Corticosteroids

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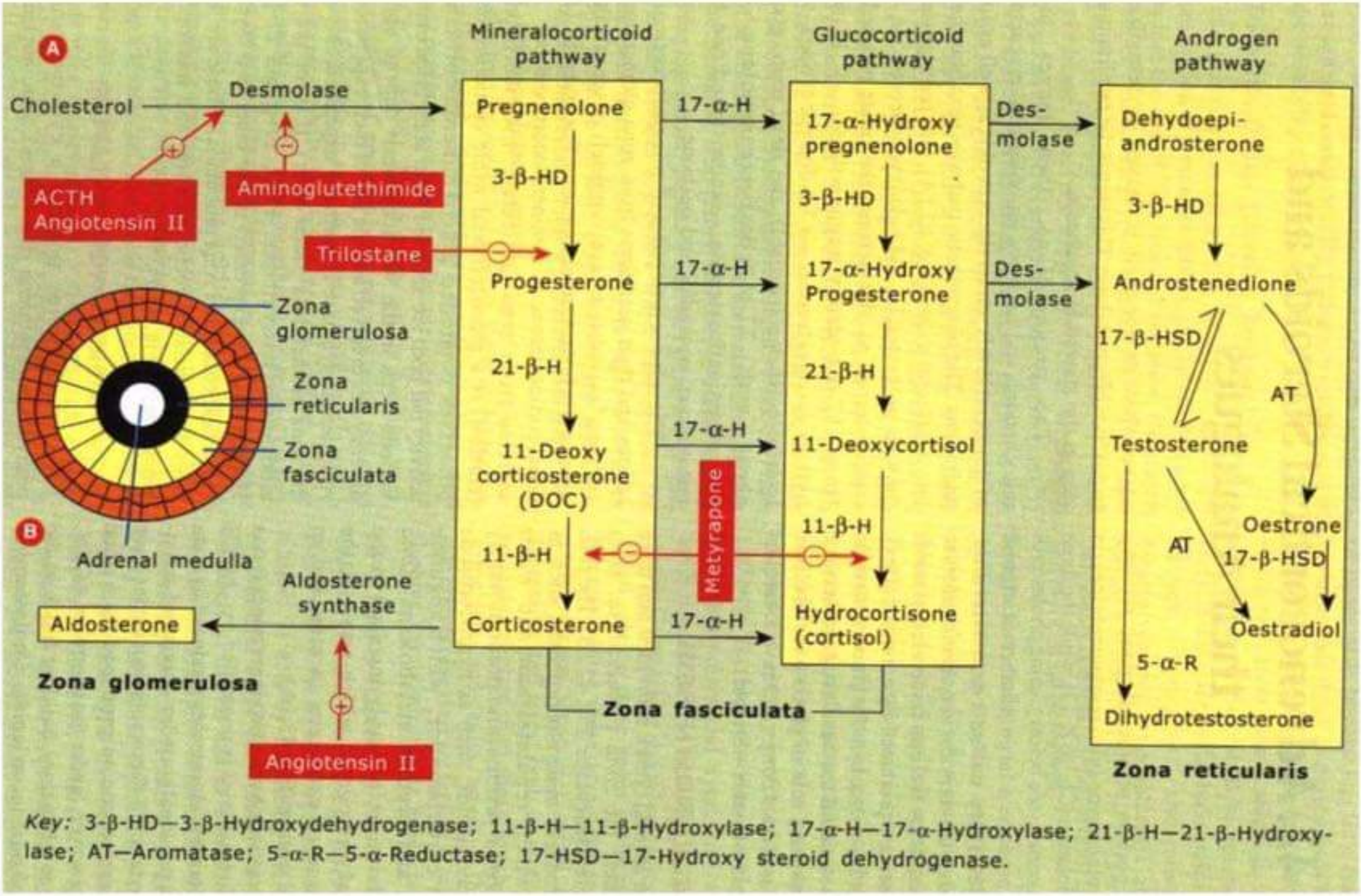
Introduction

Adenal gland

- **Medulla**
  - **Epinephrine**
- **Cortex**
  - **Z. glomerulosa**
    - **Mineralocorticoids**
  - **Z. fasciculata**
    - **Glucocorticods**
  - **Z. reticularis**
    - **Androgens**

