Antithyroid Drugs
These drugs reduce the level of thyroid hormones by reducing thyroid hormone synthesis or release or both.

- They are used in the treatment of hyperthyroid conditions.

Classification
1. Thyroid hormone synthesis inhibitors (thioamides): Propylthiouracil, methimazole, carbimazole.
3. Thyroid tissue-destroying agent: Radioactive iodine (131I).

| Site 1: Thiocyanates, perchlorates, excess iodides. |
| Sites 2 and 3: Iodides, thioamides. |
| Site 4: Iodides. |
| Site 5: Propylthiouracil, propranolol, iopanoic acid, ipodate, glucocorticoids. |
| Site 6: Radioactive iodine (destruction of thyroid tissue). |
Thioamides

Mechanism of action of thioamides
1. They inhibit thyroid peroxidase enzyme, which converts iodide to iodine.
2. They inhibit iodination of tyrosine residues in thyroglobulin.
3. They inhibit coupling of iodotyrosines (MIT and DIT).
   - Propylthiouracil also inhibits the peripheral deiodination of T4 to T3.

Pharmacokinetics
- Thioamides are well absorbed orally. Propylthiouracil is most rapidly absorbed.
- Carbimazole is converted to methimazole after absorption.
- They are widely distributed but get accumulated in thyroid gland.
- Propylthiouracil has a short half-life and needs to be given every 6–8 h.

Adverse effects
- Skin rashes are most common.
- The other side effects are joint pain, fever, hepatitis, nephritis, etc.
- A dangerous but rare adverse effect is agranulocytosis
- so regular blood counts may not be helpful.

Uses
1. For long-term treatment of thyrotoxicosis where surgery is not indicated or not feasible and radioactive iodine is contraindicated.
2. Along with radioactive iodine to hasten recovery in thyrotoxicosis.
3. For treatment of thyrotoxic crisis along with iodide and propranolol.

<table>
<thead>
<tr>
<th>Propylthiouracil</th>
<th>Carbimazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dose to dose less potent</td>
<td>About 5 × more potent</td>
</tr>
<tr>
<td>2. Highly plasma protein bound</td>
<td>Less bound</td>
</tr>
<tr>
<td>3. Less transferred across placenta and in milk</td>
<td>Larger amounts cross to foetus and in milk</td>
</tr>
<tr>
<td>4. Plasma t½ 1–2 hours</td>
<td>6–10 hours</td>
</tr>
<tr>
<td>5. Single dose acts for 4–8 hours</td>
<td>12–24 hours</td>
</tr>
<tr>
<td>6. No active metabolite</td>
<td>Produces active metabolite—methimazole</td>
</tr>
<tr>
<td>7. Multiple (2–3) daily doses needed</td>
<td>Mostly single daily dose</td>
</tr>
<tr>
<td>8. Inhibits peripheral conversion of T4 to T3</td>
<td>Does not inhibit T4 to T3 conversion</td>
</tr>
</tbody>
</table>
Iodine and Iodides

- Iodides are the oldest agents used to treat hyperthyroidism.
- They can inhibit all steps in the synthesis of thyroid hormones, but the major effect is inhibition of release of thyroid hormones.

Preparations and uses of iodine and iodides
1. Lugol’s iodine (5% iodine in 10% solution of KI): It is used orally preoperatively before thyroidectomy and in thyroid storm.
   - It renders the gland firm, less vascular and decrease its size,
   - which makes surgery convenient with less bleeding and complications.
2. As an expectorant: Potassium iodide (KI) acts as a mucolytic agent that enhances expectoration.
3. As an antiseptic: Tincture of iodine (iodine in alcohol).
4. Prophylaxis of endemic goitre: Iodized salt is used.

