Chapter 20 | Corticosteroids

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineralocorticoid and weakly androgenic activities. Conventionally, the term 'corticosteroid' or 'corticoid' includes natural gluco- and mineralo-corticoids and their synthetic analogues.

By the middle of 19th century it was demonstrated that adrenal glands were essential for life. Later it was appreciated that the cortex was more important than the medulla. A number of steroidal active principles were isolated and their chemical structures were elucidated by Kendall and his coworkers in the 1930s. However, the gate to their great therapeutic potential was opened by Hench (1949) who obtained striking relief in rheumatoid arthritis by using cortisone. The Nobel Prize was awarded the very next year to Kendall, Reichstein and Hench.

BIOSYNTHESIS

The corticoids (both gluco and mineralo) are 21 carbon compounds having a cyclopentano-perhydro-phenanthrene (steroid) nucleus. They are synthesized in the adrenal cortical cells from cholesterol. A simplified version of the biosynthetic pathways is presented in Fig. 20.1. Adrenal steroidogenesis takes place under the influence of ACTH which makes more cholesterol available for conversion to pregnenolone and induces steroidogenic enzymes. Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis. The circulating corticosteroids

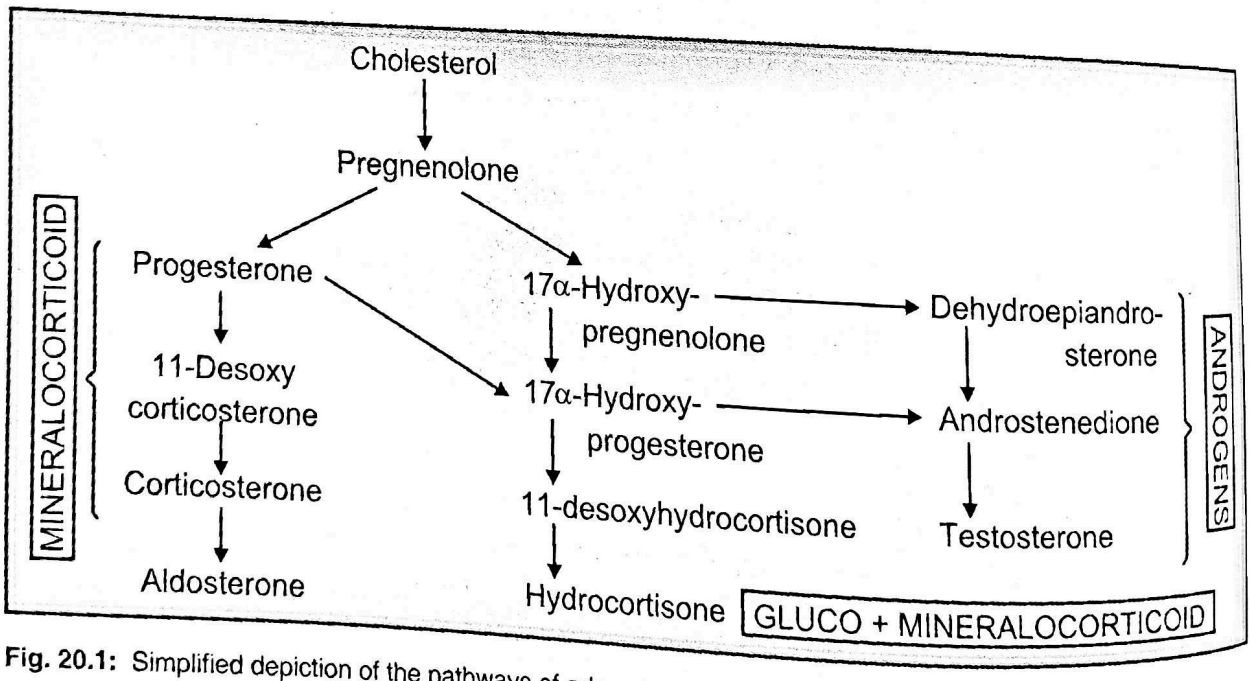


Fig. 20.1: Simplified depiction of the pathways of adrenal steroid hormone biosynthesis

inhibit ACTH release from pituitary as well as CRH production from hypothalamus (*see* Ch. 17) and thus provide negative feed back regulation of the hypothalamo-pituitary-adrenal (HPA) axis.

The normal rate of secretion of the two principal corticoids in man is—

Hydrocortisone — 10–20 mg daily (nearly half of this in the few morning hours).

Aldosterone — 0.125 mg daily.

ACTIONS

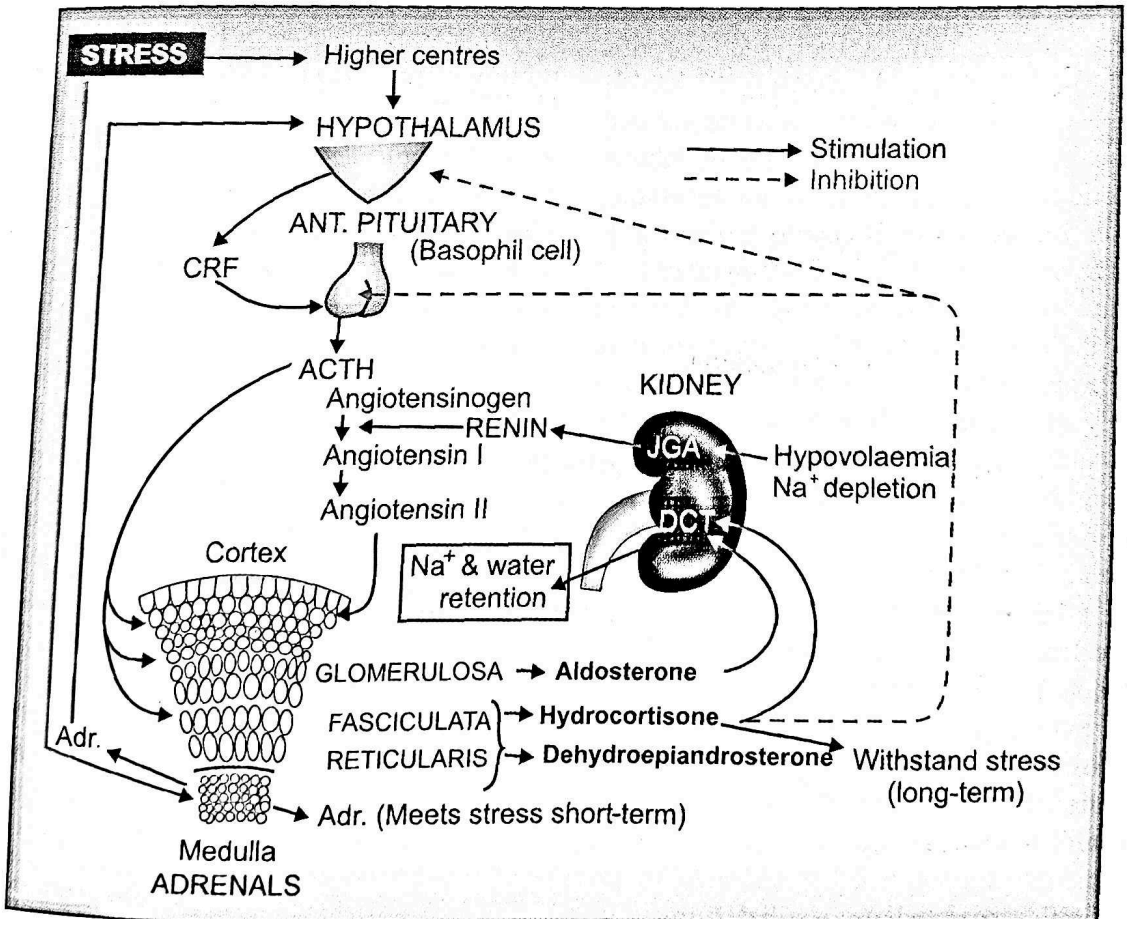
The corticoids have widespread actions. They maintain fluid-electrolyte, cardiovascular and energy substrate homeostasis as well as functional status of skeletal muscles and nervous system. They prepare the body to withstand effects of all kinds of noxious stimuli and stress. The involvement of hypothalamo-pituitary-adrenal axis in stress response is depicted in Fig. 20.2.