Steroid biosynthesis

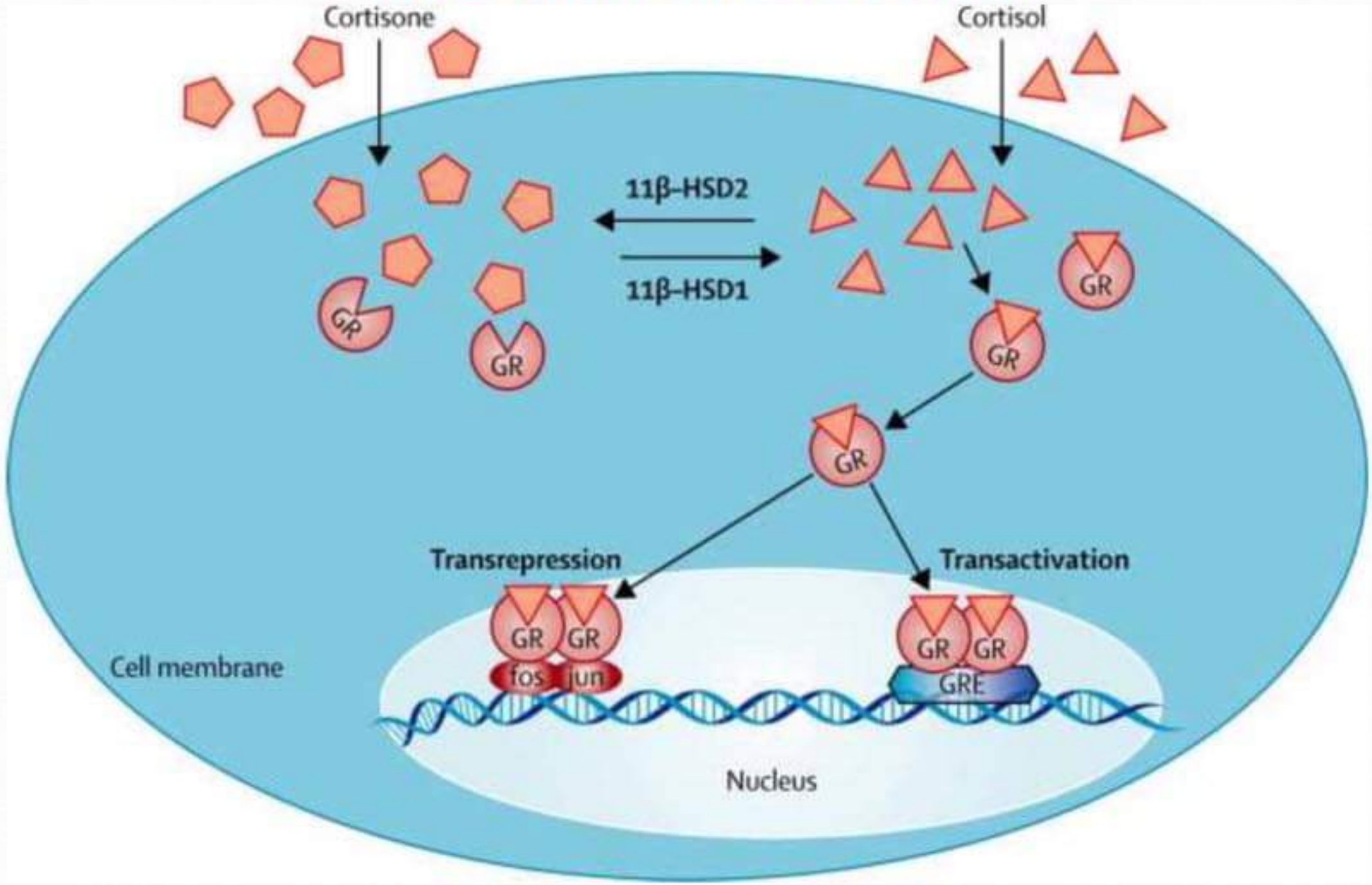


Key: 3-β-HD—3-β-Hydroxydehydrogenase; 11-β-H—11-β-Hydroxylase; 17-α-H—17-α-Hydroxylase; 21-β-H—21-β-Hydroxylase; AT—Aromatase; 5-α-R—5-α-Reductase; 17-HSD—17-Hydroxy steroid dehydrogenase.