Adverse effects
- Allergic reactions: Angioedema, laryngeal oedema, arthralgia, fever, eosinophilia, and lymphadenopathy may occur acutely (type-III hypersensitivity).
- Chronic overdose with iodide results in iodism.
- Sometimes pulmonary oedema can occur.
- Hypothyroidism may also occur; use of iodides during pregnancy may cause foetal goitre.

Radioactive Iodine

Therapeutically used radioactive iodine is $^{131}\text{I}$.
Sodium iodide containing $^{123}\text{I}$ is used for diagnostic scan.

- Radioactive iodine gets concentrated in the same way as stable iodine in thyroid, and emits Gamma rays and Beta particles.
- The Beta particles cause destruction of the follicular cells leading to fibrosis and correction of hyperthyroid state.
Preparation
- $^{131}$I is used orally as solution or capsule.
- The dose is expressed in microcurie.

Uses and contraindications
- Radioactive iodine is used in **hyperthyroidism due to adenoma** or **carcinoma** when surgery is not feasible or contraindicated.
- It is contraindicated in pregnancy, children and nursing mother.

Advantages
1. Treatment is simple; does not require hospitalization—can be done in the outpatient department.
2. Not expensive.
3. No risk of surgery and scar.
4. Permanently cures hyperthyroidism.

Disadvantages
- It is slow acting and causes local soreness in the neck.
- Incidence of hypothyroidism is high.
- It is not suitable for pregnant women, children and young patients.

Adrenoceptor Blockers [ β Blockers ]

Although β blockers are not strictly antithyroid drugs,
- They produce improvement in symptoms of thyrotoxicosis like **tachycardia**, **palpitation** and **tremors**.
- Propranolol also has an inhibitory effect on peripheral conversion of T4 to T3.

Uses
1. To control symptoms of thyrotoxicosis initially till antithyroid drugs act.
2. **In thyrotoxic crisis**.
3. **Preoperatively before thyroid surgery**.
Thyrotoxic Crisis (Thyroid Storm)

This is due to very high levels of circulating thyroid hormone.

- Besides the usual features of hyperthyroidism, this is characterized by hyperpyrexia,
- cardiac arrhythmias,
- nausea, vomiting,
- diarrhoea and
- mental confusion.
- It is usually precipitated by infection, trauma, surgery, etc.

This condition is treated with

- propylthiouracil,
- iodides,
- propranolol
- hydrocortisone.
- Diltiazem oral may be added if tachycardia is not controlled by propranolol alone
- Rehydration, anxiolytics, external cooling and appropriate antibiotics are the other measures.
Anabolic steroids

They promote protein synthesis and increase muscle mass, resulting in weight gain.

- They are synthetic androgens with greater anabolic and lesser androgenic activity.
- Testosterone has potent anabolic effect, but it cannot be used because of its strong androgenic effect.
- The anabolic to androgenic ratio with testosterone is 1.

Some of the commonly used anabolic steroids are
- Nandrolone (i.m.),
- Oxandrolone (oral),
- Stanozolol (oral),
- Ethylestrenol (oral) and
- Methandienone (oral, i.m.).

[Mnemonic: NOSE, M.]

Uses

1. In chronic illness, to improve appetite and feeling of well-being.
2. During recovery from prolonged illness, surgery, burns, trauma or chronic debilitating diseases.
3. To counteract the catabolic effects of exogenously administered adrenal cortical hormones.
4. In postmenopausal and senile osteoporosis.

Anabolic steroids are often misused by athletes to increase muscle strength and athletic performance; hence they are included in the ‘dope test’.

Adverse effects

1. In females, androgens cause virilization leading to hirsutism, menstrual irregularities, breast atrophy, acne and deepening of voice.
2. In children, impairment of growth due to premature closure of epiphyses.
3. Sodium and water retention leading to oedema.

