Introduction

The metabolic effects of the different systems of the body is controlled by autonomic nervous system and the secretions of the endocrine, or ductless glands. These secretions are a heterogeneous group of chemicals known as hormones, which are released into the blood stream and travel to all parts of the body. Hormones exert their actions either on specific organs or on specific metabolic processes. In contrast to the actions of the autonomic nervous system, they produce relatively slow compensation for changes in the internal environment.

The secretory activity of the endocrine glands is controlled by the central and autonomic nervous systems together with the secretions of other endocrine glands, and by ‘feedback’ from the metabolic effects the hormone produced. The pharmacology of the individual hormones is of importance, as the knowledge of their function is vital to the understanding of normal control of metabolism, and also because under or over production of the hormones can have striking metabolic consequences. In an effort to find substances, which can replace natural hormones in states of under production, many compounds have been synthesized which can mimic, antagonize, or interfere with the production of natural hormones.
In clinical practice, hormones and hormone-like drugs, are mainly used for:

1. Replacement therapy e.g. insulin in diabetes mellitus.
2. Testing the functional integration of an endocrine system (diagnostic).
3. Treatment of non-endocrine diseases e.g. corticosteroids in rheumatic arthritis.

However, in this chapter, we are also going to deal with other drugs, which are not hormonal in nature but can influence the function of endocrine glands, either by suppression (e.g. antithyroid drugs) or stimulation (e.g. oral hypoglycemic agents).

The ability of a cell to respond to a particular hormone depends on its possessing "specific receptors" with which the hormone interacts.

Control of Synthesis and Release of Hormones:

Several of the endocrine glands (thyroid, adrenal cortex, ovary and testis) are under the control of the anterior lobe of the pituitary gland, which is an endocrine gland. The chain of events leading to increased output of hormones from these glands involves stimulation of the release of the appropriate trophic hormone from the pituitary. The release of trophic hormones is under the control of neurons of the hypothalamus, and it is mainly at this level that integration of the nervous and endocrine systems takes place.

THYROID GLAND HORMONES AND ANTI-THYROID DRUGS

The thyroid gland synthesizes, stores and secretes the iodinated amino acid hormones, L-thyroxin and L-tri-iodothyronine (liothyronine). The thyroid hormones regulate oxygen consumption and heat production, and a wide range of metabolic processes, and are essential for normal growth and development. The thyroid gland of man also synthesizes "calcitonin" whose actions are going to be discussed with those of parathyroid hormone.

Control of The Thyroid Gland:

In normal subjects, the secretion of the thyroid hormones \( T_4 \) and \( T_3 \) is regulated by the hypothalamus and pituitary gland. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to synthesize and release the thyroid-stimulating hormone (TSH). The latter regulates the thyroid gland's ability to extract \( I_2 \) from the blood for building up the thyroid hormones.

Effects of TSH on the Thyroid Gland:

1. Promotes the uptake of iodine by the thyroid cells.
2. Promotes the synthesis of thyroglobulin.
3. Promotes the release of \( T_4 \) and \( T_3 \).
4. Increases the thyroid gland size and vascularity.

N.B. Increase in the concentration of the thyroid hormones decreases TSH levels by -ve feedback mechanism.

Biosynthesis of Thyroid Hormones (figure 5-1):

The following steps may be distinguished in the elaboration of thyroid hormones:
1. Transport of iodide into the thyroid gland (iodide trapping).
2. Oxidation of iodide, by thyroidal peroxidase, into free iodine or hypoiodite.
3. Iodine iodinates the tyrosine residue within the thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodide organification).
4. Coupling of mono and diiodotyrosine forming tri-iodothyronine (T₃) and of two diodotyrosine forming thyroxin (T₄).
5. The thyroid hormones are then stored in the thyroid gland, and are released by exocytosis and proteolysis of thyroglobulin.
6. After release from the gland, both T₃ and T₄ are extensively bound to plasma protein (thyroxin-binding globulin “TBG”) and thyroxin binding prealbumin (TBPA). However, T₄ is more firmly bound to plasma protein.

![Figure 5-1: The biosynthetic pathways of thyroid hormones.](image)

**Disorders of The Thyroid Gland Function:**

The thyroid gland could be subjected to certain disorders in function. This could be in the form of:

**I. UNDERSECRETION** (hypothyroidism).
- In infants lead to cretinism.
- In adults lead to myxoedema or Hashimoto’s disease.

**II. OVERSECRETION** (hyperthyroidism).
I. UNDERSECRETION OF THYROID GLAND

(Hypothyroidism)

Undersecretion of the thyroid gland leads to cretinism in infancy and myxoedema or Hashimoto’s disease in adults. In such cases replacement therapy (thyroid preparations) are indicated.

Thyroid Hormones (T<sub>4</sub> and T<sub>3</sub>):

**Pharmacodynamics:**

**Mechanism:**

- Free forms of thyroid hormones, T<sub>4</sub> and T<sub>3</sub>, dissociate from thyroid binding protein (TBP), then enter the cell by diffusion or by active transport.

- Within the cell, T<sub>4</sub> is converted to T<sub>3</sub> which enters the nucleus. There, T<sub>3</sub> binds to a specific T<sub>3</sub> receptor protein causing DNA-directed mRNA and protein synthesis, thus mediating a response. This explains the time lag of hours or days for the hormone to give maximal response after administration.

**Actions:**

- Stimulation of the metabolism in general, causing an increase in oxygen consumption and in metabolic rate.

- Influence growth and development.

**Pharmacokinetics:**

Table 5-1 shows some pharmacokinetic differences between T<sub>4</sub> and T<sub>3</sub> after oral administration.

Inactivation of the thyroid hormones eventually occurs by de-iodination, deamination, decarboxylation or conjugation and excreted as glucuronide and sulphate. This occurs mainly in the liver, and the free and conjugated forms are excreted partly in the bile and partly in the urine.

**Thyroid Preparations:**

1. L-Thyroxin (Eltroxin):
In tablet form (0.05-0.1 mg, each). A single dose reaches its maximal effect in about 10 days and passes off in 2-3 weeks.

2. L-Thyroxin sodium (Synthroid sodium):
   Is the synthetic sodium salt of levothyroxin. This preparation is given by IV injection in case of emergency (Myxoedema coma).

3. Liothyronine sodium (Cytomel):
   Is the synthetic sodium salt of levotriiodothyronin. It may be given IV in emergency (Myxoedema coma). It is more potent than levothyroxin (4 times as potent). It has a quicker onset of action and shorter duration. T₃ has the advantage over T₄ in that it is more readily absorbed by the GIT (table 5-1).

4. Liotrix (Euthroid):
   Is a preparation in tablet form containing a mixture of levothyroxin and liothyronine in the ratio 4:1.

   Table 5-1: Pharmacokinetics of thyroid hormones.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T₄</th>
<th>T₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut absorption</td>
<td>65%</td>
<td>95%</td>
</tr>
<tr>
<td>Biological lag</td>
<td>24 hrs.</td>
<td>6 hrs.</td>
</tr>
<tr>
<td>T1/2</td>
<td>7 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Amount bound</td>
<td>99.96%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Amount free</td>
<td>0.04%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Maximum effect</td>
<td>10 days</td>
<td>24 hrs.</td>
</tr>
<tr>
<td>Duration</td>
<td>2-3 weeks</td>
<td>1 week</td>
</tr>
<tr>
<td>Potency</td>
<td>1</td>
<td>4-5</td>
</tr>
</tbody>
</table>

Therapeutic Uses:

Replacement therapy in:

1) Hypothyroidism
2) Cretinism
3) Myxoedema coma

1) Hypothyroidism:

This is decreased activity of the thyroid gland. This comprises:

- Myxoedema
- Hashimoto’s disease:
After therapy of thyroid tumors with radioactive iodine.

Treatment: Replacement therapy by l-thyroxine

Dose: Initial dose 50-100µg/day. In old patients with heart disease or hypertension this should be achieved gradually, starting with 25µg/day for the first two weeks and then increasing the dose by 25-50µg every fortnight until symptoms are relieved, usually at 100-200µg/day. This maximum effect of a dose is not reached for about 10 days and passes off over about 2-3 weeks.

2. Cretinism:

It is due to thyroid deficiency during development, caused by congenital absence or incomplete development of the thyroid, and is characterized by gross retardation of growth and mental deficiency. Success in treatment of cretinism depends on the age at which therapy is started. If therapy is initiated within the first few weeks of life, normal physical and mental activity is always achieved. The most critical need of the thyroid hormone is during the period of myelinization of the CNS that occurs about the time of birth.

Treatment: L-thyroxine.

Dose: 10-15 µg/kg as an initial dose.

Individual l-thyroxine doses are adjusted at 4 to 6 weeks intervals during the first 6 months, at 2 months intervals during the 6 to 18 month period, and at 3 to 6 month intervals thereafter to maintain serum thyroxine concentrations in the 10-13µg/dl range and serum TSH values below 20 mU/L.

Assessments that are important guides for appropriate hormone replacement include physical growth, motor development, bone maturation, and developmental progress.

3. Myxoedema Coma:

This is a medical emergency that occurs most often in elderly patients. Common precipitating factors include pulmonary infections, cerebrovascular accidents and congestive heart failure. The patient should be treated in the intensive care unit. An untreated patient dies from hypothyroidism and too vigorously treated patient dies from cardiovascular collapse due to a precipitated rise in metabolism. A single dose of T₄ (500µg) IV or 50µg of T₃ IV is life saving. Hydrocortisone might be needed, as prolonged hypothyroidism is usually associated with adrenal or pituitary insufficiency.

Adverse Effects of Thyroid Preparations:

(Symptoms and signs are those of hyperthyroidism, minus exophthalmos and goiter).

1. Tremors
2. Nervousness
3. Insomnia
4. Weight loss
5. Heat intolerance
6. Tachycardia
N.B. Anginal pain or heart failure are liable to be provoked by vigorous therapy, if they occur, thyroxin must be discontinued for at least one week and begun again at lower dosage.

II. OVERSECRETION OF THE THYROID GLAND
(HYPERTHYROIDISM)
Is an increase in the release of thyroid hormones. Under these conditions TSH levels become very low and the pituitary becomes unresponsive to TRH. Excess thyroid hormone production will increase the metabolism together with over activity of the sympathetic nervous system giving rise to the clinical condition known as thyrotoxicosis or Grave's disease.

Preparations Used In Hyperthyroidism:
1. Iodides: e.g. potassium iodide and Lugol's solution (5% I₂ + 10% KI in aqueous solution).
2. Thiourea derivatives (Thionamides): e.g. Propyl thiouracil, Carbimazole, Methimazole.
3. Perchlorates: e.g. potassium perchlorate.
4. Radioactive iodine: e.g. I^{131} and I^{132}.

1. IODIDES

Pharmacodynamics:
Mechanism:
The exact mechanism of action is not entirely clear. In hyperthyroid subjects a moderate excess of iodine may enhance hormone production by providing "fuel" for hormone synthesis. High excess, however, has an effect on the thyroid gland, which is opposite to that of TSH i.e.
1. Decreases I-trapping.
2. Decreases synthesis of thyroid hormones.
3. Decreases release.
4. Decreases size and vascularity of the thyroid gland.

**Pharmacokinetics:**

Potassium iodide is given orally. After a variable period, the beneficial effect fades, or the condition may become more severe than it was originally. For this reason, the use of iodine and iodides should not last for more than 10-14 days. They give best results when used in preoperative preparation of patients undergoing thyroidectomy.

**Therapeutic Uses:**

1. **Preparation of thyrotoxic patients for surgery (thyroidectomy):** Iodides are usually given 7-10 days before the operation to reduce the surgically inconvenient vascularity of the gland (thionamides and propranolol may be given before iodides).
2. **Thyroid Crisis:** Iodides have rapid onset (2-7 days), therefore are useful in thyroid crisis where they inhibit hormone release.

**Adverse Effects (Iodism):**

Some people show allergic tendency to I$_2$ preparations, whether given orally or when applied on the skin as an antiseptic. These allergic reactions are called "Iodism", the signs of which are:

1. Metallic taste.
2. Excessive salivation with painful salivary glands.
3. Coryza-like syndrome.
4. Sore mouth and throat.
5. Productive cough.
6. Diarrhea.
7. Skin rash.
8. Drug fever.

**Preparations:**

1. Potassium iodide: Dose 60 mg orally/8 hr.
2. Lugol's Iodine (5% I$_2$ in 10% KI aqueous). Dose 0.5 ml/12 hr.
2. THIOUREA DERIVATIVES (THIONAMIDES)

Pharmacodynamics:

Mechanism of action:

The main action of thiourea derivatives is to reduce the formation of thyroid hormone by inhibiting the (thyroid peroxidase) catalyzed reactions to block I₂ organification i.e. inhibit the incorporation of I₂ into organic form, iodotyrosine, and by inhibiting the coupling of iodotyrosines to form T₄ and T₃ (Site "B" and "C", Figure 5-1). Thionamides, are usually slow, their onset of action range from 2-3 weeks.