Steroid transport in blood

- Glucocorticoids reversibly bind to **transcortin.**
- Transcortin is a □-globulin.
- 80% of plasma cortisol is bound to transcortin.
- Only 10% is bound to serum albumin.
- Remaining 10% is free hormone.

Mechanism of action



Transactivation

- Leads to transcription & translation.
- Induces enzymes - Camp dependent kinase.
- Induce formation of annexin-1 (lipocortin-1).
- Lipocortin-1 inhibits phospholipase A2.
- Induction of Annexin-1 is slow.
- Antiinflammatory response takes several hours.

Transrepression

- Inhibits transcription factors like- AP-1 & NF-kB.
- Inhibits transcrption of genes for-

➢ COX-2

➢ Cytokines

➢ Inducible form of NO synthase.

- Biological lag of several hours is seen before effects.
- Effects are present even when steroid levels fall.
- Side effects can be minimized by alternative day therapy

Mineralocorticoid receptor

- Binds to MRE.
- Expressed mainly in kidney, also in colon, salivary glands, sweat glands & hippocampus.
- Glucocorticoids will also bind to MRs.
- MRs bind aldosterone & hydrocortisone (cortisol) with equal affinity.
- Cortisol is inactivated by 11-β-HSD on binding to MRs.
- Aldosterone exists as hemiacetyl derivative which is resistant to degradation by 11-β-HSD.

Pharmacological actions

General considerations

- Actions of corticoids are divided in to
  - Gluco- carbohydrate, fat & protein metabolism.
    - antiinflammatory & immunosuppressant actions.
  - Mineralo- Na^+, K^+ & fluid homeostasis.
- Glucocorticoid potency **α** antiinflammatory effects.
- Direct and some permissive actions.
- Exogenous glucocorticoids depress secretion of CRH & ACTH by negative feedback mechanism.

Glucocorticoid actions

Carbohydrate & protein metabolism

- Exert anti-insulin effects by:

1. ↓ Peripheral utilization of glucose
2. ↑ gluconeogenesis
3. Inhibit protein synthesis in muscle, connective tissue & skin.

- Net result of glucocorticoid administration is-

➢ ↑ Blood sugar, liver glycogen & excretion of nitrogen.

- Prolonged high doses- DM like state, protein wasting.

