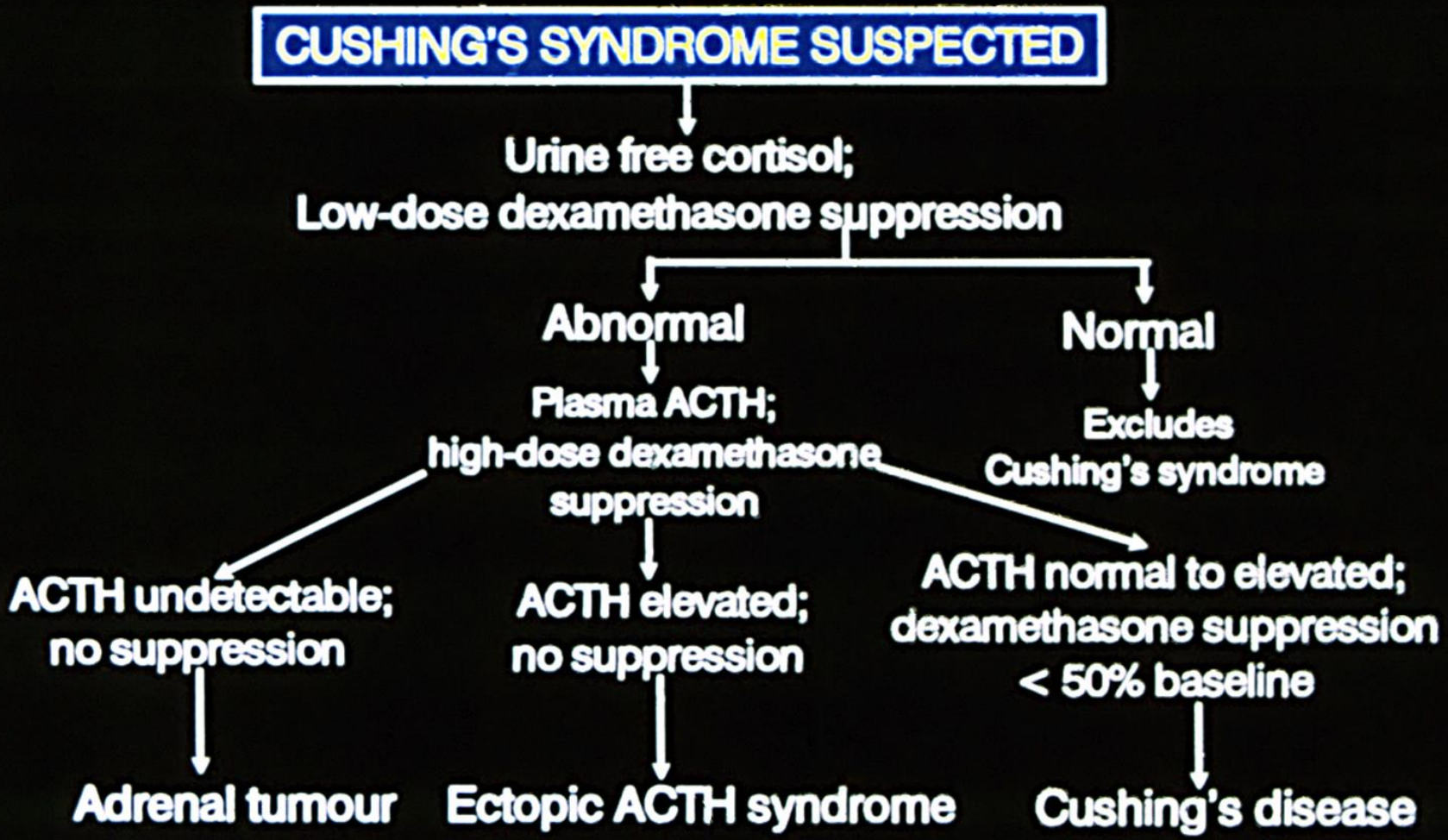
High Dose Tests:

A. OVERNIGH HIGH DOSE DEXAMETHASONE SUPPRESSION TEST

   A simple fast test – The AM cortisol after 8 mg of Dexamethasone given the night before should reduce to less than 50% of the baseline value.

B. TWO-DAY HIGH DOSE TEST

   Dexamethasone 2 mg every 6 hours is given for two days Serum and urine coritsol should suppress to less than 50% the baseline values.