Corticoids have some *direct* and some *permissive* actions. By permissive action is meant that while they do not themselves produce an effect, their presence facilitates other hormones to exert that action, e.g. they do not have any effect on BP but the pressor action of Adr is markedly blunted in their absence. Actions of corticoids are divided into:

Glucocorticoid Effects on carbohydrate, protein and fat metabolism, and other actions that are inseparably linked to these.

Mineralocorticoid Effects on Na^+, K^+ and fluid balance.

Marked dissociation between these two types of actions is seen among natural as well as synthetic corticoids. Accordingly, compounds are labelled as 'glucocorticoid' or 'mineralocorticoid'.



CHAPTER 20

Mineralocorticoid actions

The principal mineralocorticoid (aldosterone) action is enhancement of Na^+ reabsorption from the distal convoluted tubule in kidney. There is an associated increase in K^+ and H^+ excretion. Its deficiency results in decreased maximal tubular reabsorptive capacity for Na^+; kidney is not able to retain Na^+ even in the Na^+ deficient state so that Na^+ is progressively lost. Kidneys absorb water without the attendant Na^+ (to maintain e.c.f. volume, which nevertheless decreases) leading to dilutional hyponatraemia → excess water enters cells causing cellular hydration, decreased blood volume and raised haematocrit. Hyperkalaemia and acidosis accompany. These distortions of fluid and electrolyte balance progress and contribute to the circulatory collapse. As such, these actions make adrenal cortex essential for survival.

Similar action on cation transport is exerted in other tissues as well. The action of aldosterone is exerted by gene mediated increased transcription of m-RNA in renal tubular cells which directs synthesis of proteins (aldosterone-induced proteins—AIP). The Na^+K^+ ATPase of tubular basolateral membrane responsible for generating gradients for movement of cations in these cells is the major AIP (*see* Fig. 42.3). Synthesis of β subunit of amiloride sensitive Na^+ channel is also induced. Because of the time taken to induce protein synthesis, aldosterone action has a latency of 1–2 hours. In addition, aldosterone rapidly induces phosphorylation and activation of amiloride sensitive Na^+ channel.

The main adverse effect of excessive mineralocorticoid action is fluid retention and hypertension. The natural and some of the synthetic glucocorticoids have significant mineralocorticoid activity responsible for side effects like edema, progressive rise in BP, hypokalemia and alkalosis. The diuretic induced hypokalemia is aggravated by mineralocorticoid excess.

In addition to the actions on Na^+ and K^+ balance, aldosterone has been shown to promote CHF associated myocardial fibrosis and progression of the disease (*see* Ch. 38).

Glucocorticoid actions

1. *Carbohydrate and protein metabolism* Glucocorticoids promote glycogen deposition in liver (they are assayed on the basis of this action) by inducing hepatic glycogen synthase and promoting gluconeogenesis. They inhibit glucose utilization by peripheral tissues. This along with increased glucose release from liver results in hyperglycaemia, resistance to insulin and a diabetes-like state. They also cause protein breakdown and amino acid mobilization from peripheral tissues. This is responsible for side effects like muscle wasting, lympholysis, loss of osteoid from bone and thinning of skin. The amino acids so mobilized funnel into liver and are used up in gluconeogenesis, excess urea is produced resulting in negative nitrogen balance. Glucocorticoids are thus catabolic. Their function appears to be aimed at maintaining blood glucose levels during starvation—so that brain continues to get its nutrient. When food is withheld from an adrenalectomized animal—liver glycogen is rapidly depleted and hypoglycaemia occurs. Glucocorticoids increase uric acid excretion.

2. *Fat metabolism* The action of glucocorticoids on fat metabolism is primarily permissive in nature. They promote lipolysis due to glucagon, growth hormone, Adr and thyroxine. cAMP induced breakdown of triglycerides is enhanced. Fat depots in different areas of the body respond differently—redistribution of body fat occurs. Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder producing 'moon face', 'fish mouth' and 'buffalo hump'. Explanation offered is—because peripheral adipocytes are less sensitive to insulin and more sensitive to corticosteroid-facilitated lipolytic action of GH and Adr, break down of fat predominates, whereas truncal adipocytes respond mainly to raised insulin levels caused by glucocorticoid induced hyperglycaemia.