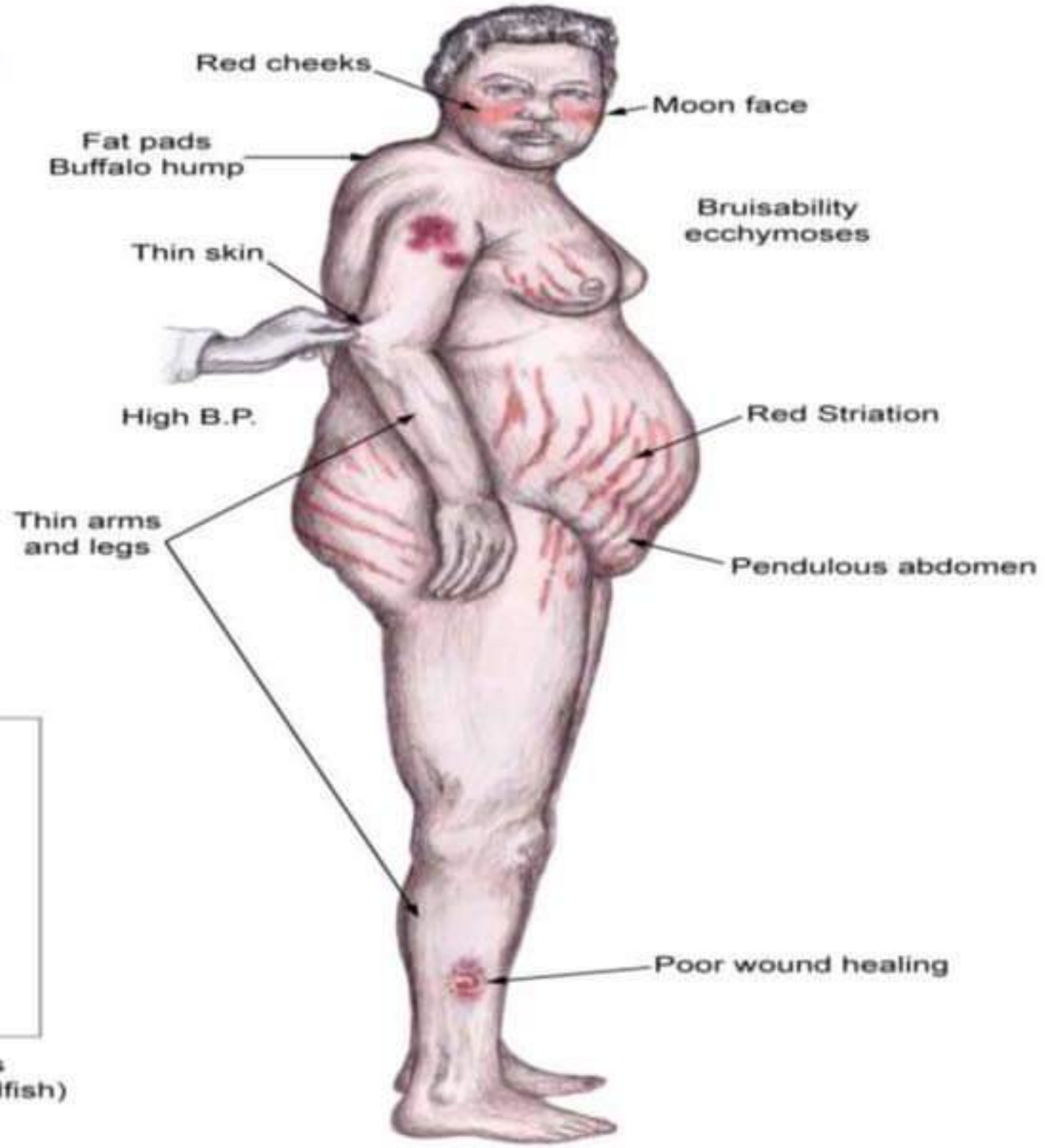
Fat metabolism

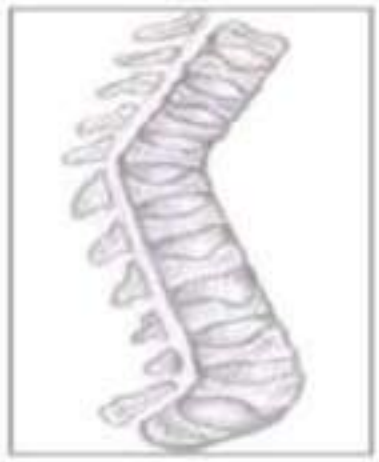
- Enhance lipolytic effects of GH, Adr, Thyroxine.
- Mobilization of free fatty acids ↑.
- Insulin release → ↑ deposition of fats.
- Prolonged high doses cause redistribution of fat.
  - Neck & shoulders- buffalo hump
  - Face- moon face, abdomen- centripetal obesity.
- Cuta striae- due to stretching of skin.
- Central adipocytes are more sensitive to insulin.

CUSHING Syndrome

Background

Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids





Osteoporosis
compressed (codfish)
vertebrae

Anti-inflammatory effects

- Endogenous GC prevent excessive defense response.
- Inhibit inflammation irrespective of its cause.

In macrophages, monocytes, endothelium & fibroblasts

- Induce the production of lipocortin.
- Inhibit cytokine release & T-cell activation.
- This reduces the process of chemotaxis.
- Inhibit synthesis of adhesion molecules- ELAM-1 & ICAM-1, promote leukocyte localization.
- Impair recruitment to the sites of inflammation.

Transrepression of proinflammatory transcription factors

- Inhibit nuclear factor-kB (NF-kB) & activatory protein (AP-1).
- These enhance transcription of genes for COX-2, various cytokines & iNOS.

Lymphocytes

- ↓Release of cytokines (IL-1, 2,4&6) from lymphocytes.
- GC ↓ L, M, E & B in circulation

Miscellaneous effects

Basophils & mast cells:

- Gc ↓ IgE dependent release of histamine LT-C4 from basophils. ↓Capillary permeability.
- Acute phase reactant production ↓.
- ↓ Production of collagenase & stromelysin , hinder tissue damage
- Prolonged therapy ↓ production of collagen – obstructs wound healing & repair.

Immune response

- Suppress CMI
- Inhibit genes for cytokines- IL-1,2,3,4,5,6,8 & INF-ɣ.
- ↓cytokines reduce T-cell proliferation.
- Also suppress humoral immunity.
- Down regulate Fc receptors on macrophages.
- Graft rejection is prevented by-

1. Reducing antigen expression from grafted tissue.
2. Delay revascularization.
3. ↓ Sensitization of cytotoxic T-lymphocytes.