N.B. With heavy dosage the reduction in hormone synthesis may be sufficient to induce the pituitary to produce more TSH, which in turn causes thyroid enlargement (hyperplasia and increase in vascularity).

Pharmacokinetics:

- Propyl thiouracil is rapidly absorbed. A peak serum level is attained after 1 hr. It is mostly excreted by the kidney as inactive glucuronides within 24 hrs. T₁/₂ = 1.5 hrs. It poorly crosses the placental barrier. Peripherally, it inhibits the conversion of T₄ into the more active T₃.
- Methimazole is completely absorbed but at variable rates. It is readily accumulated by the thyroid gland. Excretion is slower than propyl thiouracil. 65-70% of the dose is recovered in the urine within 48 hrs. T₁/₂ = 6hrs.
- Carbimazole is a prodrug, and is rapidly converted to the active form methimazole.

N.B. T₁/₂ of these drugs has little influence on the duration of their antithyroid action or the dosing interval, because both agents are accumulated in the thyroid gland.

- Thionamides are metabolized in the liver and excreted in the urine as sulphate esters and glucuronides.

Preparations:

1. Propyl thiouracil (50mg):
Is the least active thiomamide. **Dose**: 100-150 mg/8hrs/8wks initially
50-150mg/ Once (maintenance)

2. Carbimazole (Neo-mercazole) (5mg):
   This is a pro-drug. **Dose** 30mg/day (initial),
   5-15mg/day (maintenance).

3. Methimazole (Tapazole) (5mg):
   It is about 10 times as potent as propyl thiouracil. **Dose**: 30mg/day (initial), 5-15mg/day (maintenance).

**Adverse Effects:**
1. Papular skin rash.
2. Lymphadenopathy.
3. Leucopenia, agranulocytosis, aplastic anaemia (but less frequent than perchlorate = 0.1%).
4. Thyroid enlargement with increased vascularity.

**N.B.** Blood count is essential during therapy especially if the patient develops infection or anaemia.

**Contraindications:**
1. Pregnancy, since thioureas cross the placental barrier causing fetal goiter. Propylthiouracil has the least effect in this case.
2. Lactation, since the drug concentrates in milk.

**Therapeutic Uses:**
1. Preparation of patients for surgery (until the patient’s thyroid hormone level fairly decreases before giving iodine).
2. Chronic treatment of hyperthyroidism until spontaneous remission occurs.
3. Management of thyrotoxic crisis (thyroid storm) along with propranolol and other drugs (p.276).

3. **POTASSIUM PERCHLORATE**

**Mechanism of Action:**
Perchlorates act by blocking the iodide-concentrating ability of the thyroid gland and compete with $I_2$ for uptake (site "A", figure 5-1).
Potassium perchlorate is quite effective, but the high incidence of the development of agranulocytosis when given in high doses (2-3 gm daily) leading to fatal aplastic anaemia rendered it obsolete for treatment.

**Uses:**
To discharge inorganic iodide from the thyroid gland in a diagnostic test of organification.

### 4. RADIOIODINE (I\(^{131}\), I\(^{132}\))

**Pharmacodynamics:**

**Mechanism of Action:**
Both isotopes are treated by the body just like the ordinary non-radioactive I\(_2\), so when swallowed they are concentrated in the thyroid gland.

They emit mainly β radiation (90%) and some γ radiation, which penetrate the thyroid cells only without damage to the surrounding structures, particularly the parathyroid. The destructive effect of radioiodine on thyroid tissue is caused by the β radiation. The gamma rays are useful for estimating the quantity of the radioactive material in the gland and can be detected by placing a Geiger counter in front of the neck.

**Pharmacokinetics:**
- Rapidly absorbed after oral administration
- Rapidly absorbed and concentrated by the thyroid and incorporated into storage follicles.
- \(t_{1/2}\) of I\(^{131}\) = 8 days, \(t_{1/2}\) of I\(^{132}\) = 2 hrs.
- The cytotoxic effect on the gland is delayed for 1–2 months.
- Reaches maximal effect after 3-4 months.

**Therapeutic Uses:**
1. In the treatment of some cases of hyperthyroidism e.g.in patients above 40 years.
2. In combination with surgery in some cases of thyroid carcinoma.
3. Diagnosis of thyroid gland function by measuring the 24 hours thyroid I\(^{132}\) uptake

**Side Effects:**
- Hypothyroidism.

**Contraindication:**
1. In pregnancy, since it crosses the placental barrier thus affecting fetal thyroid.
2. In children.

**Preparation and Dosage:**
- The isotope is available as sodium radioiodine.
- It is generally given orally, but IV preparations are available.

**Dose:**
- For diagnostic purposes $^{132}$I is usually preferred owing to its short $t^{1/2}$ (2 hrs). $^{131}$I is usually used for treatment. The dose is calculated according to the size and approximate weight of the gland.

**Drugs that control the peripheral effects of hyperthyroidism:**
There is evidence that there is increased tissue sensitivity to catecholamines in hyperthyroidism and that this is a cause of some unpleasant symptoms especially in relation to the heart (palpitation, tachycardia...etc). Quick relief can be obtained with $\beta$-adrenoceptor blocking drugs e.g. propranolol 20-40 mg orally every 6 hrs, (inhibits sympathetic activity and decreases peripheral conversion of $T_4$ to $T_3$). Diltiazem 90 – 120 mg , 3 or 4 times daily, could be used in patients in whom $\beta$-blockers are contraindicated.

*NB. $\beta$-adrenoceptor blockers are especially useful during the long wait for the effect of radioiodine and thionamides treatment.*

**Thyroid Crisis (Thyroid Storm):**
This is a life-threatening syndrome, caused by the liberation of large amounts of hormone in the circulation. Treatment is urgently required to save life, it includes:
- Propranolol should be given immediately (1mg/min by slow IV injection to a maximal dose of 5 mg in severe cases). If propranolol is contraindicated, 5-10 mg/h IV infusion of diltiazem is given instead.
Potassium iodide (1-2g/day to reduce the release of the hormone).

Antithyroid drugs (Thiourea) may sometimes be added.

Mental disturbance may be treated with chlorpromazine.

Hyperpyrexia is treated by cooling or aspirin.

Hydrocortisone, 50 mg I.V./6 hours. This will protect the patient against shock, and will block the conversion of T4 to T3 quickly, decreasing the level of thyroactive material in the blood.

**Drug Effects and Thyroid Function:**

- **Drug-Induced Hypothyroidism as a Side Effect:** Several drugs may depress thyroid function by interfering with synthesis, secretion or transport of thyroid hormones e.g. NSAIDs, glucocorticoids, X-ray contrast agents, α and β-adrenoceptor antagonists, sulphonylureas, tranquilizers and lithium.

- **Drugs Hindering the Absorption of Oral T4:** Cholestyramine, colestipol, aluminium hydroxide, sucralfate, ferrous sulphate, and some calcium preparations.

- **Drugs which Alter T4 and T3 metabolism** (hepatic enzyme inducers) e.g. phenytoin, carbamazepine, phenobarbital, rifampin.

**PARATHYROID GLAND**

The parathyroid gland secretes parathormone which is a polypeptide whose rate of release is inversely proportional to the level of free ionized calcium in the blood i.e. plasma calcium concentration is the principal factor regulating parathormone synthesis and release. Increase synthesis and release is through activation of adenyl cyclase, which raises the level of c-AMP.

**Action of Parathormone:**

Is chiefly on bone and kidney (table 5-2); its effect on the gut is indirect due to alteration of renal synthesis of 1,25 dihydroxy cholecalciferol.

- **On the bone:** It increases the rate of resorption of calcium and phosphate from the bone.

- **On the kidney:** It increases renal tubular reabsorption of calcium and excretion of phosphate.
• **On the gut:** It enhances the active absorption of calcium from the upper gastrointestinal tract. (Indirect through stimulation of the synthesis of 1-25-dihydroxy-cholecalciferol = Calcitriol: active form of vitamin D).

**Therapeutic Uses:**

Impure bovine parathyroid preparation have been used for treatment of acute hypocalcaemic tetany, but immunological resistance soon occurs (due to the development of neutralizing antibodies), therefore it is not used as replacement in modern therapy of parathormone deficiency.

**Treatment of hypocalcaemia:**

The development of immunological resistance with the administration of bovine parathormone rendered it impractical in treatment of hypocalcaemia.

1. **Hypocalcaemic tetany:** that initially follows surgical parathyroidectomy; calcium gluconate is given slowly by IV infusion, not IM (painful and could cause tissue necrosis).

2. **Long term management of hypoparathyroidism:** A combination of vitamin D (e.g. Calcitriol or Alfacalcidol) and calcium gluconate or lactate.

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**CALCITONIN**

Calcitonin is secreted by the parafollicular cells of the thyroid gland through stimulation of adenyl cyclase. This effect is Ca$^{+2}$ dependent i.e. hypercalcaemia, rather than hypocalcaemia, is the stimulus of the synthesis and release of calcitonin.

**Mechanism of Action:**

- Through stimulation of specific receptors present in target organs (same as parathormone) through the activation of adenyl cyclase.

1. **On the Bone:** The main action of calcitonin is prevention of loss of calcium from bone by inhibiting osteoclastic activity (table 5-2).

   The higher the level of bone turnover, the greater is its effect. Its action is rapid in onset and could be sustained for months with repeated administration.

2. **On the Kidney:** It reduces the renal tubular reabsorption of calcium.
Therapeutic Uses:
Since it inhibits bone resorption, calcitonin is indicated in diseases characterized by an acute or chronic loss of bone mass:
1. Osteoporosis (in senile type or osteoporosis secondary to hormonal disorders).
2. Hypercalcaemia of malignancy (dose=100 U/12hrs)
3. Paget's disease: This is a disease characterized by both excessive formation and resorption, occurring in an irregular manner, in one or more bones. Calcitonin is used to prevent abnormal bone turnover. It is given S.C. 50-100 U/day or every other day, or by nasal inhalation 200-400 U/day.

Preparations:
- **Human Calcitonin** monomer has t₁/₂ of about 10 min.
- **Calcitonin - Salmon** (Calcimar) is a synthetic calcitonin, with longer t₁/₂ and reduced metabolic clearance. This is the most active calcitonin with highest affinity to human receptors. Its hypocalcaemic activity in man is 10-40 times greater than human calcitonin. It is given S.C. or I.M, or nasal spray (Miacalcin): 200 IU/puff.

| Table 5-2: Actions of Parathormone, Vitamin D and Calcitonin. |
|---------------------|---------------------|---------------------|
|                    | **PTH**             | **Vit. D**           | **Calcitonin**       |
| **Intestine**       | ↑Ca⁺⁺ and PO₄⁻⁻     | ↑Ca⁺⁺ and PO₄⁻⁻     | ↓Resorption          |
| Absorption          | Absorption          | Absorption          |                    |
| **Bone**            | ↑Resorption         | ↑Resorption and     | ↓Resorption         |
|                    |                    | formation           |                    |
| **Kidney**          | ↓Ca⁺⁺ and ↑PO₄⁻⁻   | ↓Ca⁺⁺ and ↑PO₄⁻⁻   | ↑Ca⁺⁺ and ↑PO₄⁻⁻   |
| excretion           | excretion           | excretion           | excretion           |
| **Serum Ca⁺⁺**      | ↑Ca⁺⁺               | ↑Ca⁺⁺               | ↓Ca⁺⁺               |
| **Serum PO₄**       | ↓PO₄                | ↑PO₄                | ↓PO₄                |

Non Hormonal Agents Affecting Bone Mineral Homeostasis:
Several substances may be of value in conditions of disturbed calcium and phosphate homeostasis. The most important of which is:

- **Diphosphonates** (Bisphosphonates) e.g. Etidronate

**Pharmacodynamics:**

It retards formation and dissolution of hydroxyapatite. The clinical utility of bisphosphonates resides in their ability to inhibit bone resorption. The mechanism is not completely known, but is thought that the bisphosphonate becomes incorporated into bone matrix and is embibed by osteoclasts during resorption, leading to the inhibition of their action, and stimulation of their apoptosis.

**Pharmacokinetics:**

- Less than 10% of an oral dose is absorbed.
- Food reduces absorption even further, therefore, must be administered on an empty stomach.
- Nearly half of the administered drug is accumulated in bone, the remainder is excreted in the urine.
- The portion bound to bone is retained for months, depending on the turnover of bone itself.