Difference in the sensitivity of adipocytes at different locations to glucocorticoids is believed to arise from different levels of expression of the isoenzyme 11β-hydroxysteroid dehydrogenase type 1 (11β HSD1) which generates active hydrocortisone from inactive cortisone in the target tissues. Greater expression of 11βHSD1 in peripheral adipocytes

than in truncal adipocytes would direct glucocorticoid-facilitated lipolysis to the subcutaneous fat in the limbs.

$$\text{Cortisone} \underset{11\beta\text{HSD2}}{\overset{11\beta\text{HSD1}}{\rightleftharpoons}} \text{Hydrocortisone}$$

On the other hand, high expression of the type 2 isoenzyme (11βHSD2) in the kidney tubule (also colon and salivary gland) which express mineralocorticoid receptor (MR) is believed to account for only weak mineralocorticoid activity of hydrocortisone whose inherent potency on MR is similar to that of aldosterone. As shown above, 11βHSD2 catalyses the reverse reaction inactivating hydrocortisone.

3. *Calcium metabolism* Glucocorticoids inhibit intestinal absorption and enhance renal excretion of Ca^{2+}. Loss of osteoid (decreased formation and increased resorption) indirectly results in loss of Ca^{2+} from bone, producing negative calcium balance. Spongy bones (vertebrae, ribs, pelvis, etc.) are more sensitive.

4. *Water excretion* The effect on water excretion is independent of action on Na^+ transport; hydrocortisone and other glucocorticoids, but not aldosterone, maintain normal g.f.r. In adrenal insufficiency, the capacity to excrete a water load is markedly reduced—such patients are prone to water intoxication from i.v. infusions.

Glucocorticoids also enhance secretory activity of renal tubules.

5. *CVS* Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility. Applied topically, they cause cutaneous vasoconstriction. They play a permissive role for the pressor action of Adr and angiotensin, as well as a permissive role in the development of hypertension. Corticosteroids should be used cautiously in hypertensives.

Adrenal insufficiency is attended by low cardiac output, arteriolar dilatation, poor vasoconstrictor response to Adr (repeated doses of Adr cause destructive changes in blood vessels) and increased permeability of capillaries. These changes along with hypovolemia (due to lack of mineralocorticoid) are responsible for cardiovascular collapse.

6. *Skeletal muscles* Optimum level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo- and hypercorticism, but the basis are different.

Hypocorticism: diminished work capacity and weakness are primarily due to hypodynamic circulation.

Hypercorticism: excess mineralocorticoid action produces hypokalaemia → weakness;
Excess glucocorticoid action causes muscle wasting and myopathy → weakness.

7. *CNS* Mild euphoria is quite common with pharmacological (supraphysiological) doses of glucocorticoids. This is a direct effect on brain, independent of relief of disease symptoms, and sometimes progresses to cause increased motor activity, insomnia, hypomania or depression. On the other hand, patients of Addison's disease suffer from apathy, depression and occasionally psychosis.

Glucocorticoids also maintain the level of sensory perception and normal level of excitability of neurones. High doses lower seizure threshold. Use of corticosteroids in epileptics requires caution. This action is independent of electrolyte changes in the brain and is not shared by aldosterone.

8. *Stomach* Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

9. *Foetal lungs* Glucocorticoids promote structural and functional maturation of foetal lungs near term. They stimulate production of pulmonary surfactants which are essential for inflation of foetal lungs at birth and air breathing.

10. *Lymphoid tissue and blood cells* Glucocorticoids enhance the rate of destruction of lymphoid cells (T cells are more sensitive than B cells); but in man the effect on normal lymphoid tissue is modest. However, a marked lytic response is shown by malignant lymphatic cells. This is the basis of their use in lymphomas.

Glucocorticoids increase the number of RBCs, platelets and neutrophils in circulation. They decrease lymphocytes, eosinophils and basophils. This is not due to destruction of the concerned cells, but due to their sequestration in tissues. Blood counts come back to normal after 24 hours.

11. *Inflammatory responses* Irrespective of the type of injury or insult, the attending inflammatory response is suppressed by glucocorticoids. This is the basis of most of their clinical uses. The action is nonspecific and covers all components and stages of inflammation. This includes attenuation of—increased capillary permeability, local exudation, cellular infiltration, phagocytic activity and late responses like capillary proliferation, collagen deposition, fibroblastic activity and ultimately scar formation. This action is direct and can be restricted to a site by local administration. The cardinal signs of inflammation—redness, heat, swelling and pain are suppressed.

Glucocorticoids interfere at several steps in the inflammatory response (*see* cellular mechanism below), but the most important overall mechanism appears to be limitation of recruitment of inflammatory cells at the local site and production of proinflammatory mediators like PGs, LTs, PAF through indirect inhibition of phospholipase A_2.

Corticoids are only palliative; do not remove the cause of inflammation; the underlying disease continues to progress while manifestations are dampened. They favour spread of infections because capacity of defensive cells to kill microorganisms is impaired. They also interfere with healing and scar formation: peptic ulcer may perforate asymptomatically. Indiscriminate use of corticoids is hazardous.

12. *Immunological and allergic responses* Glucocorticoids impair immunological competence. They suppress all types of hypersensitization and allergic phenomena. At high concentrations and *in vitro* they have been shown to interfere with practically every step of the immunological response, but at therapeutic

Gene mediated cellular actions of glucocorticoids

Mechanism	*Action*
• Translocation of glucose transporters from plasma membrane to deeper sites.	• ↓ glucose uptake and utilization in peripheral tissues.
• Induction of hepatic gluconeogenetic enzymes.	• ↑ production of glucose from amino acids.
• Induction of hepatic glycogen synthase.	• Deposition of glycogen in hepatocytes.
• Site specific changes in sensitivity of adipocytes to GH, Adr, insulin.	• Altered distribution of body fat.
• ↑ expression of vascular adrenergic and AT_1 receptor.	• Enhanced reactivity to vasopressor substances.
• ↓ expression of POMC gene in pituitary corticotropes	• ↓ production of ACTH.
Antiinflammatory and Immunosuppressant actions	
• Induction of annexins in macrophages, endothelium and fibroblasts.	• Annexins inhibit phospholipase A_2 → decreased production of PGs, LTs & PAF.
• Negative regulation of COX-2	• ↓ inducible PG production.
• Negative regulation of genes for cytokines in macrophages, endothelial cells and lymphocytes.	• ↓ production of IL-1, IL-2, IL-3, IL-6, TNFα, GM-CSF, γ interferon → fibroblast proliferation and T-lymphocyte function are suppressed, chemotaxis interfered.
• ↓ production of acute phase reactants from macrophages and endothelial cells	• Complement function is interfered.
• ↓ production of ELAM-1 and ICAM-1 in endothelial cells.	• Adhesion and localization of leukocytes is interfered.
• ↓ expression of transcription factors AP-1, NF-κB	• ↓ histone acetylation
• ↓ production of collagenase and stromolysin	• ↓ MAP kinase
	• Prevention of tissue destruction

POMC—Proopiomelanocortin; IL—Interleukin; TNFα—Tumour necrosis factor α; GM-CSF—Granulocyte macrophage colony stimulating factor; ELAM-1—Endothelial leukocyte adhesion molecule-1; ICAM-1—Intracellular adhesion molecule-1; AP-1–Activator protein-1; NF-κB–Nuclear factor κB; MAP kinase–Mitogen activated protein kinase.

doses *in vivo* there is no impairment of antibody production or complement function. The clinical effect appears to be due to suppression of recruitment of leukocytes at the site of contact with antigen and of inflammatory response to the immunological injury.