Calcium metabolism

- Inhibit Abs & enhance renal Exc of Ca2+.
- Loss of osteoid results in loss of $Ca2^{+}$ from bone.
- Produces negative calcium balance.
- Spongy bones (vertebrae, ribs etc.) are more sensitive.

Stomach

- Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

CVS effects

- Directly stimulate cardiac output.
- Potentiates pressor effects of catecholamines & AngII.
- Predisposes to HTN & CHD.

Haematopoietic system

- ↑RBC, platelets & neutrophils in circulation.
- ↓Lymphocytes, eosinophils & basophils.
- Marked lytic effect on malignant lymphatic cells.
- Used in treating lymphomas.

Miscellaneous effects

- Cortisol is needed for maintaining normal GFR.
- Stimulates surfactant production in foetal lung.
- Higher doses ppt peptic ulcer.
- Increases renal excretion of uric acid.
- Depress TRH secretion

Mineralocorticoid actions

- Aldosterone is the most important MC.
- ↑Na^+ reabsorption in DCT & CD, ↑K^+ & H^+ excretion.
- 3 types of mechanisms operate for Na^+ reabsorption.

❑Rapid non genomic effect by stimulation of Na^+/H^+ exchanger in the apical membrane.

❑Delayed effect by binding to MC receptor & synthesizing aldosterone induced proteins (AIP).

❑↑No. of Na+/K+ ATPase molecules in basolateral membrane.

Steroid	Duration of action	Gluco-corticoid activity	Mineralo-corticoid activity	Equivalent dose (mg)	Preparation available
GLUCOCORTICOIDS				(Anti-inflammatory)	
Hydrocortisone (cortisol)	8–12 hrs SHORT	1	1	20	O/I/T
Cortisone	8 hrs	0.8	0.8	25	O/I/T
Prednisone		4	0.5–0.8	5	O
Prednisolone*	12–36 hrs	5	0.5–0.8	5	O/I/T
Methylprednisolone	Intermediate	5	0–0.5	4	O/I/T
Triamcinolone		5	0	4	O/I/T
Deflazacort		5–6	0	6	O
Paramethasone	36–72 hrs	10	0	2	O/I
Betamethasone	Long acting	25	0	0.65	O/I/T
Dexamethasone*		30	0	0.75	O/I/T
MINERALOCORTICOIDS				(Na^+ Retaining dose)	
Aldosterone	30 min	0.3	3000	Not used	Endogenous
Fludrocortisone	18–30 hrs	10	200	0.2	O
Desoxycortico-sterone	70–80 min	0	20	2.5	SL/IM

Steroid	Preparation
Alclometasone	Topical
Amcinonide	Topical
✓ Beclomethasone	Topical/Inhalation*
✓ Budesonide	Inhalation*
Clobetasol	Topical
Clocortolone	Topical
Desonide	Topical

Steroid	Preparation
Dexsoximetasone	Topical
Flucinolone	Topical
✓ Flunisolide	Inhalation
Fluoromethalone	Ophthalmic
✓ Fluticasone	Topical/Inhalation
Halcinonide	Topical
Medrysone	Ophthalmic