**Therapeutic Uses:**

1. Paget’s Disease: to inhibit bone resorption. Calcitonin is reserved for initial treatment while awaiting a response to bisphosphonates (5mg/kg/day orally).
2. Malignancy- associated Hypercalcaemia (7.5mg/kg in 250 –500 ml saline by infusion for 3 days)
3. Postmenopausal Osteoporosis (400mg/day Etidornate) or (10mg/day Alendronate).

**Adverse Effects:**

Gastric irritation (should be administered with a glass of water to minimize the adverse effects).
Pharmacology of the Endocrine System

Contraindication:
1. Decreased renal function.
2. Peptic ulcer.

Preparations:
1. Etidronate (Didronel) Oral: 200, 400 mg tablets. Parenteral: 300mg/6ml.
2. Alendronate (Fosamax) Oral: 5, 10, 40 mg tablets. A 70 mg/tablet (long acting) may be administered as 1 tablet/week.

INSULIN AND ORAL ANTIDIABETIC AGENTS

I. Insulin
Insulin is a hormone produced by the β cells of the pancreas, in response to changes in blood glucose level, and was first isolated in 1921 by Banting and Best; it was used in the treatment of diabetes mellitus in 1922, and was successfully synthesized in 1966. It is a polypeptide containing 51 amino acids arranged in two chains (A and B) linked by disulphide bridge. There is species difference in amino acids of both chains (figure 5-2).

**Figure 5-2:** Amino acid sequence of human insulin (Porcine: B30 = Alanine. Bovine: B30 = Alanine, A8 = Alanine, A10 = Valine. Insulin lispro: B28 = Lysine, B29 = proline)

**Pharmacodynamics:**

**Mechanism of Release (figure 5-3):**

- The specific stimulus for insulin secretion involves elevations in circulatory levels of glucose and to a much less extent other substrates.
- Glucose enters the β cell by facilitated transport, which is mediated by (Glut 2), a specific subtype of glucose transporter.
- As shown in the figure, hyperglycaemia results in increased intracellular ATP levels which close the ATP-dependent potassium channels.
- Decreased outward potassium current through this channel results in depolarization of the β cell and opening voltage–dependent calcium channels.
- The resultant influx of Ca$^{+2}$ triggers the release of the hormone.
- Secretion of insulin occurs by exocytosis.
Glucose Stimulated Insulin Release Is Biphasic: (figure 5-4)

a) An initial rapid phase, which reflects the release of stored hormone.

b) A slower, delayed phase, which reflects, both the release of stored hormone, and the newly synthesized.

Other Factors That Stimulate Insulin Release:
Pharmacology of the Endocrine System

These include glucagon, amino acids (particularly arginine and leucine), fatty acids, various hormones from GIT, sulphonylureas and meglitinides.

**Actions of Insulin:** (table 5-3)

- Insulin is the main factor controlling the storage and metabolism of ingested metabolic fuels. In doing so, it affects directly or indirectly the function of every tissue in the body, and its overall effect is the conservation of the body fuel supplies.
- Its most obvious action when secreted or injected, is **reduction in blood glucose**, and this reflects its general physiological function of **facilitating the uptake, utilization and storage of glucose, amino acids and fats after a meal**.
- Insulin affects all three main sources of metabolic energy—**carbohydrate, fat and protein**, and its action involves the three principal tissues—liver, muscle and adipose tissue.

**Table 5-3:** The effects of insulin on carbohydrate, fat and protein metabolism.

<table>
<thead>
<tr>
<th>Type of metabolism</th>
<th>Liver cells</th>
<th>Fat cells</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metabolism</td>
<td>↓ gluconeogenesis</td>
<td>↑ glucose uptake</td>
<td>↑ glucose uptake</td>
</tr>
<tr>
<td></td>
<td>↓ glycogenolysis</td>
<td>↑ glycolysis</td>
<td>↑ glycolysis</td>
</tr>
<tr>
<td></td>
<td>↑ glycolysis</td>
<td>↑ glycogenesis</td>
<td>↑ glycogen synthesis</td>
</tr>
<tr>
<td>Fat metabolism</td>
<td>↑ lipogenesis</td>
<td>↑ synthesis of triglycerides fatty acid synthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ lipolysis</td>
<td>↓lipolysis</td>
<td></td>
</tr>
<tr>
<td>Protein metabolism</td>
<td>↓ Protein breakdown</td>
<td></td>
<td>↑ Amino acids uptake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Protein synthesis</td>
</tr>
</tbody>
</table>

**Insulin Receptors:**
Insulin receptors are found on the membranes of most tissues.

The insulin receptor consists of two heterodimers, containing an $\alpha$ subunit, which is entirely extracellular and constitutes the recognition site, and a $\beta$ subunit that spans the membrane.

The $\beta$ subunit contains a tyrosine kinase.

When insulin binds to the $\alpha$ portion, at the outside surface of the cell, tyrosine activity is stimulated in the $\beta$ portion and an initiation of a cascade of events of phosphorylation takes place. The tyrosine kinase activity of the insulin receptor appears to be required for signal transduction.

The concentration of these specific receptor molecules, as well as their affinity for binding insulin, seems to be affected by the concentration of insulin molecules to which they are exposed.

In clinical situations associated by elevated blood insulin levels, such as obesity or insulinoma, the concentration of insulin receptors is reduced. This down regulation of insulin receptors seems to provide an intrinsic mechanism whereby target cells limit their response to excessive hormone concentrations (insulin resistance).

With low insulin concentrations, the number of receptors increases (up regulation) and responsiveness to insulin increases e.g. obese type II diabetics may recover insulin responsiveness as a result of dieting so that the insulin secretion diminishes, cellular receptors increase and insulin sensitivity is restored.

**Control of Blood Glucose:**

- After food intake, more fuel is available than is immediately required. Glucose is the main fuel utilized, and the excess calories are stored as glycogen or fat. After fasting, the energy stores need to be mobilized in a regulated manner.

- The blood glucose concentration is controlled by a feedback system between liver, muscle and fat and the pancreatic islets, the main regulator being **insulin**.
Table 5-4: The effect of hormones on the control of blood glucose.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Main actions</th>
<th>Main stimulus for secretion</th>
<th>Main effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Glucose uptake ↑</td>
<td>Moment-to-moment fluctuations in blood glucose</td>
<td>Decrease blood glucose</td>
</tr>
<tr>
<td></td>
<td>Glycogen synthesis ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycogenolysis ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gluconeogenesis ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>Glycogenolysis ↑</td>
<td>Hypoglycaemia i.e. blood glucose less than 50mg/100ml</td>
<td>Increase blood glucose</td>
</tr>
<tr>
<td></td>
<td>Gluconeogenesis ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Glycogenolysis ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose uptake ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Gluconeogenesis ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucose uptake and utilization ↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Glucose uptake ↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Counter regulatory hormones (table 5-4) counteract the actions of insulin and tend to raise blood sugar, to maintain blood glucose homeostasis. This is especially evident in the basal state.

**Diabetes Mellitus:**

- *Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycaemia), which is due to insulin deficiency or insulin resistance.*
- *The hyperglycaemia occur because the liver and skeletal muscle cannot store glycogen, and the tissues are unable to utilize glucose.*
- *When the kidney threshold for glucose is exceeded (above 180mg/100ml), glucose is excreted in the urine (glycosuria) and causes an osmotic diuresis (polyuria), which in turn results in dehydration and increased sensation of thirst (polydipsia). The diuresis also contributes to electrolyte imbalance.*
- *An increase in the rate of lipolysis results in a high level of free fatty acids (FFA) in the blood. These are converted in the liver to ketone bodies and acetone, and contribute to the ketosis and acidosis in diabetes.*

**Diabetes is commonly classified into two types:**

1. **Insulin Dependent Diabetes:** (IDDM or type I)
   - Usually develops during childhood or puberty.
• Has an acute onset and is associated with complete failure of endogenous insulin release.
• Diabetes in this case is labile and severe, with tendency to ketoacidosis.
• Moderate genetic predisposition.
• Because of lack of endogenous insulin, these patients depend on exogenous insulin and are thus classified as "insulin dependent".

2. Non Insulin Dependent Diabetes: (NIDDM or Type II)
• Develops later in life, usually over 40 years of age, especially in obese.
• Characterized by a gradual onset.
• Very strong genetic predisposition.
• The syndrome is often mild, with little or no tendency to ketoacidosis.
• Characterized by the absence of the initial phase of glucose induced insulin release, and/or low response of insulin receptors to elevated blood glucose.

The alterations in insulin secretion in the two forms of diabetes are illustrated in figure 5-4.

Insulin Preparations: (table 5-5)
Insulin preparations differ mainly in their rate of absorption following subcutaneous injection. Preparations are classified into FOUR main classes:

1. Ultra-short acting: with very rapid onset of action and short duration.
2. Short-acting: with rapid onset of action.
3. Intermediate acting.
4. Long acting: with slow onset of action

1. Ultra-Short Acting: eg. Insulin lispro
- Insulin lispro is a monomeric insulin produced by recombinant technology, wherein two amino acids near the carboxyl terminal of the B chain have been reversed in position: proline at position B_{28} has been moved to B_{29} and lysine at position B_{29} has been moved to B_{28} (fig.5-2)
- This reversal does not interfere with its ability to bind to insulin receptors, its circulating half-life, or its immunogenicity, which are identical with human regular insulin (soluble neutral insulin).
When injected S.C., it is absorbed very quickly reaching peak serum values as early as 1hr.

Preprandial insulin lispro is 5 min.

Its duration of action is 3-4hrs.

Being monomeric, it has the advantage of being mixed with lente or ultralente zinc insulin to possess the virtue of an ultra quick effect and long duration without being precipitated by the zinc, as does the short acting regular insulin.

2. Short Acting Insulin:

i) Soluble insulin:

- This is a clear aqueous solution of insulin.
- Its action is rapid in onset, but very short in duration.
- Two principal forms of soluble insulin are available:
  a) Soluble insulin (acidic in reaction (pH3), which causes irritation at the site of injection.
  b) Soluble insulin, neutral in reaction (pH7) causes no discomfort at the site of injection.
- It is standardized to contain 20, 40, 80 and 100 units/ml.
- Usually is given S.C. 30 minutes before meals, and can also be given I.V. in emergency e.g. diabetic ketoacidotic coma.
- Its hexameric formulation takes twice or three times as much to dissociate and become absorbed compared to lispro when given SC. However, insulin lispro has no advantage over regular human insulin, which is 30-40% less costly and is instantly converted to the monomeric form when given by IV route.
- It could be mixed with NPH (intermediate acting) in the same syringe to give a preparation which is fast acting and has a longer duration of action.

ii) Semilente insulin:

- Is the amorphous preparation of insulin zinc suspension.
The particle size of this preparation allows a quick onset of action (1 hr.) and a somewhat longer duration (14 hr.) as compared to soluble insulin.

3. Intermediate acting insulin:
   i) Isophane insulin (Neutral Protamine Hagedorn, NPH):
      • Is a combination of insulin and protamine just enough to bind together.
      • This preparation is sparingly soluble, and therefore the absorption of the drug is somewhat delayed having an intermediate onset of action (2 hr.), and delayed duration of action (24 hr.), due to the slow release of insulin from the combination by proteolytic enzymes.
   ii) Lente insulin:
      • Is a mixture of 3 parts amorphous and 7 parts crystalline insulin zinc suspension.
      • It has onset and duration of action intermediate between the semilente (short acting) and ultralente (long acting) preparations.

4. Long acting insulin:
   i) Protamine zinc insulin (PZI):
      • Is a combination of insulin and protamine containing a trace of zinc.
      • This preparation is sparingly soluble and therefore the absorption of the drug is delayed and its duration of action is prolonged (36 hr.) due to the slow release of insulin from this combination by proteolytic enzymes.
   ii) Ultralente:
      • Is the crystalline preparation of insulin zinc suspension.
      • This is a very slow onset (7 hr.) and a markedly prolonged duration of action (36 hr.).
   iii) Insulin Glargine (Lantus):
      • It is a new long-acting insulin analogue, approved for use in patients with type 1 and type 2 diabetes. Insulin glargine is produced by substituting amino acid glycine for asparagine at position A21 of the A chain of human insulin and by adding two
arginine molecules to the NH2 terminal end of the B-chain of human insulin, using recombinant DNA technology.