Glucocorticoids cause greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection. Suppression of CMI is the basis of their use in autoimmune diseases and organ transplantation (*see* Ch. 65). Factors involved may be inhibition of IL-1 release from macrophages; inhibition of IL-2 formation and action → T cell proliferation is not stimulated; suppression of natural killer cells, etc.

The broad action seems to be interruption of communication between cells involved in the immune process by interfering with production of lymphokines and/or their action.

Mechanism of action at cellular level

Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein, due to which a structural change occurs in the steroid receptor complex that allows its migration into the nucleus and binding to glucocorticoid response elements (GRE) on the chromatin promoting transcription of specific m-RNA → regulation of protein synthesis (*see* Fig. 4.10). This process takes at least 30–60 min : effects of corticosteroid are not immediate, and once the appropriate proteins are synthesized—effects persist much longer than the steroid itself. In many tissues, the overall effect is catabolic, i.e. inhibition of protein synthesis. This may be a consequence of steroid directed synthesis of an inhibitory protein.

The glucocorticoid receptor (GR) is very widely distributed (in practically all cells). It has been cloned and its structure determined. It is made up of ~ 800 amino acids.

Several *coactivators* and *corepressors* modulate the interaction of liganded GR with the GREs, altering the intensity of response.

Because the GR largely maintains uniformity throughout the body, tissue specificity is not exhibited by different glucocorticoids, and all members produce the same constellation of effects.

The functional scheme of GR is presented in Fig. 4.10. Direct evidence of gene expression mediated action has been obtained for actions listed in the box (*see* p. 310).

Some actions of corticoids are exerted more rapidly (like inhibition of ACTH release from pituitary). These may be mediated by a cell membrane receptor or a different mechanism not involving protein synthesis.

PHARMACOKINETICS

All natural and synthetic corticoids, except DOCA are absorbed and are effective by the oral route. Absorption into systemic circulation occurs from topical sites of application as well, but the extent varies depending on the compound, site and area of application, and use of occlusive dressing. Water soluble esters, e.g. hydrocortisone hemisuccinate, dexamethasone sod. phosphate can be given i.v. or i.m., act rapidly and achieve high concentrations in tissue fluids. Insoluble esters, e.g. hydrocortisone acetate, triamcinolone acetonide cannot be injected i.v., but are slowly absorbed from i.m. site and produce more prolonged effects.

Hydrocortisone undergoes high first pass metabolism, has low oral: parenteral activity ratio. Oral bioavailability of synthetic corticoids is high.

Hydrocortisone is 90% bound to plasma protein, mostly to a specific cortisol-binding globulin (CBG or transcortin) as well as to albumin. Transcortin concentration is increased during pregnancy and by oral contraceptives—corticoid levels in blood are increased but hypercorticism does not occur, because free cortisol levels are normal.

The corticosteroids are metabolized primarily by hepatic microsomal enzymes. Pathways are—

- Reduction of 4, 5 double bond and hydroxylation of 3-keto group.
- Reduction of 20-keto to 20-hydroxy form.
- Oxidative cleavage of 20C side chain (only in case of compounds having a 17-hydroxyl group) to yield 17-ketosteroids.

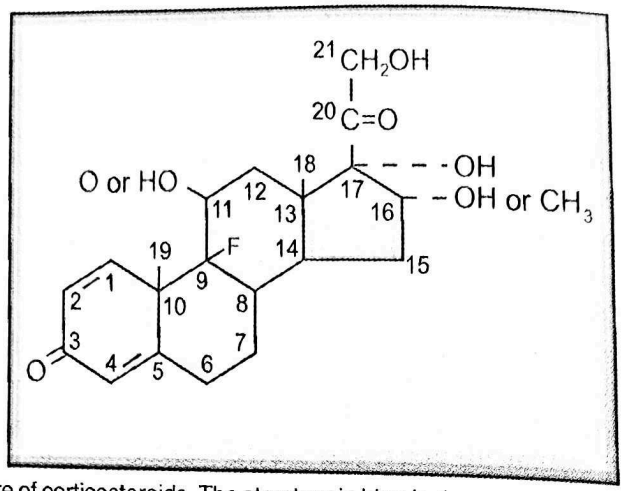


Fig. 20.3: Chemical structure of corticosteroids. The structure in blue is desoxycorticosterone. Important substitutions which yield other useful compounds are shown in red

+ OH at 11	— Corticosterone
+ OH at 11 + OH at 17	— Hydrocortisone
(if O at 11) + OH at 17	— Cortisone
+ OH at 11 + OH at 17 + Δ 1, 2	— Prednisolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + OH at 16	— Triamcinolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 α at 16	— Dexamethasone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 β at 16	— Betamethasone
Hydrocortisone + F at 9	— Fludrocortisone
Corticosterone + CHO at 18	— Aldosterone

These metabolites are further conjugated with glucuronic acid or sulfate and are excreted in urine.