CUSHING'S SYNDROME SUSPECTED
Urine free cortisol;
Low-dose dexamethasone suppression
Abnormal
Normal
Excludes
Cushing's syndrome
Plasma ACTH;
high-dose dexamethasone
suppression
ACTH undetectable;
no suppression
ACTH elevated;
no suppression
ACTH normal to elevated;
dexamethasone suppression
< 50% baseline
Adrenal tumour
Ectopic ACTH syndrome
Cushing's disease

Radiological:

CT scanning will help in localizing pituitary and adrenal tumors and in some instances, ectopic ACTH production.

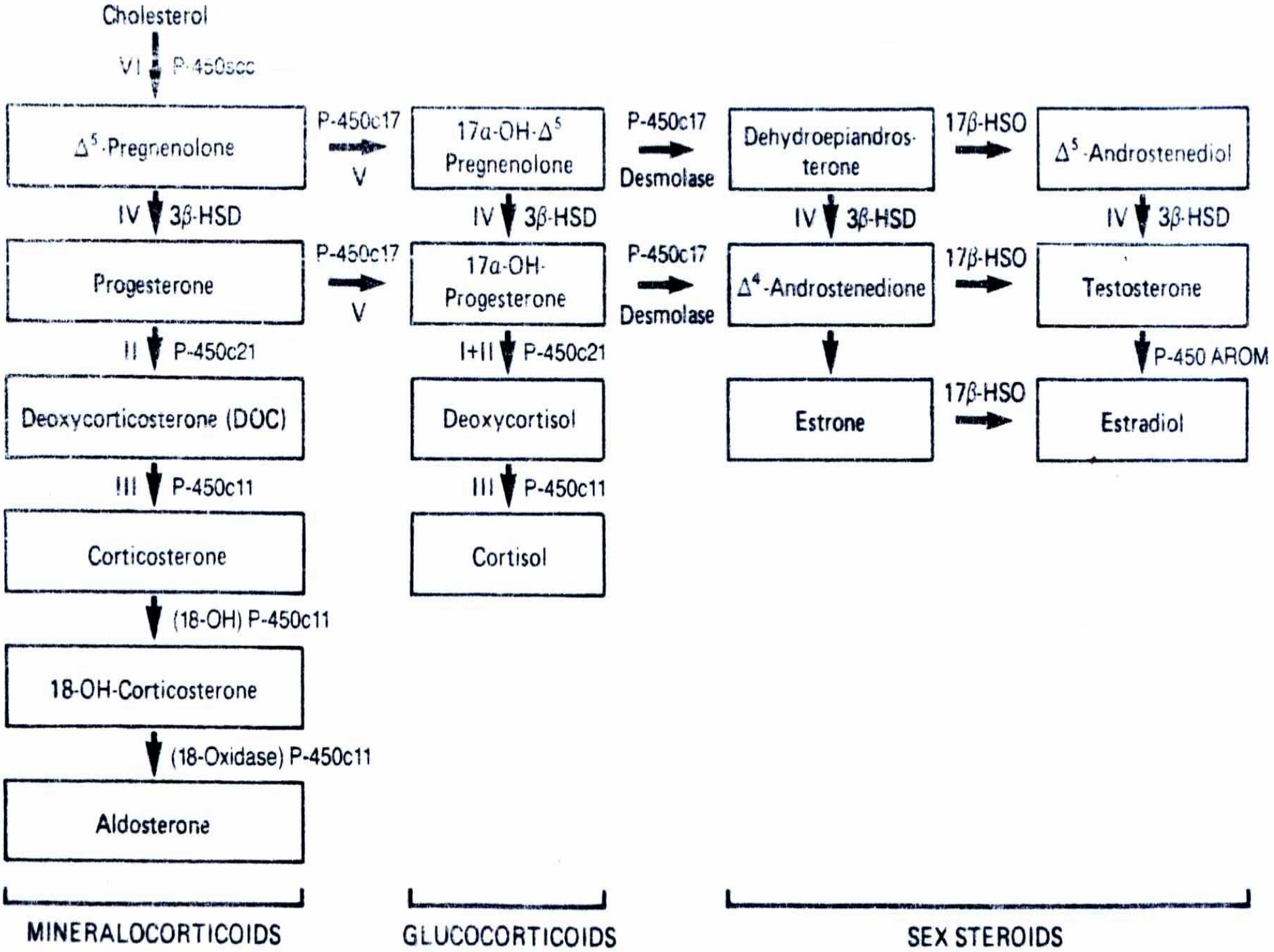
Small tumors may be difficult to detect and selective venous sampling may be needed. In some cases, more detailed isotope scanning and arteriography or venography may be needed.

Treatment:

Cushing's Disease – Hypercortisolism has a lot of complications and can be fatal if left untreated.