- It is supplied as clear, colourless solution at acidic pH (a cause of some pain at site of injection). Upon subcutaneous injection, the acid in the vehicle is neutralised and glargine precipitates, thereby delaying its absorption and prolonging its action.
- Glargine has a flat concentration/action profile mimicking continuous subcutaneous insulin infusion, onset of action at 2-4 hrs and a duration over 24 hrs.
- Its use could be optimised by a regimen of insulin glargine once daily with short acting insulin analogue at meal times, in type 1 diabetics.
- For people with type 2 diabetes, therapy may consist of a once-daily long-acting insulin (LANTUS®) in combination with oral anti-diabetes medication or short-or rapid acting insulin before meals.
- Care must be taken to educate the patient about the danger of mixing glargine with other insulin formulations, as glargine will precipitate instantly.

Table 5-5: Insulin Preparations.

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Onset (hr)</th>
<th>Max.Effect (hrs)</th>
<th>Duration (hrs)</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrashort acting</td>
<td>Insulin lispro</td>
<td>5 min</td>
<td>1</td>
<td>3-4</td>
<td>Neutral</td>
</tr>
<tr>
<td>Short acting</td>
<td>1. Soluble insulin</td>
<td>0.5-1</td>
<td>2 - 3</td>
<td>6-8</td>
<td>Acidic</td>
</tr>
<tr>
<td></td>
<td>2. Neutral insulin</td>
<td>0.5-1</td>
<td>2 - 3</td>
<td>6-8</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>3. Semilente insulin</td>
<td>1</td>
<td>6-10</td>
<td>14</td>
<td>Neutral</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1. Isophane insulin</td>
<td>2</td>
<td>10-20</td>
<td>24</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>2. Lente insulin</td>
<td>2</td>
<td>8-12</td>
<td>24</td>
<td>Neutral</td>
</tr>
<tr>
<td>Long acting</td>
<td>1. Protamine insulin</td>
<td>7</td>
<td>14-20</td>
<td>36</td>
<td>Alkaline</td>
</tr>
<tr>
<td></td>
<td>2. Ultralente insulin</td>
<td>7</td>
<td>16-24</td>
<td>36</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>3. Insulin glargine</td>
<td>2-4</td>
<td>No peak</td>
<td>&gt; 24</td>
<td>Acidic</td>
</tr>
</tbody>
</table>

**N.B.:** Long acting insulin preparations are undesirable in:
a. Unstable diabetics.
b. During pregnancy.
c. When more than 80 units/day are required.

Pharmacokinetic Aspects:

- Insulin is destroyed in the GIT therefore it is given by injection, usually SC.
- Absorption can be erratic, however, the new monomeric insulins e.g. insulin lispro, overcome this difficulty and give quicker response and better control of blood sugar.
- Intravenous and intraperitoneal infusion is also used in critical clinical situations.
- Insulin can be administered intranasal if given with an adjuvant, that facilitates transmucosal absorption.
- Once in the blood, insulin has $t_{1/2}$ of about 10 minutes.
- It is inactivated in the liver and kidney, and 10% is excreted unchanged.

Source of Insulin:

Most of the insulin used clinically is derived from either beef or pig. Recently, human-like insulin has been produced.

- Pig insulin differs from human insulin by one amino acid.
- Beef insulin differs from human insulin by three amino acids, rendering it slightly more antigenic in humans than is pig (pork) insulin. (figure 5-2)
- Human-like insulin has been produced either by chemical modification of pork insulin (emp) or by microbiological synthesis (crb).

Therapeutic Uses of Insulin:

A. In diabetes mellitus:

1. Insulin-dependent diabetes mellitus (Type I).
2. Non-insulin dependent diabetes mellitus not controlled by diet and oral hypoglycaemics.
3. Diabetic ketoacidosis, (soluble insulin).
5. During and after surgery in diabetic patients (soluble insulin).
6. During infection and severe illness in diabetic patients controlled by diet or oral hypoglycaemics (soluble insulin).

7. To control symptoms in patients with diabetes secondary to pancreatectomy and chronic pancreatitis.

B. In non-diabetic conditions:

To treat certain cases of hyperkalaemia, due to renal failure, since insulin when given together with glucose, promotes the intracellular passage of potassium.

**Adverse Effects of Insulin:**

1. Hypoglycaemia.
2. Skin reactions.
3. Immunological reactions.
4. Hypokalaemia.

1- **Hypoglycaemia:**

Mild attacks of insulin hypoglycaemia are common and are difficult to prevent especially in patients with unstable diabetes. This could be due to:

i) Too much insulin injected.
ii) A missed meal.
iii) Extra effort or physical exercise.

Prolonged hypoglycaemia may result in permanent brain damage, convulsions, and coma leading to death.

**Treatment of Hypoglycaemic Coma:**

The aim of treatment is to restore the blood glucose to normal levels. This is achieved by the administration of either:

1. Glucose I.V., 20-100 ml (50%) if the patient is in complete coma and cannot swallow. Sugar may be given by mouth if the patient is not in complete coma.

If the patient has been severely hypoglycaemic for hours and very large amounts of insulin have been taken, then large amounts of glucose may have to be given by I.V. infusion for several days.
2. Glucagon, 1 mg I.V., I.M. or S.C., if IV glucose therapy is unavailable, IM glucagon could be given, this usually restores conscious within 15 min. to permit ingestion of glucose.

2- **Skin reactions:**

- Generalized allergic reactions such as itching...... etc. The antigen here may be the protein (protamine) or some impurities from animal tissue(beef,pig). These give rise to antibodies such as IgE, which sensitize mast cells to release histamine. Human and porcine (pig) insulin causes less allergic reactions than bovine (beef) insulin
- Lipoatrophy at the site of injection (SC) after being used repeatedly. This usually develops from impure forms of insulin. However, pure human insulin causes hypertrophy of subcutaneous fatty tissue, which could be treated by liposuction.

3- **Insulin resistance:**

Chronic insulin resistance is said to occur when there is a persistent requirement for more than 200 units of insulin/day. One of the main causes of this condition is the development of high titre of circulating IgG anti-insulin antibodies that neutralize the action of insulin. This condition is more likely to occur with bovine insulin than with porcine insulin. Human insulin is less immunogenic than animal insulin.

**Treatment of Insulin Resistance:**

a) Change to pure human or porcine insulin.

b) Administration of a sulphonylurea to release endogenous insulin (non-antigenic) and to increase insulin binding to its receptors.

c) Sensitivity to insulin may sometimes be restored by a corticosteroid (prednisolone 20-40 mg/day) over weeks or months, to suppress antibody production. (rarely used).

4- **Hypokalaemia:**

Sometimes alteration in the ECG tracings due to excessive insulin treatment are related to hypokalaemia. Potassium supplements or orange juice could be of benefit.
Factors Affecting Insulin Requirements:

Patients stabilized on insulin may have to readjust the dose under certain circumstances. Failure to know these circumstances may expose the patient to the occurrence of either severe ketosis or severe hypoglycaemia.

A) Factors requiring increase of insulin dose:

1. Weight gain.
2. Increase food intake.
3. Acute infection.
4. Treatment with some drugs e.g. corticosteroids, thyroid preparations, thiazides......etc.
5. Surgery.
7. Pregnancy. (Close control of diabetes is of primary importance to avoid fetal loss and teratogenesis).
8. Hyperthyroidism, acromegaly or hyperadrenocorticism (Cushing).

B) Factors requiring decrease of insulin dose:

1. Increase physical exercise. Vigorous physical activity is synergistic with insulin in its effect on blood glucose. If decrease of dose is not possible, additional amount of food (supplementary calories) is useful.
2. Weight reduction.
3. In hypothyroidism, hypopituitarism and Addisonian patients.
4. After recovery from infection.
5. After stopping the administration of drugs tending to increase blood glucose level e.g. corticosteroids, thyroid preparations and thiazide diuretics ..... etc.

II. ORAL ANTIDIABETIC AGENTS
Classification:

1. **Sulphonylureas**: e.g. Tolbutamide and Chlorpropamide (1st generation) 
   Glibenclamide and Gliclazide (2nd generation). Glimepiride (3rd generation)
2. **Biguanides**: e.g. Phenformin and Metformin.
3. **α Glucosidase inhibitors** e.g. Acarbose.
4. **Meglitinides** e.g. Repaglinide.
5. **Thiazolidindiones** (Glitazones) e.g. Troglitazone, Rosiglitazone and Pioglitazone.

### 1. SULPHONYLUREAS

**Pharmacodynamics:**

**Mechanism of Action (Figure 5-3):**

1. Sulphonylureas (SU) act primarily by **stimulating the β pancreatic islets to produce insulin.**
   - They are therefore ineffective in totally insulin-deficient and for successful therapy probably require about 30% of normal β cell function.
   - This is done by binding to the high affinity receptors for SU that is associated with a β cell inward rectifier-type ATP-sensitive potassium channel (figure 5-3). Binding of a SU inhibits potassium ions efflux causing depolarization of the β cell. Depolarization in turn opens the voltage–dependant calcium channels and results in Ca++ influx, which triggers insulin release by exocytosis.

2. **Reduction of glucagon** secretion is another recently described mechanism contributing to the hypoglycaemic effect of these drugs.

3. **Increase insulin binding** to receptors.

**Therapeutic Uses:**

In non-insulin dependent diabetes mellitus (NIDDM).

- **First Generation Sulphonylureas** (table 5-6):

  I. **Tolbutamide** (Rastinon)

**Pharmacokinetics:**

- Is rapidly absorbed being detectable in the blood after about 30min.
• Is a short acting drug, half-life = 5 hours.
• Extensively bound to plasma proteins (98%).
• It is rapidly metabolized by the liver into inactive metabolites, and excreted in the urine. (Contraindicated in liver failure).
• It is the safest SU for use in elderly diabetics.

Adverse Effects:
1. Mild G.I. disturbance, which can be minimized by taking the drug after meals or by antacids.
2. Skin rash.
3. Hypoglycaemia (very rare).
5. Hypothyroidism.

Preparations and Dosage:

Tolbutamide (Rastinon) tablets 500 mg.
**Dose:** 500 mg., two or three times/day. Maximum dose 3g/day.

II. Chlorpropamide: (Diabinase)

Pharmacokinetics:
• Is rapidly absorbed and highly plasma protein bound.
• Slowly metabolized by the liver, 80% only is metabolized to inactive compounds and 20% excreted in the urine unchanged (thus it is dangerous and contra-indicated in kidney failure).
• Is the longest-acting sulphonylurea; its half-life is 35 hrs. and even longer in the elderly. It is taken once/day.

Adverse Effects:
Similar to tolbutamide with incidence twice as frequent, plus alcohol intolerance (flushing of face and neck) and water retention (antidiuretic effect).

Preparations and Dosage

Chlorpropamide: (Diabinase) tablets, 100, 250 mg.
**Dose:** 250-500 mg as one single dose, given at breakfast.

**N.B. Chlorpropamide is not the drug of choice in the elderly.**
- **Second Generation of Sulphonylureas** (table 5-6):
  
  **I. Glibenclamide**: (Daonil)
  
  Highly potent hypoglycaemic compound used with great caution of fear of hypoglycaemia.

  **Pharmacokinetics**:  
  - Metabolized in the liver to almost inactive compounds.  
  - Effect lasts for 24 hours after one single dose.  
  - Excreted by the kidney.  
  - Particularly contraindicated in hepatic impairment.

  **Preparation and Dosage**
  
  **Glibenclamide**: (Daonil) tables 5 mg.  
  **Dose**: 2.5-20 mg/day given as a single morning dose.

  **II. Gliclazide** (Diamicron) Tablets, 80mg.
  - Almost equally as potent as Glibenclamide.

  **Pharmacokinetics**:  
  - Metabolized in the liver to almost inactive compounds.  
  - Excreted by the kidney.  
  - Duration of action 6-12 hours.  
  - It has the theoretical advantage of reducing platelet aggregability.  
  - Contraindicated in hepatic impairment.

  **Preparation and Dosage**
  
  **Gliclazide** (Diamicron) Tablets, 80mg.  
  **Dose**: 80-240 mg/day,

- **Third Generation Sulphonylureas**
  
  **I. Glimepiride** (Amaryl)

  **Pharmacokinetics**
  - Rapidly absorbed.  
  - T1/2 = 5hrs.  
  - Metabolized by the liver to inactive compounds.  
  - Excreted by the kidneys.

  **Glimepiride possess a number of advantages over other SUs.**
a) Rapid onset of action.
b) Long duration.
c) Lower insulin level.
d) An insulin –sensitizing effect.
e) Reduction of blood glucose during physical exercise with less risk of hypoglycaemia(by virtue of releasing lower levels of insulin) in contrast to other SU, which reduces glucose but maintains insulin with the risk of hypoglycaemia.
f) Low dosage.
g) No special risk in elderly.

Preparations and Dosage:

Glimepiride (Amaryl) Tablets (1,2,3 mg).
Dose: 1 –8 mg/ Once daily.