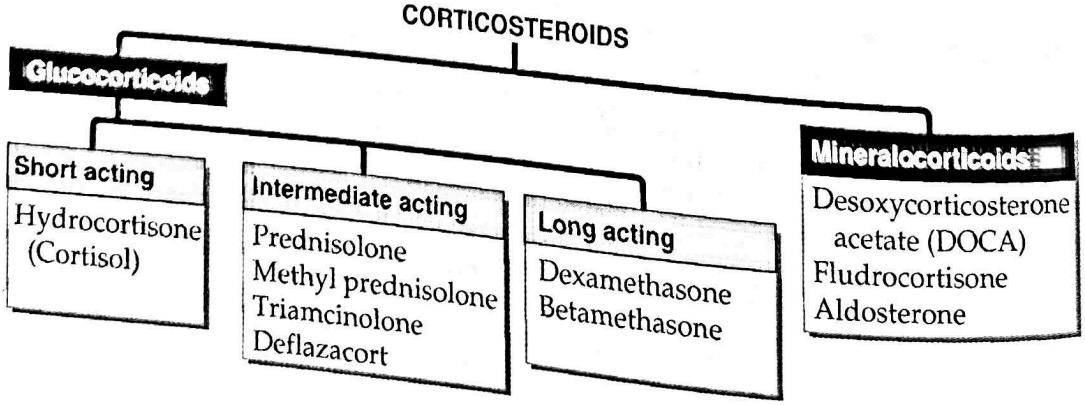
The plasma t½ of hydrocortisone is 1.5 hours. However, the biological t½ is longer because of action through intracellular receptors and regulation of protein synthesis—effects that persist long after the steroid is removed from plasma.

The synthetic derivatives are more resistant to metabolism and are longer acting.

Phenobarbitone and phenytoin induce metabolism of hydrocortisone, prednisolone and dexamethasone, etc. to decrease their therapeutic effect.

CHEMISTRY AND RELATIVE ACTIVITY OF CORTICOIDS

Fig. 20.3 depicts the chemical structure of desoxycorticosterone in blue line. It is a selective mineralocorticoid. Chemical modifications that result in clinically useful compounds are also indicated. Fluorination at position 9 or 6 has resulted in highly potent compounds. Synthetic steroids have largely replaced the natural compounds in therapeutic use, because they are potent, longer acting, more selective for either glucocorticoid or mineralocorticoid action and have high oral activity.



DISTINCTIVE FEATURES

The relative potency and activity of different natural and synthetic corticosteroids employed systemically is compared in Table 20.1.

1. Hydrocortisone (cortisol) It acts rapidly but has short duration of action. In addition to primary glucocorticoid, it has significant mineralocorticoid activity as well. Used for:
Replacement therapy—20 mg morning + 10 mg afternoon orally.
Shock, status asthmaticus, acute adrenal insufficiency—100 mg i.v. bolus + 100 mg 8 hourly i.v. infusion.
Topically (*see* Ch. 66) and as suspension for enema in ulcerative colitis (*see* Ch. 49).

LYCORTIN-S 100 mg/3 ml, 200 mg/5 ml inj; EFCORLIN SOLUBLE 100 mg/2 ml inj. (as hemisuccinate for i.v. inj.) WYCORT, EFCORLIN, HYDROCORTISONE ACETATE 25 mg/ml inj (as acetate for i.m./intraarticular inj.). PRIMACORT 100, 200, 400 mg/vial inj.

2. Prednisolone It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid retention does occur with high doses. It has intermediate duration of action: causes less pituitary-adrenal suppression when a single morning dose or alternate day treatment is given. Used for allergic, inflammatory, autoimmune diseases and in malignancies: 5–60 mg/day oral, 10–40 mg i.m., intraarticular; also topically.

DELTACORTRIL, HOSTACORTIN-H, 5, 10 mg tab, 20 mg/ml (as acetate) for i.m., intraarticular inj., WYSOLONE, NUCORT, 5, 10, 20, 30, 40 mg tabs, OMNACORTIL 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg tab, 5 mg/5 ml oral susp, 5 mg/ml oral drops.

3. Methylprednisolone Slightly more potent and more selective than prednisolone: 4–32 mg/day oral. Methylprednisolone acetate has been used as a retention enema in ulcerative colitis.

Pulse therapy with high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) has been tried in nonresponsive active rheumatoid arthritis, renal transplant, pemphigus, etc. with good results and minimal suppression of pituitary-adrenal axis.

SOLU-MEDROL Methylprednisolone (as sod. succinate) 4 mg tab; 40 mg, 125 mg, 0.5 g (8 ml) and 1.0 g (16 ml) inj, for i.m. or slow i.v. inj, DEESOLONE 4, 16 mg tabs, 0.5 g and 1.0 g. inj.

DEPOT MEDROL Methylprednisolone acetate 40 mg/ml and 80 mg/ml susp. for i.m. or intraarticular injection.

The initial effect of methylprednisolone pulse therapy (MPPT) is probably due to its antiinflammatory action, while long term benefit may be due to temporary switching off of the immunodamaging processes as a consequence of lymphopenia and decreased Ig synthesis.

4. Triamcinolone Slightly more potent than prednisolone but highly selective glucocorticoid:

Table 20.1: Relative activity of systemic corticosteroids

		Compound	Relative activity		Equiv. dose (antiinflammatory)
			Gluco	Mineralo	
Glucocorticoids	Short acting (Biological t½ < 12 hr)	1. Hydrocortisone (cortisol)	1	1	20 mg
	Intermediate acting (Biological t½ 12–36 hr)	2. Prednisolone	4	0.8	5 mg
		3. Methylprednisolone	5	0.5	4 mg
		4. Triamcinolone	5	0	4 mg
		5. Deflazacort	3–4	0	6 mg
	Long acting (Biological t½ > 36 hr)	6. Dexamethasone	25	0	0.75 mg
		7. Betamethasone	25	0	0.75 mg
Mineralocorticoids					*Equiv. salt retaining dose*
		8. Desoxycorticosterone acetate (DOCA)	0	100	2.5 mg (sublingual)
		9. Fludrocortisone	10	150	0.2 mg
		10. Aldosterone	0.3	3000	not used clinically

4–32 mg/day oral, 5–40 mg i.m., intraarticular injection. Also used topically.
KENACORT, TRICORT 1, 4, 8 mg tab., 10 mg/ml, 40 mg/ml (as acetonide) for i.m., intraarticular inj., LEDERCORT 4 mg tab.

5. Dexamethasone Very potent and highly selective glucocorticoid. It is also long-acting, causes marked pituitary-adrenal suppression, but fluid retention and hypertension are not a problem.

It is used for inflammatory and allergic conditions 0.5–5 mg/day oral. For shock, cerebral edema, etc. 4–20 mg/day i.v. infusion or i.m. injection is preferred. It can also be used topically.
DECADRON, DEXONA 0.5 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops; WYMESONE, DECDAN 0.5 mg tab, 4 mg/ml inj.