USES

Replacement therapy

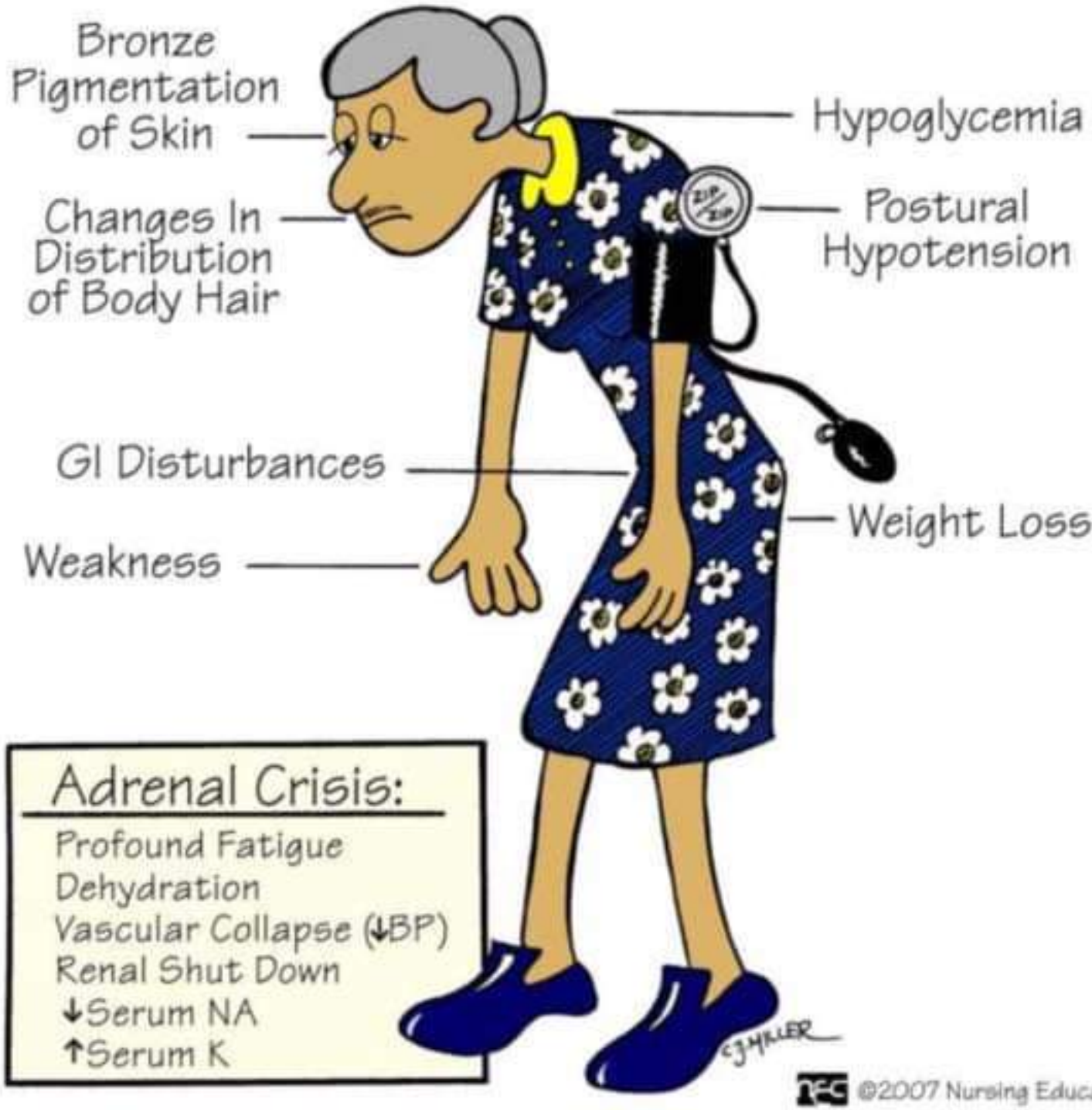
Acute adrenal insufficiency

- Hydrocortisone or dexamethasone are given i.v., first as a bolus injection and then as infusion, along with isotonic saline and glucose solution.

Chronic adrenal insufficiency (Addison's disease)

- Hydrocortisone given orally.
- Adequate salt and water allowance.
- Patients who excrete excess Na+ need additional mineralocorticoid: fludrocortisone is added.

ADDISON'S DISEASE



Cong. adrenal hyperplasia (Adrenogenital syndrome)

- Genetic deficiency of mostly 21-hydroxylase.
- Synthesis of hydrocortisone and aldosterone ↓.
- ACTH secretion↑ leads to adrenals hypertrophy;
- Enzyme deficiency is partial in most cases,
- Excessive amounts of weak androgens → virilization and/or precocious sexual development.
- If the deficiency is severe, salt wasting also occurs.

Treatment

- Hydrocortisone 0.6 mg/ kg daily in divided doses.
- Salt wasting persists, fludrocortisone 50–200 μg/d

Arthritides

Rheumatoid arthritis

- Indicated only in severe cases as adjuvants to NSAIDs.
- To suppress exacerbations, or systemic manifestations.

Osteoarthritis

- Intra-articular inj to control an acute exacerbation.
- Repeated 2–3 times a year, but have the potential to cause joint destruction.

Rheumatic fever

- Used only in severe cases with carditis and CHF
- Aspirin is given in addition and is continued after corticoids have been withdrawn.