<table>
<thead>
<tr>
<th>Name</th>
<th>Tolbutamide</th>
<th>Chlorpropamide</th>
<th>Glibenclamide</th>
<th>Gliclazide</th>
<th>Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>6-12hrs</td>
<td>&gt; 24hrs</td>
<td>24 hrs</td>
<td>6-12hrs</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Inactive compds by the liver</td>
<td>80% inactive compds and 20% unchanged</td>
<td>Inactive compds by the liver</td>
<td>Almost inactive compds by the liver</td>
<td>Inactive compds by the liver</td>
</tr>
<tr>
<td>Excretion</td>
<td>URINE</td>
<td>URINE</td>
<td>URINE</td>
<td>URINE</td>
<td>URINE</td>
</tr>
<tr>
<td>Dose/day</td>
<td>500mg/2-3 times/day</td>
<td>250-500 mg/day</td>
<td>2.5-20 mg/day</td>
<td>80-250 mg/day</td>
<td>1-8mg/day</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Rastinon</td>
<td>Diabenase</td>
<td>Daonil</td>
<td>Diamicron</td>
<td>Amaryl</td>
</tr>
</tbody>
</table>

Potency

1
6
100
100
100

2. BIGUANIDES

Pharmacodynamics:

- Increase glucose uptake and utilization by tissues.
- Decrease hepatic gluconeogenesis.
- Decrease glucose absorption from the G.I.T.
• Increase binding to insulin receptors.

**N.B.** Patients with NIDDM have considerably less fasting hyperglycaemia as well as postprandial hyperglycaemia after biguanides; however, occurrence of hypoglycaemia during biguanide therapy is unknown. i.e. "euglyceamic" rather than "hypoglycaemic" drugs.

**Therapeutics Uses:**

1. In NIDDM together with sulphonylureas when the latter alone has failed.
2. They are especially useful in obese diabetics as they help with weight reduction (appetite suppressive).
3. Metabolic syndrome and polycystic ovaries.

1. **Phenformin**: now replaced by metformin.

2. **Metformin**: (Glucophage)

**Pharmacokinetics:**

• Readily absorbed from G.I.T.
• Not metabolized and excreted unchanged by the kidney.

**Preparation and Dosage**

**Metformin**: (Glucophage), tablets, 500, 850 mg/tablet.

**Dose**: 1.5-3 gm/2-3 times daily with meals.

**Adverse Effects of Biguanides:**

2. Lactic acidosis (more common with phenformin especially in renal impairment).
3. Long term use may lead to vitamin B₁₂ malabsorption and folate deficiency.

**Contraindication:**

1. Renal insufficiency.
2. Pregnancy.
3. Cardiopulmonary insufficiency.
4. Alcoholics

**N.B.** These conditions increase the risk of lactic acidosis.
3. ALPHA-GLUCOSIDASE INHIBITORS
   e.g. Acarbose (Glucobay)

Pharmacodynamics:
Mechanism of action:
   It reduces the absorption of carbohydrates by competitively inhibiting the action of \( \alpha \)-glucosidase. Inhibition of this enzyme slows the absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects. Acarbose also inhibit brush-border glucoamylase, sucrase and maltase, with slight inhibition of \( \alpha \)-amylase

Pharmacokinetics:

- More than 75% of an oral dose of acarbose is broken down by amylase in the small intestine and by bacteria in the large bowel.
- Some metabolites, and a little acarbose itself, are absorbed and excreted in the urine.

Therapeutic Uses:

1. Effectively used in NIDDM (monotherapy or in combination with sulphonylureas).
2. In IDDM to decrease insulin requirements

*N.B. Acarbose is highly effective with good dietary compliance and when taking the drug together with each meal.*

Adverse Effects of Acarbose:

1. Malabsorption.
2. Diarrhoea.
3. Flatulence.

*N.B. Gradual increase in the dose of acarbose is necessary to decrease GIT side effects.*

Contraindication:

1. Hypersensitivity to acarbose.
2. Pregnancy.
3. Patients less than 18 years.
4. Patients with chronic digestion, absorption disorders.
5. Conditions aggravated by increased intestinal gases (e.g. constrictions and ulcers of large intestine.)

**Preparation and Dosage:**

Acarbose (Glucobay) 50, 100mg/tablet.

**Dose:** 50 - 300 mg/day.

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### 4. MEGLITINIDES

e.g. Repaglinide

They are benzoic acid derivatives.

**Pharmacodynamics:**

**Mechanism of action:**

Stimulation of $\beta$ pancreatic cell to release insulin. This is done by binding to the high affinity receptors overlapping that for SU that is associated with a $\beta$ cell inward rectifier- type ATP-sensitive potassium channel. Binding to receptors inhibits potassium ions efflux causing depolarization of the $\beta$ cell. Depolarization, in turn, opens the voltage –dependant calcium channels and results in Ca++ influx, which triggers insulin release. Unlike SU, they have no direct effect on insulin exocytosis.

**Action:** Reduces postprandial and fasting blood glucose level.

**Pharmacokinetics:**

- Well absorbed from the GIT with fast onset of action.
- Peak concentration after 1 hr. from ingestion.
- Cleared by the liver.
- Plasma $t_{1/2} = 1$ hr.

**Therapeutic uses:**

- Used as monotherapy in patients allergic to SUs.
- Used in combination with biguanides.

**Preparation and Dosage:**

Repaglinide tablets: (Novonorm) 0.5, 1, 2mg/ tablet.
Dose: 0.25 – 4 mg before meals.

NB: Hypoglycaemia could occur if the meal is delayed or with inadequate carbohydrates.

Contraindication:
Hepatic impairment

5. THIAZOLIDINDIONES (GLITAZONES)

Are oral antidiabetic drugs that enhance target tissue insulin sensitivity. These agents are considered euglucemic i.e they never cause hypoglycaemia when used as monotherapy.

Pharmacodynamics:

Mechanism of action:
They appear to possess:

a) An acute post receptor insulin mimetic activity.

b) Chronic effects on the transcription of genes involved with peroxisome proliferator – activated receptor gamma (PPARγ) nuclear receptor.

Actions:

• Diminish insulin resistance by increasing glucose uptake and metabolism in muscle and adipose tissue.

• Restrain hepatic gluconeogenesis.

• Exerts additional effects on lipid metabolism, ovarian steroidogenesis, systemic blood pressure and the fibrinolytic system

• Causes redistribution of body fat (decline in visceral fat mass and enhance development of peripheral small adipocytes).

Pharmacokinetics:

• Well absorbed from the GIT.

• Metabolized through the hepatic cytochrome P<sub>450</sub> system.

Therapeutic uses:

• In type II diabetes either as monotherapy or combined with a SU, biguanides or insulin.

Adverse Effects:
Pharmacology of the Endocrine System

1) Edema
2) Hypoglycaemia (if used together with insulin or SU)
3) May affect other medications, which are metabolized by cytochrome P$_{450}$ as e.g. oral contraceptives.
4) Liver failure (only Troglitazone)

Contraindications:
Although rosiglitazone and pioglitazone were reported not to cause hepatotoxicity, clinical experience is still too limited. It is highly recommended that these drugs should not be given to individuals with liver disease, and to monitor liver function during administration.

Preparations and Dosage:

Troglitazone (Rezulin)
Dose: 200 – 600 mg once daily with food.

Pioglitazone (Actos) 15,30,45 mg/ tablet
Dose: 15 – 45 mg once daily.

Rosiglitazone (Avandia): 2,3,8 mg/ tablet  Dose: 2 –8 mg once daily.

LINES OF TREATMENT IN DIABETES MELLITUS

The aim of treatment, is to keep the blood sugar level within the normal range throughout the 24 hours, to avoid ketosis, infection and long term complications.

A) Diet Control:
All patients with diabetes mellitus should be given advice about diet. If the patient is over-weight, calories should be restricted so that weight may be lost, but even in patients whose weight is ideal it is desirable to alter the types of food they eat.
Advice should be tailored to the individual’s own habits and abilities. Dietary fat intake, particularly animal fat, should be reduced in favor of carbohydrate. Cholesterol intake should be reduced to under 300mg/day.

B) Weight Control:
• Elderly fat diabetics (Type II) form a group whose blood often contains much insulin, but are resistant to its action. These patients seldom develop ketosis. Glycosuria may cease when their weight is reduced. Biguanides particularly help in weight reduction.

• Young patients with diabetes (Type I) are often under weight and need insulin to restore normal weight. The blood of these young diabetics contains no insulin (they are sensitive to its action), and they readily become ketotic.

C) Selection of therapy for diabetics:

• Diabetic ketoacidosis: the need for insulin is urgent.

• Glycosuria: if present, is managed by:
  i) Diet control (especially if obese) or
  ii) Diet + oral antidiabetic or
  iii) Diet + insulin.

Choice of Oral Antidiabetic Agents:

• Choice should first fall on a sulphonylurea. If the patient shows any signs of allergic reactions, repaglinide may be used instead.

• The biguanides are used as:
  a) Supplementary to a sulphonylurea, metiglinide or glitazone.
  b) In over weight diabetics, especially in those who find the control of diet difficult, since biguanides tend to decrease the patient's appetite.
  c) Care should be taken not to give biguanides to patients with any of the contraindications, to avoid the risk of lactic acidosis.
CORTICOSTEROIDS
(Adrenal Steroids)

Learning Objectives:
By the end of the topic the student will be able to:

1. Deduce the proper timing for administration of exogenous corticosteroids.
2. Clarify the differences between corticosteroid preparations.
3. List the therapeutic uses, side effects, contradictions of corticosteroids.
4. Evaluate the important precautions taken during prolonged corticosteroid therapy.
5. List therapeutic uses and side effects of estrogen and progesterone.
6. Discuss different hormonal contraception schedules explaining their mechanisms, side effects, and contraindication.
7. Identify two different schedules for induction of ovulation illustrating the indication of each one.
8. Enumerate therapeutic uses and side effects of testosterone and anabolic steroids.
9. Discuss the mechanism of action, uses and side effects of cyproterone.
10. Enumerate the different hormonal predations of pituitary gland illustrating their therapeutic applications.

Introduction

Corticosteroids are synthetically prepared hormones, which are steroidal in nature. Naturally occurring steroids are synthesized and released by the adrenal cortex. They are divided into three main groups according to their physiological functions:

1. Glucocorticoids: e.g. hydrocortisone (cortisol).
2. Mineralocorticoids: e.g. aldosterone and deoxy-corticosterone.
3. Sex hormones: e.g. oestrogens and androgens (secreted in relatively small amounts).
Regulation of Adrenocortical Secretion:

During stress, corticotrophin releasing factor (CRF) is released by the hypothalamus into the pituitary portal circulation to stimulate corticotrophin (ACTH) release. The released ACTH will stimulate the synthesis and release of cortisol from the adrenal cortex. A negative feedback relationship exists between cortisol blood level and ACTH release.

![Figure 5-5: Circadian rhythm of plasma cortisol](image)

Activation of the hypothalamic-pituitary-adrenal system also accounts for the diurnal or circadian rhythm of cortisol secretion. Plasma cortisol concentration reaches maximal level between 6-8 a.m., while minimal levels are attained at midnight (figure 5-5).

Pharmacodynamics:

Mechanism Of Action: (figure 5-6)

In most tissues the glucocorticoids interact with intracellular receptors, which then act on DNA to induce synthesis of some mediator proteins and inhibition of others.

- For metabolic actions, most mediator proteins are enzymes e.g. c-AMP dependent kinase.
- For anti-inflammatory and immunosuppressive actions, one mediator may be a lipocortin lipomodulin which inhibits phospholipase A$_2$, resulting in the
inhibition of the synthesis of eicosonoids and platelet–activating factor. Also, generation of interleukin–1 and other mediators is suppressed (p.221).

**Figure 5-6: Mechanism of action of steroids**

**Action of Glucocorticoids: (Prototype Hydrocortisone)**

1. **On Metabolism:**
   a) Carbohydrates:
      i) Inhibits glucose utilization.
      ii) Stimulates gluconeogenesis $\rightarrow$ hyperglycaemia.
   b) Proteins: reduces anabolism and enhances catabolism leading to:
      i) Negative nitrogen balance with muscle wasting
      ii) Osteoporosis.
      iii) Retardation of growth in children.
      iv) Skin atrophy + capillary fragility $\rightarrow$ bruising and stria.
      v) Decreased healing power of wounds and peptic ulcer.
   c) Fats: fat deposition on shoulders, face and abdomen.
2. **Inflammation**: is inhibited regardless of the cause (it can be of great benefit in "useless" or excessive inflammation but can be a source of danger in infection by limiting useful protective inflammation). Mechanism of inhibition is through inhibition of phospholipase $A_2$ resulting in a decrease in the synthesis of prostaglandins leading to the inhibition of inflammatory mediators.