6. Betamethasone Similar to dexamethasone, 0.5–5 mg/ day oral, 4–20 mg i.m., i.v. injection or infusion, also topical.
BETNESOL, BETACORTRIL, CELESTONE 0.5 mg, 1 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops. BETNELAN 0.5 mg, 1 mg tabs.

Dexamethasone or betamethasone are preferred in cerebral edema and other states in which fluid retention must be avoided.

7. Deflazacort The glucocorticoid potency of this newer steroid is somewhat less than of prednisolone, but it lacks mineralocorticoid activity. It is claimed to produce fewer adverse effects, but that may be due to its lower potency. In some trials it caused lesser growth retardation in children; has been particularly recommended for pediatric patients. It is used mainly for inflammatory and immunological disorders.
Dose: 60–120 mg/day initially, 6–18 mg/day for maintenance; children 0.25–1.5 mg/kg daily or on alternate days.
DEFGLU 6, 30 mg tabs, DEFLAR, DEFZA, DFZ 1, 6, 30 mg tabs, DEFCORT 1 mg, 6 mg, 12 mg, 18 mg, 24 mg, 30 mg tabs, 6 mg/5 ml syr.

8. Desoxycorticosterone acetate (DOCA) It has only mineralocorticoid activity. Used occasionally for replacement therapy in Addison's disease: 2–5 mg sublingual, 10–20 mg i.m. once or twice weekly.

9. Fludrocortisone A potent mineralocorticoid having some glucocorticoid activity as well, orally active, used for:
Replacement therapy in Addison's disease 50–200 µg daily.
Congenital adrenal hyperplasia in patients with salt wasting 50–200 µg/day.
Idiopathic postural hypotension 100–200 µg/day.
FLORICORT 100 µg tab.

10. Aldosterone It is the most potent mineralocorticoid. Not used clinically because of low oral bioavailability and difficulties in regulating doses.

In addition a number of *topically* active glucocorticoids have been developed.

Beclomethasone dipropionate budesonide, fluticasone, etc. are used by inhalation in asthma, as spray in nasal allergy, as well as for skin and mucous membrane lesions (*see* Ch. 16).

Fluocinolone acetonide, fluocortolone, clobetasol propionate and esters of betamethasone, dexamethasone, triamcinolone are described in Ch. 66.

USES

A. Replacement therapy

1. *Acute adrenal insufficiency* It is an emergency. Hydrocortisone (100 mg) or dexamethasone (8–16 mg) are given i.v., first as a bolus injection and then as infusion, along with isotonic saline in glucose solution. The amount of fluid infused i.v. is guided by monitoring central venous pressure, because these patients have reduced capacity to excrete water load. Short-term i.v. infusion of a vasopressor (dopamine) may be needed. The cause of adrenal insufficiency should be treated.

2. *Chronic adrenal insufficiency (Addison's disease)* Hydrocortisone given orally is the most commonly used drug along with adequate salt and water allowance. Some patients who continue to excrete excess Na^+ need additional mineralocorticoid: fludrocortisone is added.

3. *Congenital adrenal hyperplasia (Adrenogenital syndrome)* It is a familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase. As a result the synthesis of hydrocortisone and aldosterone suffers. There is compensatory increase in ACTH secretion causing adrenocortical hypertrophy. Enzyme deficiency being only partial in most cases, normal amounts of gluco- and mineralocorticoids are produced along with excessive amounts of weak androgens which produce virilization and/or precocious sexual development. If the deficiency is severe, salt wasting also occurs.

Treatment is to give hydrocortisone 0.6 mg/kg daily in divided doses round the clock to maintain feed back suppression of pituitary. If salt wasting persists—fludrocortisone 50–200 µg/day may be added.

B. Pharmacotherapy (for nonendocrine diseases)

Systemic as well as topical corticosteroids have one of the widest spectrum of medicinal uses for their antiinflammatory and immunosuppressive properties. Corticosteroids are powerful drugs. They have the potential to cause dramatic improvement in many severe diseases as well as produce equally dramatic adverse effects if not properly used. The use of corticosteroids in nonendocrine diseases is empirical and palliative, but may be life saving. The following *general principles* must be observed.

- A single dose (even excessive) is not harmful: can be used to tide over mortal crisis, even when benefit is not certain.
- Short courses (even high dose) are not likely to be harmful in the absence of contraindications; starting doses can be high in severe illness.
- Long-term use is potentially hazardous: keep the duration of treatment and dose to minimum, which is found by trial and error; even partial relief may have to be tolerated.
- Initial dose depends on severity of the disease; start with a high dose in severe illness—reduce gradually after symptoms subside, while in mild cases start with the lowest dose and titrate upwards to find the correct dose. The dose should be reassessed from time-to-time.
- No abrupt withdrawal after a corticoid has been given for > 2 to 3 weeks: may precipitate adrenal insufficiency.
- Infection, severe trauma, surgery or any stress during corticoid therapy—increase the dose.
- Use local therapy (cutaneous, inhaled, intranasal, etc.) wherever possible.

1. *Arthritides*

(i) *Rheumatoid arthritis*: Corticosteroids are indicated only in severe cases as adjuvants to NSAIDs when distress and disability persists despite other measures, or to suppress exacerbations, or when there are systemic manifestations (*see* Ch. 15).

(ii) *Osteoarthritis*: It is treated with analgesics and NSAIDs; systemic use of corticoids is rare. Intraarticular injection of a steroid may be given to control an acute exacerbation. Injections may be repeated 2–3 times a year, but have the potential to cause joint destruction.

(iii) *Rheumatic fever:* Corticoids are used only in severe cases with carditis and CHF with the aim of rapid suppression of symptoms, because they act faster than aspirin, or in patients not responding to aspirin. Aspirin is given in addition and is continued after corticoids have been withdrawn.

(iv) *Gout:* Corticoids (short course) should only be used in *acute gouty arthritis* when NSAIDs have failed to afford relief and colchicine is not tolerated. Intraarticular injection of a soluble glucocorticoid is preferable to systemic therapy but is reserved for selected cases (*see* p. 232).

Though they are uricosuric—use in chronic gout is not recommended.

2. *Collagen diseases* Most cases of systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, nephrotic syndrome, glomerulonephritis and related diseases need corticosteroid therapy. They may be life saving in these diseases. Therapy is generally started with high doses which are tapered to maintenance dose when remission occurs. Later other immunosuppressants may be added or substituted.

3. *Severe allergic reactions* Corticoids may be used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness. However, even i.v. injection of a glucocorticoid takes 1–2 hours to act and is not a substitute for Adr (which acts immediately) in anaphylactic shock and angioedema of larynx. Topical use is made in allergic conjunctivitis and rhinitis.