Gout

- Corticoids (short course) should only be used in
  - Acute gouty arthritis when NSAIDs have failed
  - Colchicine is not tolerated.
- Intra-articular inj of a soluble GC is preferred.
- Though they are uricosuric- use in chronic gout is not recommended.

Bronchial Asthma

- Inhaled/systemic steroids are preferred for mod/severe
- Inhaled steroids:
  - Beclomethasone
  - Budesonide
  - Flunisolide
  - Fluticasone
  - Mometasone
  - Triamcinolone
- Concomitant β–agonists or theophylline ↓dose of steroids

Other lung diseases

- Benefit aspiration pneumonia and pulmonary edema from drowning.
- To Prevent respiratory distress syndrome in premature infants.
- Two doses of betamethasone 12 mg i.m. at 24 hour interval may be administered to the mother if premature delivery is contemplated.

Infective diseases

- Tuberculosis (miliary, meningeal, renal, etc.),
- Severe lepra reaction,
- Bacterial meningitis
- Pneumocystis carinii pneumonia with hypoxia in AIDS patients.

Skin diseases

- Topical corticosteroids are highly effective in many eczematous skin diseases.
- Systemic therapy is needed (may be life-saving) in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other severe afflictions.

Intestinal diseases

- Ulcerative colitis, Crohn's disease, coeliac disease are inflammatorybowel diseases with exacerbations and remissions.
- Corticoids are indicated during acute phases.

Malignancies

- Useful in haematopoietic malignancies, Hodgkin's & other lymphomas.
- Secondary role in hormone responsive breast carcinoma, act probably by causing HPA suppression

Cerebral edema

- Due to tumours, tubercular meningitis, etc., respond.
- Dexa-or betamethasone are preferred.
- Reduce neurological sequelae after spinal injury.
- Bell's palsy- oral prednisolone X 2–4 weeks.
- Multiple sclerosis- methyl prednisolone 1 g i.v. daily for 2–3 days may be given in the beginning.

Septic shock

- Recent studies have documented beneficial effects of low-dose (hydrocortisone 100 mg 8 hourly i.v. infusion for 5–7 days) therapy in patients who are adrenal deficient and do not respond adequately to fluid replacement and vasopressors.

Thyroid storm

- Many patients in thyroid storm have concomitant adrenal insufficiency.
- Corticosteroids reduce peripheral T4 to T3 conversion.

To test pituitary-adrenal axis function

- Dexamethasone suppression test is used for diagnosis of cushings syndrome.
- Normal suppression of cortisol- HPA axis intact.
- Failure- hypersecretion of ACTH by pitutary tumor or cortisol by adrenal tumor.
- Dexamethasone 1mg orally at 11PM, sample obtained at 8AM.
- Normal- cortisol levels <3mg/dl.
- Cushing's- >5mg/dl.

Adverse effects

- Altered distribution of fat.
- Oedema, hypokalemia & hypertension
- Suppression of HPA axis
- Osteoporosis & osteonecrosis
- Hyperglycemia & glycosuria
- Peptic ulcer
- Ocular effects- cataract & glaucoma

- Myopathy & muscle wasting
- Susceptibility to infections
- CNS side effects- euphoria, insomnia & nervousness
- Delayed healing: of wounds and surgical incisions.
- Growth retardation: in children
- IUGR can occur after prolonged therapy.
- Pregnancy- increases the risk of gestational diabetes, pregnancy induced hypertension and preeclampsia.

Contraindications

1. Peptic ulcer
2. Diabetes mellitus
3. Hypertension
4. Viral and fungal infections
5. Tuberculosis and other infections
6. Osteoporosis
7. Herpes simplex keratitis
8. Psychosis
9. Epilepsy
10. CHF
11. Renal failure

Metyrapone

- Inhibits 11-β hydroxylase in adrenal cortex
- Prevents synthesis of hydrocortisone.
- Level falls → increased ACTH release → increased synthesis, release and excretion of 11-desoxycortisol in urine
- Used to test the responsiveness of pituitary and its ACTH producing capacity.

- Aminoglutethimide,
- Trilostane and
- High doses of Ketoconazole also
- Inhibit steroidogenic enzymes—can be used to treat Cushing's disease when surgery or other measures are not an option.
- Ketoconazole reduces gonadal steroid synthesis as well.