3. **Allergy**: (Suppression), antigen - antibody interaction is unaffected, but its harmful inflammatory consequences are prevented.

4. **Antibody production**: is decreased when using heavy doses.

5. **Lymphoid tissue**: (including leukaemic lymphocytes) are decreased.

6. **Uric acid**: excretion is increased.

7. **Blood eosinophils**: decreases in number (this has been used as a test for activity).

8. **Euphoria or psychotic states**: may occur (probably due to CNS electrolyte changes).

9. **Calcium metabolism**: increases urinary excretion and decreases absorption from intestine (antivitamin D action).

10. **Suppression of hypothalamic-pituitary-adrenocortical axis**: occurs with high doses and long periods of treatment. Sudden withdrawal of corticosteroids will produce a state of adrenocortical insufficiency.

11. **Electrolytes and water metabolism**: (Mineralocorticoid effect). Increases sodium retention by the renal tubule and potassium excretion in urine.

**Pharmacokinetics:**

- Hydrocortisone and its synthetic analogues are effective when given orally.
- Parenteral forms are also available.
- Corticosteroids are also absorbed systemically when given from sites of local administration (e.g. skin, respiratory tract, conjunctival sac, synovial spaces etc.)
- Following absorption, 90% or more of cortisol in plasma is reversibly bound to protein. Only the unbound free form can enter cells and mediate corticosteroid effects.
• Corticosteroids bind to globulin (CBG) and albumin.
• Corticosteroids compete with each other for binding sites on CBG, which have relatively, have high affinity to cortisol and most of its synthetic derivatives, and low affinity for aldosterone.
• Corticosteroids are metabolized by the liver and excreted as soluble sulphates in the urine.

**Preparation and Administration:** (table 5-7)

i. **Hydrocortisone (Cortisol):**
   - Is the principal naturally occurring steroid.
   - It is either prepared as:
     a) Hydrocortisone sodium succinate injection (soluble) given IV for rapid effect in emergency.
     b) Hydrocortisone acetate injection (insoluble) prepared as suspension, given IM for prolonged effect and may be also injected intra-articularly.

ii. **Cortisone (tablets, injection):**
   - Given orally or IM (suspension).
   - It is a pro-drug, i.e. biologically inactive, and is converted to hydrocortisone in the liver. It is unsuitable for topical application and in patients suffering from hepatic disease.

iii. **Prednisolone (tablets, injection):**
   - Is a synthetically prepared corticosteroid.
   - It is mostly anti-inflammatory in action with little sodium retaining activity.
   - Prednisolone sodium phosphate is the soluble injection form used as an alternative to hydrocortisone.

iv. **Prednisone (tablets):**
   - It is similar to prednisolone but biologically inactive (i.e. pro-drug) and converted to prednisolone in the liver.
   - Used orally.

v. **Fluorinated Corticosteroids** e.g. Betamethasone and Dexamethasone.
• These have greater anti-inflammatory and anti-allergic activity compared to hydrocortisone.
• Have no sodium retaining effect.
• Have the disadvantage of causing muscle wasting and anorexia, at high dosage.
• Used systemically or topically.

vi. Beclomethasone:
• Its only use is by inhalation in bronchial asthma.

vii. Fludrocortisone (tablets):
• Has a highly potent sodium-retaining effect in relation to its anti-inflammatory action.
• Its non-electrolyte effects should only be considered at high dosage.
• It is used to replace aldosterone in primary Addison's disease.

viii. Deoxycortone (parenteral):
• Has an exclusive mineralocorticoid effect.
• Is eliminated by hepatic first-pass metabolism to inactive metabolites therefore it is ineffective when given orally.
• Used to replace aldosterone in acute adrenal insufficiency.

ix. Aldosterone:
• Is the natural salt retaining hormone.
• Can be given IM (0.5 mg) several times a day in acute adrenal insufficiency or shock.
• Is rapidly inactivated when swallowed therefore has no place in routine therapy and is largely replaced by fludrocortisone.

### Table 5-7: Relative potency of corticosteroids

<table>
<thead>
<tr>
<th>Drug’s Name</th>
<th>Approximate Relative Potency</th>
<th>Equivalent Dose for Anti-inflammatory Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-inflammatory (Glucocorticoid)</td>
<td>Sodium retaining (Mineralocorticoid)</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>1</td>
</tr>
</tbody>
</table>
Therapeutic Uses Of Corticosteroids:

1. Replacement therapy.
2. Anti-inflammatory and Immunosuppressant.

I- REPLACEMENT THERAPY:

i) Acute adrenal insufficiency (Addisonian Crisis):

   This is an emergency therefore immediate treatment is necessary:
   • Large amounts of parental hydrocortisone should be given. Cortisol hemisuccinate or phosphate in doses of 100 mg IV should be given every 6-8 hours until the patient is stable. The dose is then gradually reduced achieving maintenance dosage in 5 days.
   • Fluids and electrolytes should be corrected.
   • Treatment of precipitating factors.

   N.B. The condition usually occurs in Addisonian patients subjected to stress e.g. infection, accident.

ii) Chronic primary adrenal insufficiency (Addison's disease):

   • Hydrocortisone or cortisone, are used (20-30 mg/day orally) + small amount of mineralocorticoid (fludrocortisone, 0.1 mg orally).

   N.B. The timing of replacement therapy should mimic the natural circadian rhythm i.e. 20 mg hydrocortisone is given at 7 am. and 10 mg at 1 pm. with none given later at the day.

iii) Chronic secondary adrenal insufficiency:

   • This occurs in hypopituitarism.
   • Replacement therapy with hydrocortisone is essential.

   N.B. Sodium retaining hormone is seldom required for the pituitary has little control over aldosterone production.
II- ANTI-INFLAMMATORY and IMMUNOSUPPRESSANT EFFECT:

- Corticosteroids have been used in virtually every untreatable or obscure disease.
- Drugs with high glucocorticoid effect (table 7-3) e.g. dexamethasone or prednisone is chosen, so that the dosage is not limited by the mineralocorticoid effects that are found with hydrocortisone.
- It remains essential to use only minimum doses that will achieve the desired effect. Sometimes therapeutic effect must be partly sacrificed to avoid adverse effects.

Corticosteroids are therapeutically used for the management of the following:

1. Severe allergic reactions e.g. serum sickness, angioneurotic oedema... etc.
2. Organ transplantation (to minimize rejection).
3. Active chronic hepatitis: Cortisone and prednisone are not used as liver may fail to transfer it to the active form.
4. Rheumatic fever.
5. Rheumatoid arthritis.
7. Nephrotic syndrome.
8. Bronchial asthma.
9. Raised intracranial pressure: e.g. in cerebral tumour.
10. Acute gout (resistant) to other drugs.
11. Blood disease due to circulating antibodies: e.g. haemolytic anaemias, thrombocytopenic purpura, agranulocytosis ... etc.
12. A variety of skin disease e.g. eczema.

Topical Application:

- Corticosteroids topically applied are effective in a variety of skin disease particularly where there is an allergic factor.
- Creams, inhalation. ointments ... etc. are used in an attempt to obtain local, whilst avoiding systemic effects whenever possible.
- The most effective and potent steroids for use on the skin are the fluorinated compounds while hydrocortisone is now classed as weak.
Adverse Effects of Corticosteroid Therapy:
1. Iatrogenic Cushing Syndrome:
   a) Moon face.
   b) Deposition of fat on the body.
   c) Oedema.
   d) Hypertension.
   e) Striae, bruising, acne.
   f) Hirsutism.
   g) Muscle wasting and osteoporosis.
2. Depression and psychosis (especially with patients having history of mental disorders).
3. Gastric ulceration: Particularly with patients taking an adrenal steroid + aspirin. Delay healing of pre-existing ulcer could occur.
4. Impairment of defense mechanism against serious infections e.g. previously dormant T.B. may become active.
5. Aggravation of diabetes mellitus.
6. Hypothalamic-pituitary-adrenal (HPA) suppression: This depends on the dose and time of administration. A single morning dose of less than 20 mg prednisolone is not followed by suppression, where as, a dose of 5 mg given late in the evening is suppressive of the early morning activation of the HPA axis (circadian rhythm). To minimize this side effect, we have to avoid administration of corticosteroids late at the evening or follow alternate day therapy.

Precautions with corticosteroid therapy:
1. Check the patient regularly with an awareness of the possibilities of adverse effects including:
   a) Fluid retention (weight gain).
   b) Hypertension.
   c) Glycosuria.
   d) Hypokalaemia (potassium supplement may be necessary).
   e) Back pain (osteoporosis).
2. Doubling the maintenance dose when the patient is subjected to any form of stress. (e.g. surgery, infection, trauma, etc.). This precaution is necessary if therapy with corticosteroids had been prolonged. It should be considered as long as 2 years after stopping the therapy, because their hypothalamic-pituitary-adrenal axis though adequate for ordinary life may fail to respond to severe stress.

3. Withdrawal of steroid therapy should be gradual. The longer the duration of therapy the slower must be the withdrawal. Sudden withdrawal is accompanied by the dual risk of flare up of the disease and of adrenal insufficiency crisis (Addisonian crisis). Such relapse can be extremely severe, sometimes life-threatening.

4. Time of administration should follow the natural circadian rhythm to minimize hypothalamo-pituitary-adrenal axis impairment (as possible).

5. In pregnancy, adrenal insufficiency due to hypothalamic pituitary suppression in the newborn probably only occurs with mothers taking high doses, therefore dosage during pregnancy should be kept as low as possible. Fluorinated steroids should be specially avoided, as they may be more teratogenic (e.g. dexamethasone, betamethasone).

6. In children, prolonged use of corticosteroids, presents essentially the same problems as in adults in addition to retardation of growth, roughly in proportion to the dose.

To minimize this withdraw back, intermittent dosage schedules (alternate days) may be followed if therapy exceeds 6 months.

Other problems, as common childhood virus infections may be more severe (decrease resistance). Live virus vaccination is unsafe as it may cause the disease, but active immunization with killed vaccines or toxoids are less dangerous.

**Contraindications to the use of corticosteroids for anti-inflammatory purposes:**

1. Diabetes mellitus.
2. Peptic ulcer.
3. History of mental disorders.
Pharmacology of the Endocrine System

4. Epilepsy.
5. Tuberculosis.
6. Hypertension or heart failure.
7. Presence of infection requires effective chemotherapy before the administration of the steroid.

N.B. Corticosteroids containing fluorine intensify diabetes more than others and so should be avoided in that disease.

SEX HORMONES

Sex hormones are steroidal in nature. They are synthesized and released mainly by the gonads. They are responsible for the maturation of the reproductive organs and development of secondary sexual characters.

I. FEMALE SEX HORMONES

Two types of steroid hormones are synthesized in the ovary:

1. **Oestrogens**, which are produced by the developing ovarian follicle and corpus luteum.
2. **Progestogens** (progestins), which are produced by the corpus luteum.
   - Oestradiol is the most active oestrogen.
   - Progesterone is the most active progestogen.

N.B. The ovary is not the only tissue in which these hormones are made; they are also synthesized in the adrenal cortex and in the placenta during pregnancy.

Pituitary-Gonadal Relationship:

The secretion of gonadotrophins viz. FSH and LH is controlled by the gonadotrophin-releasing hormone, GnRH.

FSH and LH secretion vary in a cyclic manner during the menstrual cycle.

Menstrual Cycle:

The rise of serum FSH and LH concentrations in the early phase of the cycle is probably responsible for the initial growth and development of the follicles. FSH and LH act synergistically with regard to follicular maturation. Ovulation is preceded by a surge of LH, which is of primary importance in causing rupture of the follicle. Progesterone secretion follows the LH surge (figure 5-7).

I. OestroGENS

Pharmacodynamics:

Mechanism of action:
Similar to other steroids, the action of oestrogen involves the binding to intracellular receptors, the interaction of the resultant complexes with nuclear sites and subsequent DNA – directed RNA and protein synthesis.

**Oestrogen Receptors:**

- Oestrogen receptors occur mainly in the cells of its principal target tissues e.g. reproductive system (uterus, vagina, mammary glands), anterior pituitary and hypothalamus.
- The liver, kidney, adrenal and ovary have smaller number of oestrogen receptors.
- Progesterone decreases oestrogen receptor expression in the reproductive tract, even in the presence of high plasma oestrogen concentration (interfere with the de novo synthesis of the receptors).
- Prolactin, on the other hand, increases the number of oestrogen receptors in the mammary gland and liver, but has no effect on those in the uterus.
Figure 5-7: The menstrual cycle, showing plasma levels of pituitary and ovarian hormones and histologic changes.