4. *Autoimmune diseases* Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis respond to

corticoids. Prednisolone 1–2 mg/kg/day is given till remission, followed by gradual withdrawal or low-dose maintenance depending on the response. Remission may also be induced in severe cases of myasthenia gravis, in which their use is adjunctive to neostigmine. Patients requiring long term maintenance therapy are better shifted to other immunosuppressants.

5. *Bronchial asthma* Early institution of inhaled glucocorticoid therapy is now recommended in most cases needing inhaled β_2 agonists almost daily (*see* Ch. 16). Systemic corticosteroids are used only for:

- Status asthmaticus: give i.v. glucocorticoid; withdraw when emergency is over.
- Acute asthma exacerbation: short-course of high dose oral corticoid, followed by gradual withdrawal.
- Severe chronic asthma not controlled by inhaled steroids and bronchodilators: add low dose prednisolone daily or on alternate days.

6. *Other lung diseases* Corticosteroids benefit aspiration pneumonia and pulmonary edema from drowning. Given during late pregnancy, corticoids accelerate lung maturation and surfactant production in the foetal lung and prevent respiratory distress syndrome at birth. Two doses of betamethasone or dexamethasone 12 mg i.m. at 24-hour interval may be administered to the mother if premature delivery is contemplated. Betamethasone or dexamethasone are preferred because of their higher placental transfer.

7. *Infective diseases* Administered under effective chemotherapeutic cover, corticosteroids are indicated only in serious infective diseases to tideover crisis or to prevent complications. They are indicated in conditions like severe forms of tuberculosis (miliary, meningeal, renal, etc.), severe lepra reaction, certain forms of bacterial meningitis and *Pneumocystis carinii* pneumonia with hypoxia in AIDS patients.

8. *Eye diseases* Corticoids are used in a large number of inflammatory ocular diseases. In certain severe conditions, they may prevent blindness. Topical instillation as eye drops or ointment is effective in diseases of the anterior chamber, e.g. allergic conjunctivitis, iritis, iridocyclitis, keratitis, etc. Ordinarily, steroids should not be used in infective conditions. But if inflammation is severe, they may be applied in conjunction with an effective antibiotic. Steroids are contraindicated in herpes simplex keratitis and in ocular injuries. Posterior segment afflictions like retinitis, optic neuritis, uveitis require systemic steroid therapy. Retrobulbar injection is occasionally given to avoid systemic side effects.

9. *Skin diseases* (*see* Ch. 66) Topical corticosteroids are widely employed and 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.

10. *Intestinal diseases* Ulcerative colitis, Crohn's disease, coeliac disease are inflammatory bowel diseases with exacerbations and remissions. Corticoids are indicated during acute phases—may be used orally or as retention enema (for colonic involvement). They are particularly valuable for patients with systemic manifestations, and are given in addition to sulfasalazine/mesalazine ± other measures (*see* Ch. 49). Some specialists advocate small maintenance doses to prevent relapses.

11. *Neurological conditions* Cerebral edema due to tumours, tubercular meningitis, etc., responds to corticoids. Dexa- or betamethasone are preferred because they donot have Na^+ retaining activity. Their value in traumatic and poststroke cerebral edema is questionable. Large doses given i.v. soon after spinal injury may reduce the resulting neurological sequelae.

A short course (2–4 weeks) of oral prednisolone can hasten recovery from Bell's palsy and acute exacerbation of multiple sclerosis. In the latter, methyl prednisolone 1 g i.v. daily for 2–3 days may be given in the beginning.

Neurocysticercosis: When albendazole/praziquantel is used to kill cysticerci lodged in the brain, prednisolone 40 mg/day or equivalent is given for 2–4 weeks to suppress the reaction to the dying larvae.

12. *Nausea and vomiting* Dexamethasone 8–20 mg i.v. is frequently used to augment the antiemetic effect of ondansetron or metoclopramide against highly emetogenic cancer chemotherapy. High dose glucocorticoids by themselves afford modest protection from chemotherapy induced as well as general anaesthesia associated nausea and vomiting, probably due to their anti-inflammatory action.

13. *Malignancies* Corticoids are an essential component of combined chemotherapy of acute lymphatic leukaemia, Hodgkin's and other lymphomas, because of their marked lympholytic action in these conditions. They have a secondary place in hormone responsive breast carcinoma—act probably by causing HPA suppression so as to reduce production of adrenal androgens which are converted to estrogens in the body (*see* Ch. 64).

Corticoids also afford symptomatic relief in other advanced malignancies by improving appetite and controlling secondary hypercalcaemia. For hypercalcaemia, however, bisphosphonates are more effective and have superseded corticosteroids.

14. *Organ transplantation and skin allograft* High dose corticoids are given along with other immunosuppressants to prevent the rejection reaction. Low maintenance doses may be continued over long term ± maintenance doses of companion drugs (*see* Ch. 65).

15. *Septic shock* High-dose corticosteroid therapy for septic shock has been abandoned, because it worsens the outcome. However, many such patients have relative adrenal insufficiency. 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 who do not respond adequately to fluid replacement and vasopressors.

16. *Thyroid storm* Many patients in thyroid storm have concomitant adrenal insufficiency. Moreover, corticosteroids reduce peripheral T_4 to T_3 conversion. Hydrocortisone 100 mg i.v. 8 hourly may improve the outcome.

17. *To test pituitary-adrenal axis function* Dexamethasone suppresses pituitary-adrenal axis at doses which do not contribute to steroid metabolites in urine. Responsiveness of the axis can be tested by measuring daily urinary steroid metabolite excretion after dosing with dexamethasone.

ADVERSE EFFECTS

These are extension of the pharmacological action which become prominent with prolonged therapy, and are a great limitation to the use of corticoids in chronic diseases.

A. Mineralocorticoid Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids.

Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid

1. Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.
2. Fragile skin, purple striae—typically on thighs and lower abdomen, easy bruising, telangiectasis, hirsutism. Cutaneous atrophy localized to the site occurs with topical application as well.
3. Hyperglycaemia, which may lead to glycosuria, precipitation of diabetes.
4. Muscular weakness: proximal (shoulder, arm, pelvis, thigh) muscles are primarily affected. Myopathy occurs occasionally, warrants withdrawal of the corticoids.
   To offset the catabolic state, patients receiving corticosteroid therapy longer than 2 weeks should be put on high protein, high potassium diet.
5. Susceptibility to infection: this is nonspecific for all types of pathogenic organisms. Latent tuberculosis may flare; opportunistic infections with low grade pathogens (*Candida,* etc.) set in.