Treatment is directed at control of ACTH hypersecretion by the pituitary and available methods include:

1. Microsurgery
2. Radiotherapy
3. Pharmacological inhibition of ACTH secretion


Cholesterol
VI P-450scc
Δ5-Pregnenolone
P-450c17
V
17α-OH-Δ5 Pregnenolone
P-450c17
Desmolase
Dehydroepiandros-terone
17β-HSO
Δ5-Androstenediol
IV 3β-HSD
IV 3β-HSD
IV 3β-HSD
Progesterone
P-450c17
V
17α-OH-Progesterone
P-450c17
Desmolase
Δ4-Androstenedione
17β-HSO
Testosterone
II P-450c21
I+II P-450c21
P-450 AROM
Deoxycorticosterone (DOC)
Deoxycortisol
Estrone
17β-HSO
Estradiol
III P-450c11
III P-450c11
Corticosterone
Cortisol
(18-OH) P-450c11
18-OH-Corticosterone
(18-Oxidase) P-450c11
Aldosterone
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX STEROIDS

Treatment:

Drugs:

1. Mitotane acts by inhibiting cortisol synthesis through inhibiting the P450 enzyme responsible for 11B hydroxylation.
2. Metyrapone also blocks cortisol synthesis by inhibiting 11B hydroxylase action and also the cholesterol side-chain cleavage.
3. Ketocenazole is a potent inhibition of the P450 enzymes with a principle effect on the 17-20 lyase enzymes but it also inhibits 11B hydroxylase, 18 hydroxylase and cholesterol side-chain cleavage.

Ectopic ACTH Syndrome

Therapy is directed at removal of the tumour which is only successful in the benign tumours otherwise drugs that block steroid synthesis can be used, e.g. Metyrapone and mitotane with steroid replacement if necessary.

Adrenal Tumors

Adenomas are successfully treated by adrenalectomy while this treatment for carcinoma is usually unsuccessful and medical therapy can control hypercortisolism in these patients

Primary Mineralocorticoid Excess

The principle mineralocorticoid hormone is aldosterone. It is produced in the zona glomerulosa exclusively and is primarily controlled by the renin-angiotensin system.

Other regulators include:

1. Potassium level
2. ACTH
3. Neural Components of the adrenergic and dopamenergic systems.

Primary Hperaldosteronism

There is increased production of aldosterone by abnormal zona glomerulosa tissue (adenoma or hyperplasia) which leads to :

- Increased sodium retention
- Expansion of the extracellular fluid volume
- Increased total body sodium content that leads to suppression of renin production.
- Potassium depletion occur decreasing the total body and plasma concentration of potassium and producing alkalosis.
- With moderate potassium depletion. There is decreased carbohydrate tolerance and resistance to antidiuretic hormone.

Primary Hyperaldosteronism

Because aldosterone biosynthesis is intensified, the entire biosynthetic pathway becomes activated and precursors like DOC corticosterone and 18-hydroxycorticosterone are present in increased amount in person with an aldosterone producing tumour.

There is no abnormalities in cortisol production, plasma cortisol levels or cortisol metabolism.

CAUSES

1. Aldosterone producing adenoma (APA)
2. Bilateral adrenal hyperplasia; idiopathic AH
3. Indeterminate hyperaldosteronism
4. Dexamethasone suppressible hyperaldoesteronism
5. Adrenocortical carcinoma.

Clinical Features

Patient usually come to medical attention because of symptoms of hypokalemia or detection of previously unsuspected hypertension.

There are no characteristic symptoms and often nonspecific complaints, e.g. tiredness, lethargy, weakness, nocturia and symptoms of potassium depletion.

Clinical Features

If potassium depletion is severe with alkalosis, there is increased thirst and polyuria and maybe parasthesia. Headache is a frequent complaint. Blood pressure can range from borderline to severe hypertensive levels.

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- Accelerated/malignant hypertension is rare and a postural fall in blood pressure without reflex tachycardia is observed in severe potassium depletion because of blunting of the baroreceptors.
- Retinopathy is mild with haemorrhages being rare.