Corticosteroids
### 1. Glucocorticoids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Activity</th>
<th>Equivalent dose (mg)</th>
<th>Uses and route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiinflammatory</td>
<td>Salt retaining</td>
<td></td>
</tr>
<tr>
<td>(a) Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Hydrocortisone (cortisol)</td>
<td>1</td>
<td>1</td>
<td>It has a rapid onset but short duration of action. It is the drug of choice for replacement therapy in acute adrenal insufficiency. Other uses are status asthmaticus and anaphylactic shock (emergency uses). Routes: Oral, i.m., i.v., intra-articular and topical</td>
</tr>
<tr>
<td>(ii) Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>It is cheap; predrug, converted to hydrocortisone after metabolism in liver; rarely used at present</td>
</tr>
<tr>
<td>(b) Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>It is the most commonly used preparation for allergic, inflammatory, autoimmune disorders and in malignancies. It causes less HPA axis suppression if given once daily in the morning. Routes: Oral, i.m., intra-articular and topical</td>
</tr>
<tr>
<td>(ii) Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>It is a predrug; gets converted to prednisolone in liver; less efficacious, hence rarely used</td>
</tr>
<tr>
<td>(iii) Methylprednisolone</td>
<td>5</td>
<td>0.5</td>
<td>It is used for its antiinflammatory and immunosuppressant effects; as high-dose pulse therapy in renal transplant. Pemphigus vulgaris, etc. Routes: i.m., i.v., retention enema in ulcerative colitis</td>
</tr>
<tr>
<td>(iv) Triamcinolone*</td>
<td>5</td>
<td>0</td>
<td>More potent and relatively more toxic than prednisolone. It has no mineralocorticoid activity. Routes: Oral, i.m., intra-articular and topical</td>
</tr>
</tbody>
</table>

### (c) Long acting

<table>
<thead>
<tr>
<th>Agent</th>
<th>Activity</th>
<th>Equivalent dose (mg)</th>
<th>Uses and route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiinflammatory</td>
<td>Salt retaining</td>
<td></td>
</tr>
<tr>
<td>(i) Betamethasone*</td>
<td>30</td>
<td>0</td>
<td>Long acting have highly potent antiinflammatory and immunosuppressant effects. Have no mineralocorticoid activity. They cause severe HPA axis suppression. Used in allergic and inflammatory conditions; cerebral oedema due to neoplasms, where water retention is undesirable and to promote lung maturation in fetus when premature delivery is anticipated. Routes: Oral, i.v., i.m. and topical</td>
</tr>
<tr>
<td>(ii) Dexamethasone*</td>
<td>30</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Local acting glucocorticoids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Activity</th>
<th>Equivalent dose (mg)</th>
<th>Uses and route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiinflammatory</td>
<td>Salt retaining</td>
<td></td>
</tr>
<tr>
<td>(i) Bectomethasone</td>
<td>+</td>
<td>−</td>
<td>They have local action</td>
</tr>
<tr>
<td>(ii) Budesonide</td>
<td>+</td>
<td>−</td>
<td>It is used by inhalation in bronchial asthma, as nasal spray for allergic rhinitis; as ointment for skin and mucous membrane lesions. HPA axis suppression is minimal</td>
</tr>
<tr>
<td>(iii) Fluicasone</td>
<td>+</td>
<td>−</td>
<td>Same as beclomethasone, but is more potent than beclomethasone</td>
</tr>
</tbody>
</table>

### 2. Mineralocorticoids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Activity</th>
<th>Equivalent dose (mg)</th>
<th>Uses and route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiinflammatory</td>
<td>Salt retaining</td>
<td></td>
</tr>
<tr>
<td>(i) Desoxycorticosterone acetate (DOCA)</td>
<td>0</td>
<td>100</td>
<td>It has selective mineralocorticoid activity and is used in Addison’s disease as replacement therapy</td>
</tr>
<tr>
<td>(ii) Fludrocortisone</td>
<td>10</td>
<td>125</td>
<td>Has potent mineralocorticoid activity. It is used with hydrocortisone for replacement therapy in Addison’s disease</td>
</tr>
<tr>
<td>(iii) Aldosterone</td>
<td>0.3</td>
<td>3000</td>
<td>Not used</td>
</tr>
</tbody>
</table>
Pharmacological actions

- Corticosteroid with predominant sodium and water retaining property, e.g. aldosterone and desoxycorticosterone, are mineralocorticoids.
- Corticosteroid with predominant liver glycogen deposition and gluconeogenic effects, e.g. hydrocortisone (cortisol) and cortisone, are glucocorticoids.