**Actions of Oestrogens:**

I. **On genital system:**
   1. Maturation of primary female sex organs and the development of the secondary sexual characters.
   4. The induction of synthesis of progesterone receptors in target tissues such as uterus, vagina, anterior pituitary and hypothalamus.

II. **On Anterior Pituitary:**
   Decrease FSH and LH release (by feedback mechanism).

III. **Metabolic Actions:**
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1. Increase of salt and water retention.
2. Decrease bone resorption.
3. Alteration in composition of plasma lipids.

IV. Blood: Increases blood coagulability.

Pharmacokinetics:

1) Natural oestrogens are not given orally for they are rapidly metabolized by the liver to inactive compounds.
2) Synthetic and semisynthetic oestrogens are readily absorbed by GIT.
3) Oestradiol strongly binds to sex hormone-binding globulin (SHBG) and to albumin with lower affinity. Only the free unbound form is physiologically active.
4) Oestrogen is also excreted in small amounts in the breast milk of nursing mothers.
5) Most oestrogens are readily absorbed from the skin and mucus membranes and can be given as transdermal patches or as vaginal pessaries or creams.
6) Small amounts of orally administered oestrogen and its metabolites are excreted in the bile.
7) Natural oestrogens are excreted in the urine as glucuronides and sulphates.

Therapeutic Uses:

1. Oral contraception (+ progestogen).
2. Hypo-ovarian conditions: e.g. 1\textsuperscript{st} ovarian failure, premenopausal hysterectomy.
3. To alleviate menopausal symptoms: given together with progesterone, to minimize incidence of endometrial carcinoma.
4. Osteoporosis: which can occur after menopause or after early oophorectomy. (+ progesterone) or replaced by one of the" specific estrogen receptor modulators" (SERM) e.g. raloxifene.
5. Dysmenorrhea.
6. Treatment of hirsutism and amenorrhea due to excessive secretion of androgens by the ovary.
7. Prostatic carcinoma: which is androgen dependent, however, its use leads to undesirable side effects e.g. feminization and gynaeomastia, thus specific androgen antagonists are preferred.

**Adverse Effects:**
1. Gastrointestinal upsets (oral).
2. Withdrawal uterine bleeding.
3. Thromboembolism.
4. Oedema (sodium and water retention).
5. Long term treatment (replacement therapy) in post-menopausal women is associated with incidence of gall bladder disease and endometrial carcinoma.
6. When used in treatment of prostatic carcinoma, causes gynaeomastia and impotence.

**Contraindications:**
1. Women with an oestrogen-dependent neoplasm.
2. Pregnancy (teratogenic effect).
3. Patients with predisposing tendency to thromboembolism.
4. Hypertension.
5. Liver disease or gallstones.
7. Fibroids.

**Preparations:**
1. Natural preparations: e.g.
   i) Oestradiol, this is the natural hormone (IM).
   ii) Oestrone, as sulphate prepared as solution in oil, suspensions and vaginal suppositories.
2. Semisynthetic: e.g. Ethinyl Estradiol is an orally active semisynthetic oestrogen.
3. Synthetic: e.g. Diethylstilbestrol, is the most potent nonsteroidal oestrogen and can be used orally and parenterally.

**II. PROGESTERONE**
Progesterone is the most important progestin in humans. In addition to having important hormonal effects, it serves as a precursor to estrogens, androgens, and adrenocortical steroids. It is synthesized in the ovary, testis, and adrenals from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy.

**Pharmacodynamics:**

**Mechanism of action:**
Similar to other steroids, involving binding to specific receptors with subsequent DNA–directed RNA and protein synthesis.

**Actions:**
1. Changes the endometrium from the proliferative to the secretory phase (Menstrual cycle).
2. Causes the secretion of a viscid material from the endocervical glands.
3. Modifies the effect of oestrogen on the maturation of the vaginal epithelium.
4. Essential for maintenance of pregnancy and implantation of the fertilized ovum.
5. Decreases oestrogen receptor expression in the reproductive tract even in the presence of high plasma oestrogen concentration (interferes with the de novo synthesis of the receptors).

**Pharmacokinetics:**
- Rapidly absorbed following administration by any route.
- $T_{1/2} = 5–15$ min.
- Small amounts are temporarily found in body fat.
- The natural hormone is inactivated by first bypass in the liver therefore not administered orally.
- Excreted in the urine as glucuronide conjugates.

**Therapeutic Uses:**
1. Contraception.
2. Treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated.
3. Amenorrhoea.
4. Diagnosis of pregnancy.
5. To decrease risk of endometrial carcinoma during oestrogen therapy.

Preparation:

Progestogens:

1. Progesterone: Is the natural hormone available for parenteral administration.
2. Norethindrone: Is a highly effective oral progestogen available as tablets.

HORMONAL CONTRACEPTION

A- ORAL CONTRACEPTIVES

Progestins, alone or in combination with estrogens, can be used to prevent conception (Pregnancy).

Classification:

1- Combination pills:
Products contain a combination of estrogen and a progestin. The dose of estrogen is constant over 21 days, but the dose of progestin may be constant or increasing over 3 successive 7-day periods (called the "triphasic regimen").

2- Progestin only (mini-pill):
Is less effective compared to the combined pill, i.e. possibility of pregnancy is higher because ovulation is not fully suppressed (50% only by – ve feedback with LH). They are taken daily on a continuous schedule. They may produce irregular menstrual cycles more frequently than the combination product.

3- Postcoital contraception:
High-dose of estrogen can be administered within 72 hours of coitus and continued twice daily for 5 days (the morning –after pill). Alternatively, two doses of combined pills are given within 72 hours of coitus, followed by another two doses 12 hours later.

Mechanism of Action:
1. Inhibition of ovulation: By suppressing the release of gonadotrophins from the anterior pituitary. Oestrogen mainly inhibits the release of FSH, while
progestogen mainly inhibits the release of LH. This may be due to direct inhibition of pituitary gland or inhibition of secretion of "hypothalamic GnRF".

2. Inhibition of implantation: Production of endometrial changes that prevent implantation of the fertilized ovum.

3. Inhibition of fertilization: Progestogen increases the viscosity of the cervical mucus secretion, making the female genital tract unfavorable for sperm penetration.

**Adverse Effects of "Combined pills":**

1) GIT disturbances.

2) Oedema (weight gain).

3) Mastalgia

4) Headache

5) Breakthrough bleeding.

6) Increase in weight.

7) Increase in pigmentation.

8) Thromboembolism.

9) Mental depression and change in libido (few cases).

10) Carcinogenesis.

11) Ocular reactions due to optic neuritis and retinal thrombosis (few).

12) Gall bladder disease.

13) Metabolic disorders: increase of serum triglycerides and total phospholipids and decrease of glucose tolerance.

14) Interference with lactation.

**Contraindications:**

1. Oestrogen dependent neoplasm.

2. Thromboembolic disease, myocardial infarction ... etc.

3. Abnormal uterine bleeding.

4. Known or probable pregnancy.

5. Hepatic dysfunction.

6. Hyperlipidemia.

7. Diabetes.
8. Hypertension.
10. Depression and epilepsy.

**Preparations and Administration:**
Orally stable oestrogens and progestogens are the ones included e.g.:

**Oestrogen:** Ethinyl Estradiol, Mestranol.

**Progestogens:** Norethindrone, Norgestrel, and Ethynodiol.
- Combined pills usually contain one of the above-mentioned oestrogen + progestogen.
- Mini-pills contain one of the above-mentioned progestogen only.

**Administration:**
Starts on the 5th day of the menstrual cycle, and continued daily for 21 days.

**B-CONTRACEPTION WITH LONG ACTING (SLOW RELEASE) PROGESTIN**

**I - Medroxyprogesterone**
- Is given intramuscularly, 50mg/month or 150mg/3-4 months.
- This is effective and medically claimed to have no significant dangers.
  However, menstrual irregularities are very common, and infertility may persist for many months after stopping treatment

**II – Progestin implants**
Subdermal capsules containing levonorgestrel offer long-term contraception. Six capsules are placed subcutaneously in the upper arm. The progestin is slowly released from the capsules providing contraceptive protection for approximately 5 years, the implant is nearly as reliable as sterilization, and totally reversible if the implants are surgically removed. This method of contraception does not rely on patient compliance. This may, in part, explain its low failure rate. Principal side effects of the implants are irregular menstrual bleeding and headaches.
OVULATORY (FERTILITY) AGENTS

It is sometimes possible by drug treatment to mimic the normal ovulatory cycle and thereby increase the chance of fertilization to take place.

Clomiphene (Clomid):

Is a nonsteroidal drug that has some anti-estrogenic properties.

Pharmacodynamics:

Mechanism of Action:

Competitively blocks the oestrogen-binding receptors in the hypothalamus and anterior pituitary and thereby prevent the normal oestrogen-controlled -ve feedback release of GnRH. This action will in turn increase the secretion and release of pituitary LH and FSH, resulting in ovarian stimulation.

Pharmacokinetics:

- Well absorbed from the GIT.
- Drug and metabolites are eliminated primarily in the feaces and to a lesser extent in the urine.
- $T_{1/2} = 5–7$ days.
- Long $T_{1/2}$ largely due to plasma protein binding, enterohepatic circulation and accumulation in fatty tissue.

Therapeutic Use:

For the induction of ovulation in anovulatory infertility of women with functioning hypothalamo-pituitary axis and whose blood oestrogen levels are within normal.

Clomiphene administration appears to result in an incidence of multiple births greater than in the normal population.

Adverse Effects:

1. Ovarian enlargement, which may be accompanied with ovarian cyst formation.
2. Hot flushes and discomfort.
5. Abnormal uterine bleeding.
7. Cyclic ovarian pain.

**Contraindications:**
1. Suspected pregnancy.
2. Liver disease.

**Preparation and Administration:***

**Clomiphene (Clomid): Tablets (50 mg)**

Recommended dose for the 1st course is 50 mg/day for 5 days. If failure of treatment, increase the dose to 100mg/day for another 5 days after menstruation.

**II. ANDROGENS and ANABOLIC STEROIDS**

Androgens are male hormones steroidal in nature, secreted primarily by the testes. The main androgen in humans is testosterone, which is synthesized by the Leydig cells in the testes, and in smaller amounts by cells in the ovary of the female and in the adrenal cortex.

**Pituitary–Gonadal Relationship:**

In adult males, testosterone is synthesized and released by the Leydig cells under the influence of hormonal signals from the hypothalamus (Gn-RH), by way of the pituitary gland secretion of FSH and LH. The latter stimulates steroidogenesis in the Leydig cells and the former is necessary for the process of spermatogenesis.

**Pharmacodynamics:**

**Mechanism of Action:**

- Testosterone is converted to dihydrotestosterone (DHT) in most target cells by a 5α-reductase enzyme.
- Testosterone and DHT bind to the intracellular androgen receptor, initiating a series of events similar to those described for estradiol and progesterone, leading to growth, differentiation, and synthesis of a variety of enzymes and other functional proteins.
Actions:
1. Responsible for the growth and maturation of male sexual organs and maintaining their function.
2. Together with FSH, stimulates spermatogenesis.
3. Is responsible for the development of male 2ry sexual characters.
5. Potent nonspecific stimulator of erythropoiesis.

Pharmacokinetics:
- Bound to plasma protein – mainly to the sex-steroid-binding globulin (SSBG).
- $T_{1/2} = 10 – 20$ min
- Inactivated in the liver.
- 90% of the metabolites are excreted in the urine.
- Synthetic androgens are less rapidly metabolized and some are excreted in the urine unchanged.

Therapeutic Uses:
1. Androgen replacement therapy in men, i.e. in pre-and post-pubertal hypogonadism.
2. Gynecological disorders:
   a) Together with oestrogen to decrease menopausal symptoms.
   b) Oestrogen dependent breast cancer but is now replaced by tamoxifen (refer to anticancer drugs).
3. Refractory anaemia, (large doses).
4. Osteoporosis.
5. Protein anabolic agent: Testosterone, possesses both virilizing and protein anabolic properties. Synthetic androgens possessing high anabolic activity and low virilizing action e.g. Nandrolone phenpropionate (Durabolin) and Methandrostenolone (Dianabol) are thus preferred.

Anabolic steroids:
These are synthetically prepared androgens, used mainly for their anabolic effect. They increase anabolism (muscle build up) directly through increasing the incorporation of amino acids to proteins and stimulation of RNA polymerase activity in skeletal muscle, and indirectly by antagonizing the protein catabolic action of glucocorticoids.