- A positive trousseau or chevostek sign may suggest alkalosis with severe potassium depletion. The ECG shows signs of modest LVH and potassium depletion

Laboratory & Radiological Diagnosis

Diuretics should be stopped three weeks prior to potassium measurement. Other features include:

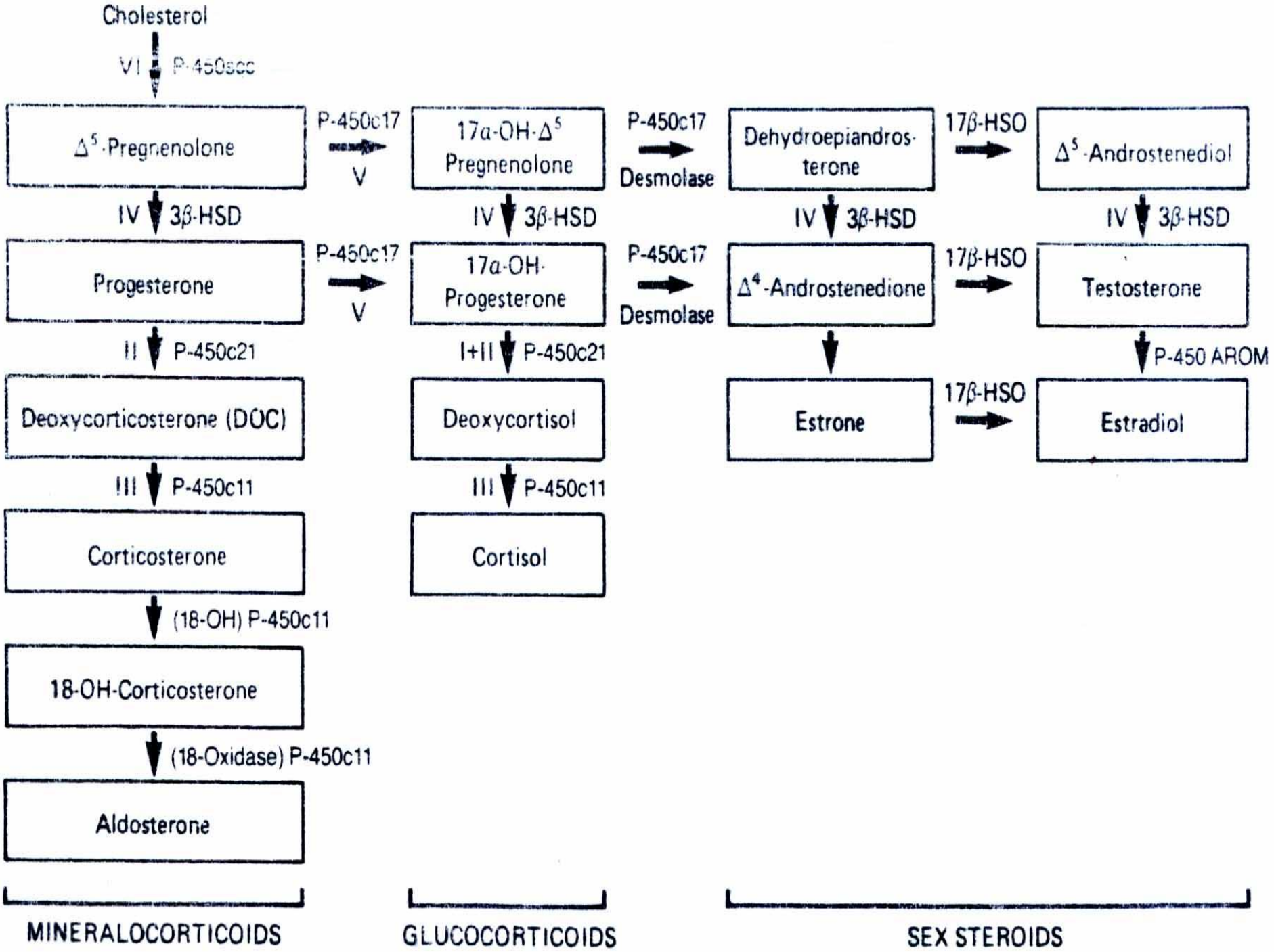
- A high serum sodium in the presence of reduced haematocrit value (due to increased extracellular fluid and plasma volume from sodium retention)
- There is also failure to concentrate urine.
- Abnormal glucose tolerance
- Alkalosis
- All features of potassium depletion.

Laboratory & Radiological Diagnosis

If hypokalemia is documented, the next step is to assess the renin angiotensin system by doing a random plasma renin activity level and if normal or high in the absence of diuretics therapy, then primary aldosteronism is very unlikely but if it is suppressed, then primary aldosteronism is a likely diagnosis.

Measurement of Aldosterone & Other Steroids

Aldosterone – both plasma and urinary aldosterone measurement should be performed while the patient is taking a high salt diet with sodium chloride supplementation. Assessment of aldosterone production can be best done by measurement of urinary aldosterone excretion over 24 hour period and it is superior to plasma aldosterone measurement in detecting abnormal production of aldosterone but cannot discriminate between adenoma and hyperplasia. While the plasma levels can differentiate between the two conditions in most cases.