The net result is: (i) hyperglycaemia, (ii) decreased tissue sensitivity to insulin and (iii) diabetes may be precipitated or exacerbated.

- Therefore, glucocorticoids are (relatively) contraindicated in diabetics.

Lipid metabolism

- Prolonged use of glucocorticoids causes redistribution of body fat that is deposited over the neck, face, shoulder, etc. resulting in ‘moon face’, ‘buffalo hump’ and thin limbs.

Protein Metabolism

Glucocorticoids have weak mineralocorticoid action, cause sodium and water retention and promote potassium excretion.
Thus, prolonged use of these drugs may cause oedema and hypertension. The synthetic glucocorticoids (dexamethasone, betamethasone, and triamcinolone) have no sodium and water retaining property.

**Calcium metabolism (anti-vitamin D action)**

Prolonged use of these drugs may lead to **osteoporosis and pathological fracture of vertebral bodies.**

![Calcium metabolism diagram]

**Cardiovascular system**

- Glucocorticoids have sodium and water retaining property
- On chronic administration, these drugs may cause **hypertension and worsening of congestive cardiac failure (CCF).**

**Skeletal muscles**

- Corticosteroids are required for the normal function of skeletal muscles.
- Weakness occurs in both hypocorticism and hypercorticism.

![Skeletal muscles diagram]
Central nervous system
Corticosteroids have a number of indirect effects on the CNS through maintenance of
(i) blood pressure,
(ii) blood glucose concentration and
(iii) electrolyte levels.
They also have direct effects on the CNS and
- influence mood and behaviour.
- Patients with Addison’s disease show mental depression, irritability and even psychosis.
- On the other hand, glucocorticoid therapy can cause euphoria, insomnia, restlessness and psychosis.

Gastrointestinal Tract

Blood and lymphoid tissue
- Glucocorticoid therapy leads to a decrease in the number of circulating lymphocytes, eosinophils, basophils and monocytes.
- This is due to redistribution of cells. They have a marked lympholytic action; therefore they are used in lymphomas and leukaemias.

Antiinflammatory effect
- They have powerful antiinflammatory and immunosuppressant effects.
- They prevent or suppress the clinical features of inflammation such as redness, heat, pain and swelling.
- At tissue level, they suppress the early phenomena (capillary permeability, oedema, cellular infiltration and phagocytosis) and late responses like capillary proliferation, collagen deposition, fibroblast activity and scar formation.
2. **Tumour necrosis factor-alpha** (TNF-alpha is inhibited by glucocorticoids, which is necessary for initiating inflammatory process.

3. **Glucocorticoids stabilize the lysosomal membrane** and prevent the release of inflammatory mediators.

**Immunosuppressant effect**

- Glucocorticoids have immunosuppressant effect.
- They inhibit both B-cell and T-cell lymphocyte functions, and this results in impairment of humoral and cell-mediated immunity.
- They also suppress all types of hypersensitivity or allergic reactions.
Therapeutic uses of glucocorticoids

Endocrin uses

1. Acute adrenal insufficiency:
   - It is a medical emergency.
   - It is treated with i.v. hydrocortisone and i.v. normal saline with 5% glucose to correct fluid and electrolyte imbalance.
   - Precipitating causes such as trauma, infection or haemorrhage should be treated.

2. Chronic adrenal insufficiency:
   - Treated with oral hydrocortisone (two-third of the daily dose is given in the morning and one-third in the evening) along with adequate salt and water.