6. Delayed healing: of wounds and surgical incisions.
7. Peptic ulceration: risk is doubled; bleeding and silent perforation of ulcers may occur. Dyspeptic symptoms are frequent with high dose therapy.
8. Osteoporosis: especially involving vertebrae and other flat spongy bones. Compression fractures of vertebrae and spontaneous fracture of long bones can occur, especially in the elderly. Radiological evidence of osteoporosis is an indication for withdrawal of corticoid therapy. Corticosteroid induced osteoporosis can be prevented/arrested to some extent by calcium supplements + vit D, but bisphosphonates are the most effective drugs in this regard.

   Avascular necrosis of head of femur, humerous, or knee joint is an occasional abrupt onset complication of high dose corticosteroid therapy.
9. Posterior subcapsular cataract may develop after several years of use, especially in children.
10. Glaucoma: may develop in susceptible individuals after prolonged topical therapy.
11. Growth retardation: in children occurs even with small doses if given for long periods. Large doses do inhibit GH secretion, but growth retardation may, in addition, be a direct cellular effect of corticoids. Recombinant GH given concurrently can prevent growth retardation, but risk/benefit of such use is not known.
12. Foetal abnormalities: Cleft palate and other defects are produced in animals, but have not been encountered on clinical use in pregnant women. The risk of abortion, still-birth or neonatal death is not increased, but intrauterine growth retardation can occur after prolonged therapy, and neurological/behavioral disturbances in the offspring are feared. Prednisolone appears safer than dexa/beta methasone, because it is metabolized by placenta, reducing foetal exposure. There is no evidence of foetal growth retardation occurring after short term use in the mother.

   Prolonged corticosteroid therapy during pregnancy increases the risk of gestational diabetes, pregnancy induced hypertension and preeclampsia.
13. Psychiatric disturbances: mild euphoria frequently accompanies high dose steroid treatment. This may rarely progress to manic psychosis. Nervousness, decreased sleep and mood changes occur in some patients. Rarely a depressive illness may be induced after long-term use.
14. Suppression of hypothalamo-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy. In time, the adrenal cortex atrophies. Stoppage of exogenous steroid precipitates withdrawal syndrome consisting of malaise, fever, anorexia, nausea, postural hypotension, electrolyte imbalance, weakness, pain in muscles and joints and reactivation of the disease for which the steroid was used. Subjected to stress, these patients may go into acute adrenal insufficiency leading to cardiovascular collapse.

Any patient who has received > 20–25 mg/day hydrocortisone, or ≥ 5 mg prednisolone/day or equivalent for longer than 2–3 weeks should be put on a scheme of gradual withdrawal: 20 mg hydrocortisone/day reduction every week and then still smaller fractions once this level has been achieved. Such patients may need protection with a corticosteroid (oral or i.v.) if a stressful situation develops up to one year after withdrawal. Administration of ACTH during withdrawal does not hasten recovery because it has been found that adrenals recover earlier than pituitary and hypothalamus.

If a patient on corticosteroid therapy develops an infection—the *steroid should not be discontinued* despite its propensity to weaken host defence and delay healing. Rather, the dose may have to be increased to meet the stress of infection. Surgery in such a patient should be covered by intraoperative and postoperative i.v. hydrocortisone till the condition stabilizes, followed by oral prednisolone.

Measures that minimise HPA axis suppression are:

(a) Use shorter acting steroids (hydrocortisone, prednisolone) at the lowest possible dose.

(b) Use steroids for the shortest period of time possible.

(c) Give the entire daily dose at one time in the morning.

(d) Switch to alternate-day therapy if the condition does not deteriorate on the 'off' day.

It has been found that moderate dose of a short acting steroid (e.g. prednisolone) given at 48 hr interval did not cause HPA suppression, whereas the same total amount given in 4 divided 12 hourly doses produced marked HPA suppression. Alternate-day therapy also resulted in less immunological suppression—lower risk of infection. The longer acting steroids (dexamethasone, etc.) are not suitable for alternate-day therapy. Only problem with alternate-day therapy is that many steroid dependent patients are incapacitated on the 'off day'.

(e) If appropriate, use local (dermal, inhaled, ocular, nasal, rectal, intrasynovial) preparations of a steroid with poor systemic availability (beclomethasone dipropionate, triamcinolone acetonide, fluticasone, etc.).

CONTRAINDICATIONS

The following diseases are aggravated by corticosteroids. Since corticosteroids may have to be used as a life-saving measure, all of these are relative contraindications in the presence of which these drugs are to be employed only under compelling circumstances, and with due precautions.

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

Combination of any other drug with corticosteroids in fixed dose formulation for internal use is banned.

Metyrapone It inhibits 11-β hydroxylase in adrenal cortex and prevents synthesis of hydrocortisone so that its blood level falls → increased ACTH release → increased synthesis, release and excretion of 11-desoxycortisol in urine. Thus, it is used to test the responsiveness of pituitary and its ACTH producing capacity.

Aminoglutethimide, trilostane and high doses of the antifungal drug *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.

Glucocorticoid antagonist The antiprogestin *mifepristone* (*see* p. 345–46) acts as a glucocorticoid receptor antagonist as well. In Cushing's syndrome, it can suppress the manifestations of corticosteroid excess, but blockade of feedback ACTH inhibition leads to oversecretion of ACTH → more hydrocortisone is produced, which tends to annul the GR blocking action of mifepristone. It is indicated only for inoperable cases of adrenal carcinoma and in patients with ectopic ACTH secretion.

PROBLEM DIRECTED STUDY

20.1 A 35-year female patient of inflammatory bowel disease was treated with prednisolone 40 mg/day and mesalazine 800 mg TDS. After 4 weeks, the symptoms subsided and prednisolone dose was tapered at the rate of 10 mg every 2 weeks. When she was taking 10 mg prednisolone/day, she met with a road-side accident and suffered compound fracture of both bones of the right leg. Internal fixation of the fracture and suturing of wounds under general anaesthesia is planned.

(a) Whether any additional measure needs to be taken during surgery in view of her corticosteroid therapy?

(b) Does the prednisolone therapy need discontinuation or any alteration in the postoperative period? Give reasons.

(see Appendix-1 for solution)