Cholesterol
VI P-450scc
Δ5-Pregnenolone
P-450c17
V
17α-OH-Δ5 Pregnenolone
P-450c17
Desmolase
Dehydroepiandros-terone
17β-HSO
Δ5-Androstenediol
IV 3β-HSD
IV 3β-HSD
IV 3β-HSD
Progesterone
P-450c17
V
17α-OH-Progesterone
P-450c17
Desmolase
Δ4-Androstenedione
17β-HSO
Testosterone
II P-450c21
I+II P-450c21
P-450 AROM
Deoxycorticosterone (DOC)
Deoxycortisol
Estrone
17β-HSO
Estradiol
III P-450c11
III P-450c11
Corticosterone
Cortisol
(18-OH) P-450c11
18-OH-Corticosterone
(18-Oxidase) P-450c11
Aldosterone
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX STEROIDS

Localization of Adenoma/Carcinoma

Scanning using i.v. Administered

1^{3} iodocholesterol locates tumour in 80% of the cases depending on the size of the tumour.

NP59 scan is another scan which consumes less time.

CT scanning is also useful with less radiation hazard. Other methods include adrenal venography, adrenal vein catheterization and bilateral sampling of blood for aldosterone measurements.

Treatment

In aldosterone producing adenoma, unilateral adrenalectomy is recommended provided there is adequate potassium replacement and adequate extracellular volume expansion with adequate control of BP before surgery all of which can be achieved by spironolactone with or without other medications which should be given for some time before surgery.

In hyperplasia, antihypertensive medication should be given as surgery will not ameliorate the hypertension.

The surgical cure of hypertension associated with adenoma is excellent as is reported to be over 50% in many series with reduction of hypertension in the remainder.

Pheochromocytoma

Pheochromocytomas are tumours arising from the chromaffin cells in the sympathetic nervous system.

They release epinephrine or norepinephrine (or both) and in some cases, dopamine into the circulation causing hypertension as well as other signs and symptoms.

- Only 0.1% of hypertensive patients have pheochromocytoma but recognition is important because it can be fatal during delivery or surgery if unrecognized and not properly treated.

Pheochromocytoma

Pheochromocytoma may occur as a heritable disorder either alone or in combination with other endocrine tumours, e.g. MEN type II A – hyperparathyroidism, pituitary adenoma and medullary thyroid carcinoma or MEN Type II B – pheochromocytoma with mucosal neuroma.

The Role of 10

10% bilateral

10% Familial

10% Malignant

10% Extra adrenal

Common extra adrenal sites and near the kidneys and the organ of Zuckerkandl. They can also occur in the posterior mediastinal region.

Clinical Manifestation

Most patients have symptoms that vary in intensity and are perceived to be mainly episodic or paroxysmal by about half the patients.

Most patients with persistent hypertension also have superimposed paroxysms and only few patients are entirely free of symptoms and hypertension between attacks and give no evidence of catecholamine excess during these intervals.

Clinical Manifestation

COMMONLY REPORTED SYMPTOMS AND SIGNS

Symptoms during or following paroxysms:

- Headache
- Sweating
- Forceful heart beat with or without tachycardia
- Anxiety or fear of impending death
- Tremor
- Fatigue or exhaustion
- Nausea and vomiting
- Abdominal or chest pain
- Visual disturbances

Increased sweating

cold hands and feet, weight loss, constipation

In the attack the symptoms resemble those produced by injection of epinephrine or norepinephrine.

The attacks in pheochromocytoma in those patients with paroxysmal symptoms occur several times a week or oftener and last 15 minutes or less but they may occur at intervals of months or as often as 25 times a day and may last minutes to days. With time the attacks usually increase in frequency but do not change much in character.

They are usually precipitated by activities that compress the tumour, e.g changes in position, exercise lifting, defecation or eating and by emotional distress or anxiety.

Symptoms between Paroxysms

Hypertension is usually present and characteristically there is wide fluctuations and an episode of marked hypertension might be followed by hypotension and shock. The blood pressure typically does not respond to commonly used antihypertensive medications.

Chronic constriction of the arterial and venous beds leads to reduction in plasma volume and the inability to further constrict the bed upon arising causes the postural hypotension that is characteristically observed.

A mass is felt in the neck or abdomen and palpation may produce a typical paroxysm.

Symptoms between Paroxysms

Patients with persistent symptoms and hypertension may develop hypertensive retinopathy or nephropathy as well as the other sequelae of hypertension.

CVA, CCF and MI are all observed. A significant number were found to have myocarditis post partum.