- Protein anabolic action may be useful in treatment of:
  1. **Short stature.** Treatment should be slow for if vigorous the patient may grow rapidly at first but will not achieve full final stature because of accelerated epiphysial closure that occurs.
  2. **Hypoproteinaemia of nephrosis** (Excessive loss of protein by the kidney).
  3. **Debilitated postoperative patients, burns and premature babies** (where severe -ve nitrogen balance takes place).

**N.B.** This kind of treatment promotes a sense of well being, increases appetite and anabolism, but is not recommended for normal individuals since improvement is negligible and gonadotropic suppression with decrease spermatogenesis in males and hirsutism in females could result from long term treatment.

**Adverse Effects of Androgens:**
1. **Virilization:** when used as prolonged therapy in women.
2. **Precocious puberty:** this will occur if given to children, so, extreme caution must be taken.
3. **Azoospermia and secondary gonadotropin suppression** (if taken for a period over 6 wks).
4. **Enhances growth of prostatic tumors** (in elderly males especially those with prostatic carcinoma).
5. **Fluid retention.** (Na and Cl retention).
6. **Cholestatic jaundice.**

**Preparations and Administration:**
1. **Testosterone:**
   a) Sublingual tablets.
   b) Implanted pellets used S.C. every 6 months.
Pharmacology of the Endocrine System

2. Fluoxymesterone 5-10 mg/day (Orally).

**Anabolic steroids:**
- Nandrolone phenpropionate (Durabolin) IM/wk.
- Methandrostenolone (Dianabol) oral/day.

**ANTIANDROGENS**

These are agents that prevent or decrease the action of testosterone on its target organs. *N.B. Oestrogens and progestogens are pharmacological antagonists to androgens (by decreasing gonadotrophins via-ve feedback mechanism).*

**Cyproterone: (Androcur)**
- Is a derivative of progesterone
- Acts as antiandrogen by competing with endogenous androgens for their receptors in target peripheral organs. It reduces spermatogenesis even to the level of azoospermia (reverses over about 4 months after the drug is stopped)
- Possesses some progestogenic agonist activity, which acts on the hypothalamic receptors, inhibiting gonadotrophin secretion, which in turn will inhibit testicular androgen production.

**Therapeutic Uses:**
1. In abnormally hypersexual males.
2. Precocious puberty (early puberty).
3. Female hirsutism and virilization.
4. Prostatic carcinoma (preferred to oestrogen for no feminization and impotence).
5. Acne (severe type)

**Side Effects:**
1. Decreases spermatogenesis.
2. Decreases libido and causes impotence.
Preparation and Administration:
Cyproterone acetate (Androcur) in doses of 2 mg/day.

PITUITARY GLAND HORMONES

I. ANTERIOR PITUITARY HORMONES

Figure 5-8: Anterior Pituitary Gland.

The anterior pituitary gland produces several polypeptides and glycoprotein hormones. The polypeptides are growth hormone (somatotropin), prolactin, corticotropin and lipotropin. The glycoproteins are thyrotropin, luteinizing hormone (LH), and follicular stimulating hormone (FSH). The cells of the anterior pituitary gland may secrete one or more of these hormones.

The secretion of these hormones is stimulated by hypothalamic releasing factors (figure 5-8), such as thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone, (GnRH), prolactin-inhibiting factors (PIF), corticotropin-releasing factor (CRF), growth hormone - releasing factor (GHRF), and growth hormone - release inhibitory factor (somatostatin)

1. GROWTH HORMONE: (Somatotropin, GH):
- Is a peptide hormone of high molecular weight.
- It has direct metabolic effects and indirect anabolic effects mediated through another class of factors known as somatomedins.

**Actions:**

a) **Metabolic effects:**
   i) Enhance lipolysis leading to increase level of FFA.
   ii) Increases blood glucose level (anti-insulin effect).
   iii) Urinary retention of nitrogen, potassium and phosphorus.

b) **Anabolic effects:**

The anabolic effects of growth hormone are mediated indirectly via another class of peptide hormones, the somatomedins. GH stimulates the synthesis of somatomedins, mainly in the liver, which in turn promotes uptake of sulphate into cartilage and probably responsible for longitudinal growth.

**Growth Hormone Disorders:**

- **In children:** high level lead to gigantism.
  - low level lead to dwarfism.
- **In adults:** high level lead to acromegaly.

**Therapeutic Uses of Growth Hormone:**

In children with hypopituitarism whose epiphyses have not fused, human growth hormone is used. Human growth hormone or somatotropin has been replaced by a peptide of the same amino acid sequence prepared by genetic engineering in bacteria (somatotropin)(recombinant GH)

**Preparations and Administration:**

1. **Asellacrin:** is human GH, is available for parenteral use (IM).
   - **Dose:** 2 IU/3 times/wk.
     - This preparation is very expensive and not readily available.

2. **Somatotropin:** Dose: 0.1 IU/Kg/day SC or 0.5-0.7 IU/Kg/wk in two or three divided doses.

- **Gigantism and Acromegaly:**

These conditions arise from increased GH production, usually due to a pituitary adenoma, surgical removal of the tumour is the definitive treatment, and may be supplemented by radiotherapy. If surgery is not
possible, or if GH hypersecretion persists after surgery, bromocriptine may be used.

- **Bromocriptine** (Parlodel).
  Is an ergot alkaloid acts as a dopaminergic agonist, (decreases GH levels in acromegalic patients).
  
  Administration: 15-60 mg/day (high doses) orally

**N.B.** *Bromocriptine increases GH release in normal individuals.*

2. **THYROID STIMULATING HORMONE: (TSH)**

TSH is an anterior pituitary hormone that regulates the thyroid gland function.

**Action:**

TSH activates thyroid cell adenyl cyclase resulting in the formation cAMP, which in turn causes.

1. Increased $I_2$ trapping mechanism by the thyroid gland.
2. Increased synthesis and release of thyroid hormones.
3. Increased size and vascularity of the thyroid gland.

**Clinical Use:**

Mostly used for diagnostic purposes (to distinguish between 1ry and 2ry hypothyroidism).

**Preparation and Administration:**

Thyrotropin (Thytropar) is derived from beef pituitaries (IM or SC).

3. **ADRENOCORTICOTROPHIC HORMONE:**

(ACTH; Corticotrophin). ACTH is a polypeptide hormone produced in the anterior pituitary.

**Action:**

- Stimulates the synthesis and/or release of steroids (of which hydrocortisone is the most important, and androgens) by the cells of the adrenal cortex.
- Has only minor effects on aldosterone.
Therapeutic Uses:

1. **Diagnostic:** Is the most significant use of ACTH.
   As a test of the adrenal cortex in cases of suspected Addison's disease and hypopituitarism.

2. **Treatment:**
   a) Stimulation of the adrenal cortex in patients who are on prolonged glucocorticoid therapy.
   b) Similar uses as corticosteroids (provided that the adrenal cortex is intact; i.e. not useful in Addison's disease). However, being inactive when taken orally, limits its use when prolonged therapy is intended.

**Preparation and Administration:**

1. Tetracosactrin Inj.: Is a powder dissolved in water immediately before use. Given IV or Sc (0.25 mg). It is used for diagnosis only as it has a short t1/2.
2. Tetracosactrin Zinc Inj.: Is a depot (long acting) preparation, and is given IM in a dose of 0.5-1 mg twice weekly.

4. **GONADOTROPHINS:**

   The pituitary gonadotrophic hormones include the follicle stimulating hormone (FSH) luteinizing hormone (LH) and prolactin (LTH).

**A) Follicle Stimulating Hormone:** (FSH)

Is a glycoprotein hormone produced by the pituitary

**Action:**

- Interacts with specific receptors (present in the plasma membrane of ovaries and testes).
- Released during the follicular phase of the menstrual cycle and is required for the proper development of the ovarian follicles.
- In males is responsible for the maturation of the germinal elements of the testis and stimulates spermatogenesis.

**N.B.** The binding of FSH to receptors stimulates adenyl cyclase, which increases c-AMP, which is involved in the enhancement of steroidogenesis.
B) **Luteinizing Hormone**: (LH)

In females is released from the anterior pituitary during the follicular phase of the menstrual cycle. Plasma levels rise sharply just before ovulation.

**Action:**
- In females, LH is required to stimulate oestrogen production and for the production of progesterone by the corpus luteum of the ovary and is essential for ovulation.
- In males, more precisely called interstitial cell-stimulating hormone (ICSH), acts upon the Leydig cells (interstitial cells) of the testis to stimulate testosterone biosynthesis.

N.B. Like FSH, LH stimulates specific receptors in either ovaries or testes by activation of adenyl cyclase to increase cAMP.

**Preparations and Therapeutic Indications:**

1. **HMG (Gestyl):**

   Human menopausal gonadotropin (HMG) is isolated from the urine of postmenopausal women. It is rich in LH and FSH.

   **Uses:** Used to treat infertility in women who fail to ovulate despite the presence of potentially functional ovaries.

   **Dose:** 75 IU is given parenterally for 9-12 consecutive days to stimulate ovarian follicular growth and to prime the ovaries to ensure responsiveness to the subsequent administration of Human Chorionic Gonadotrophin (HCG) which exhibit biological activity similar to that of LH.

2. **HCG (Pregnyl):**

   HCG is a hormone produced by human placenta and excreted in the urine of pregnant women.

   **Uses:**
   1. For the induction of ovulation when injected after priming of ovaries with HMG.
   2. To stimulate descent of the testis in male patients with cryptorchidism in whom no anatomical obstruction.
   3. Hypogonadism that is secondary to pituitary failure.
C) Prolactin:  
Is the hormone necessary for lactation.

Therapeutic Uses:  
There is currently no therapeutic use for prolactin. However, for patients with symptomatic hyperprolactinaemia, inhibition of prolactin secretion can be achieved with bromocriptine (dopamine agonist), which stimulates PIF.  
Bromocriptine (2.5 mg/day) is useful in treatment of galactorrhea and suppression of physiological lactation.

II. POSTERIOR PITUITARY HORMONES  
The posterior lobe of the pituitary body and the neurohypophysis contain hormones having vasoactive, antidiuretic and oxytocic properties viz.  
1. ADH (Vasopressin).  
2. Oxytocin.  
Both are polypeptides containing eight amino acids. Secretion of the posterior pituitary hormone is not regulated by hypothalamic releasing factors, as is the case with the anterior hormones.  
Posterior pituitary hormones are synthesized in the hypothalamus and then transported intracellularly to the posterior pituitary, from which they are released into the circulation.  

1. ADH (VASOPRESSIN)

Release:  
- Is released in response to increased plasma osmolarity resulting from dehydration.  
- Conversely, hydration or decrease in plasma osmolarity results in inhibition of ADH.

Action:  
ADH interacts with receptor sites in the renal collecting tubules (V2) to enhance the reabsorption of solute free water and thus producing its antidiuretic effect.
In higher concentration (above physiological) ADH produces constriction of blood vessels by stimulating V1 receptors.

**Therapeutic Uses:**

1. The primary therapeutic use is in the management of diabetes insipidus.
2. Bleeding oesophageal varices.
3. Haemophilia A: It increases antihaemophilic factor VIII or Van Willibrand factor.
4. Vasoconstriction with local anaesthetic (e.g. Flypressin).

**Preparation and Administration:**

1. **Natural Vasopressin or ADH:** (Pitressin).
   - Available as injection for IM administration.
2. **Desmopressin Acetate:**
   - Is a long acting synthetic analogue of vasopressin.
   - It is usually preferred for chronic treatment.
   - Is present as:
     a. Nasal spray: 0.1, 1.5 mg/ml solution (Nasal congestion may delay absorption)
     b. Parenteral: 4mg/ml solution for injection.
     c. Oral: 0.1, 0.2 mg/ tablet.

_N.B. Vasopressin should be used cautiously in coronary disease._

2. **OXYTOCIN**

**Release:**

Is released during lactation in response to suckling stimulus. It is the hormone responsible for milk ejection and stimulation of uterine smooth muscle contraction.

**Action:**

Specific receptor sites for oxytocin are present in the mammary glands during lactation, and in the uterus during pregnancy, particularly in the later phase.

**Therapeutic Uses:**
1. To induce or support labor.
2. Oxytocin and prostaglandin F₂ alpha are used to induce abortion.
3. Impaired milk ejection (may respond to oxytocin).
4. For control of postpartum uterine haemorrhage, however, the treatment of choice for this purpose are ergot alkaloids of which ergonovine maleate and methyl-ergonovine maleate (Methergine) are drugs of choice, due to sustained and prolonged action.

**Preparation and Administration:**

1. **Synthetic Oxytocin** (Syntocinon):
   
   Available for parenteral administration (IM or IV).

2. **Oxytocin Citrate** (Syntocinon spray):
   
   By mouth and nasal spray.