Other causes of increased sympathetic activity must be thought of:

- Angina due to coronary vasospasm
- Severe anxiety state
- Hypertension
- Hypertensive crises associated with
  - Paraplegia
  - Tabesansalis
  - Lead poisoning
  - Acute porphyria
- Menopausal hot flushes
- Thyrotoxicosis, etc.

Diagnosis

The diagnosis of pheochromocytoma should be considered in the following patients.

a. Patients with paroxysmal symptoms
b. Children with hypertension
c. Adults with severe hypertension not responding to therapy.
d. Hypertensive patients with diabetes or hypermetabolism.
e. Hypertensive patients with symptoms resembling the symptom complex described above or can be evoked by exercise position change .. ect. or certain antihypertensive medications.
f. Patients who become severely hypertensive or go into shock during anesthesia, surgery or obstetric delivery,

Diagnosis

g. Patients who have disorders sometimes associated with pheochromocytoma, e.g. neurofibromatosis, mucosal adenomes, medulary carcinoma of thyroid or those who have first degree relatives who have pheochromocytomas or other manifestations of MEN.

Ganglioneuromas and neuroblastomas can produce catecholamines with dopamine being the major product leading to a similar picture resembling pheochromocytoma.

Laboratory Diagnostic Tests & Radiological Investigations

In patients with continuous hypertension or symptoms, levels of plasma or urinary catecholamines and their metabolites are usually clearly increased, the difficulty arises in patients having brief and infrequent paroxysms with symptom-free intervals and in such cases, sampling of blood or urine should be done during a carefully observed episode to confirm the diagnosis.

Laboratory Diagnostic Tests & Radiological Investigations

TESTS USED

COMPOUND	INTERFERING SUBSTANCES
• Blood /Urine Metanephrin Normetanephrin	• Increased by catecholamines, MAOI and others
• Urine Vanilly Mandelic Acid (VMA)	• Increased by catecholamines and food that contain vanillin or L-dopa. Decreased by Clofibrale and MAOI
• Blood/Urine Catecholamines	

Laboratory Diagnostic Tests & Radiological Investigations

TESTS USED

COMPOUND	INTERFERING SUBSTANCES
• Urine Epinephrine Norepinephrine Dopamine	• May be increased with highly fluorescent compounds, e.g. tetracycline, quinidine as well as food and drugs containing catecholamines, e.g. bananas and other drugs, e.g. methyldopa, ethanol.

Once the diagnosis has been established, the tumor must be located prior to surgical removal. CT scanning gives better results than sonography or other radiological tests. MRI is evolving as very specific and excellent technique for detecting pheochromocytomas.

- Analysis of blood samples obtained for venous drainage can be of great value in locating small tumours in unusal locations.
- MIBG(meta-iodo-benzyl-guanidine) can detect even the smallest tumour but not all pheochromocytomas produce detectable images and other tumours e.g. neuroblastoma give positive images.

Treatment

Treatment is directed toward:

- Reduction of symptoms
- Lowering of BP
- Amelioration of paroxysms

Therapy with alpha adrenergic antagonists should be instituted. Such treatment will allow expansion of the vascular bed and plasma volume.

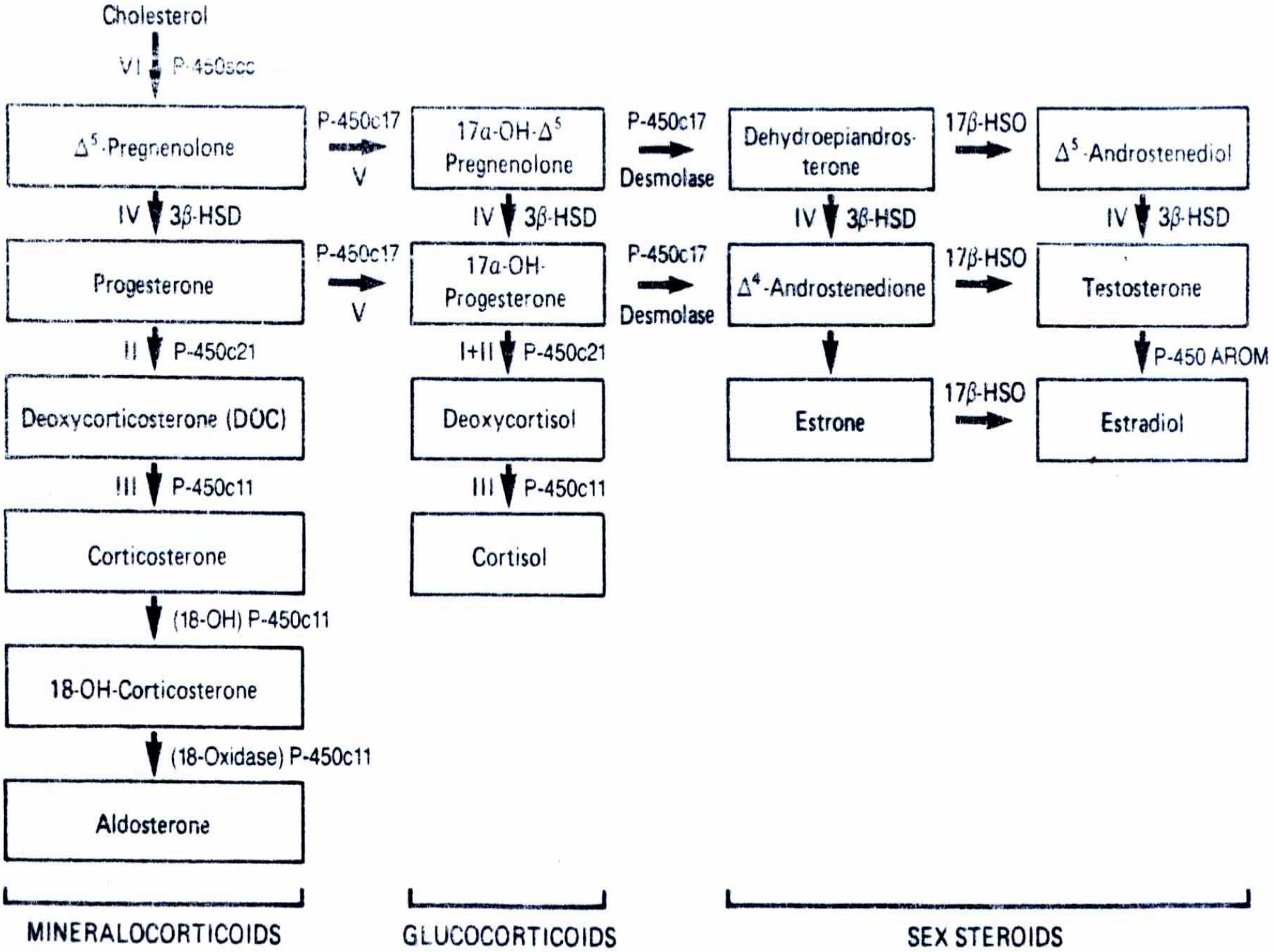
Agents commonly used include phentolamine and phenoxybenzamine, small doses of propranolol maybe required for marked tachycardia or arrhythmia prior or during surgery.

Surgery

Patients should be fully, prepared medically prior to surgery to avoid intra and post operative complications. Once the tumor is removed, the blood pressure usually falls and i.v. fluids and / or blood might be needed to restore circulatory volume. Persistence of high BP after surgery should alert physician to look for other causes, e.g. renal vascular hypertension.

Congenital Adrenal Hyperplasia

- **Classic congenital adrenal hyperplasia** (CAH) is an autosomal recessive disorder with an incidence of 1 in 7,000-15,000
- **Non-classic CAH** is less severe and effects 1 in 500-1000 individuals
- 90-95% of cases are caused by **deficiency of 21-hydroxylase**, which catalyses the synthesis of cortisol and aldosterone from cholesterol


Cholesterol
VI P-450scc
Δ5-Pregnenolone
P-450c17
V
17α-OH-Δ5 Pregnenolone
P-450c17
Desmolase
Dehydroepiandros-terone
17β-HSO
Δ5-Androstenediol
IV 3β-HSD
IV 3β-HSD
IV 3β-HSD
Progesterone
P-450c17
V
17α-OH-Progesterone
P-450c17
Desmolase
Δ4-Androstenedione
17β-HSO
Testosterone
II P-450c21
I+II P-450c21
P-450 AROM
Deoxycorticosterone (DOC)
Deoxycortisol
Estrone
17β-HSO
Estradiol
III P-450c11
III P-450c11
Corticosterone
Cortisol
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MINERALOCORTICOIDS
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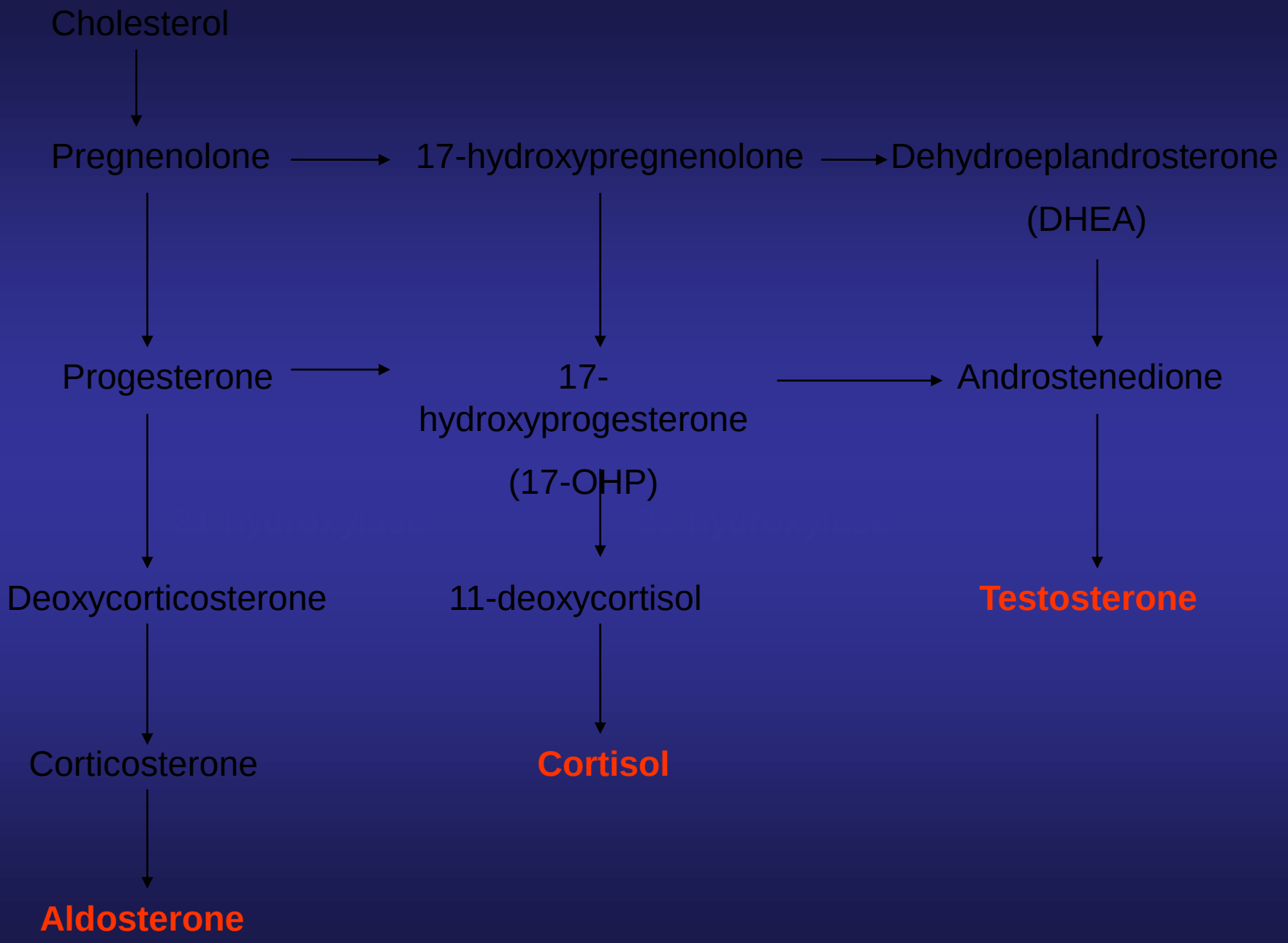
Cholesterol
Pregnenolone
17-hydroxypregnenolone
Dehydroeplandrosterone
(DHEA)
Progesterone
17-
hydroxyprogesterone
(17-OHP)
Androstenedione
Deoxycorticosterone
11-deoxycortisol
Testosterone
Corticosterone
Cortisol
Aldosterone

Clinical Presentation

- Clinical severity depends on degree of 21-hydroxylase deficiency
  - Good genotype phenotype correlations
- Classical CAH
  - **Simple Virilsing:** Ambiguous genitalia in females
  - **Salt Wasting:** Dehydration, vomiting and diarrhoea. If untreated can prove fatal
- Non-classical CAH
  - Milder than classical CAH
  - Androgen excess can cause precocious puberty in either sex
  - Males are often undiagnosed/asymptomatic

Treatment

- Glucocorticoids which suppress ACTH, are used to reduce the levels of adrenal sex steroids in the blood
- Individuals with salt wasting CAH also require mineralcorticoids and sodium chloride supplements
- Surgery on virilised females
- Growth monitoring to detect over and under treatment
- Dexamethosone can be used to prevent/reduce prenatal virilisation. Side effects for the mother include weight gain, irritability and oedema