2. Rheumatoid arthritis:
   - They produce an immediate and dramatic symptomatic relief in rheumatoid arthritis;
   - but they do not halt the progression of the disease.
   - Intra-articular injection is preferred only if one or two joints are involved.

3. Osteoarthritis:
   - They are rarely used in osteoarthritis.
   - Intra-articular injection is recommended for acute episodes.

4. Rheumatic fever:
   - They produce more rapid symptomatic relief than aspirin and are indicated in cases with carditis and CCF.
   - Prednisolone is given along with aspirin

5. Allergic diseases:
   - The manifestations of allergic diseases reactions to drugs, urticaria,
   - contact dermatitis, angioneurotic oedema and anaphylaxis, can be suppressed by glucocorticoids;

6. Bronchial asthma:
   - They have antiinflammatory and antiallergic effects; hence they reduce mucosal oedema and bronchial hyperirritability.
   - In acute severe asthma, i.v. hydrocortisone is given along with nebulized Beta 2-agonist and ipratropium bromide.
If a chronic asthmatic needs steroid, it is better to give inhalational preparations like beclomethasone, budesonide or fluticasone because

7. Collagen diseases:
   - Collagen diseases such as polymyositis, polyarteritis nodosa, etc. can be controlled with large doses of glucocorticoids.

8. Renal disease
   - Glucocorticoids are the first line drugs in nephrotic syndrome.

9. Ocular diseases
   - They are frequently used to suppress inflammation in the eye; thus they prevent damage to vision.
   - Agents may be administered **topically, subconjunctivally, systemically or by retrobulbar injection**, depending upon the condition.
   - Steroids are contraindicated in herpes simplex keratitis and ocular injuries.

10. Skin diseases:
    - They dramatically relieve itching, pain, and inflammation of skin
    - **keloids and hypertrophic scar** are sometimes treated by intralesional injection of steroids.

11. Haematological disorders:
    - Autoimmune haemolytic anaemias usually respond to glucocorticoids.
    - glucocorticoids are used to treat certain malignancies, leukaemia, lymphomas, Hodgkin’s disease, multiple myeloma, etc., usually in combination with antineoplastic drugs.

12. Cerebral oedema
    - They are very effective when the oedema is caused by brain tumours, metastatic lesions and tubercular meningitis.
    - A steroid without salt and water retaining activity (e.g. dexamethasone) is preferred.
13. **Intestinal diseases**
   - They are used in *ulcerative colitis* when the patient is not responding to other forms of treatment.
   - **Methylprednisolone** can be administered as retention enema during acute episodes.

14. **Shock**
   - Prompt intensive treatment with *i.v. glucocorticoids* may be life saving in septic shock.

15. **Organ transplantation**
   - Glucocorticoids are used to prevent as well as treat graft rejections.

16. **Hypercalcaemia** of malignant diseases, and vitamin D intoxication responds to prednisolone.

17. **Other uses** include *Bell’s palsy and acute polyneuritis*. 
Adverse reactions

The use of glucocorticoids in supraphysiological doses for more than 2–3 weeks causes a number of undesirable effects.

1. **Metabolic effects**: Hyperglycaemia, precipitation of diabetes mellitus (DM) or aggravation of preexisting diabetes.

2. **Cushing’s habitus**: Abnormal fat distribution causes peculiar features with moon face, buffalo hump and thin limbs.
3. **Gastrointestinal tract**: Peptic ulceration sometimes with haemorrhage or perforation.

4. **Salt and water retention**: Mineralocorticoid effect may cause oedema, hypertension and even precipitation of CCF, particularly in patients with primary hyperaldosteronism.

5. **Muscle**: Steroid treatment can cause hypokalaemia leading to muscle weakness and fatiguability.
Long-term steroid therapy leads to steroid myopathy.

6. **Bone**: Osteoporosis with pathological fractures of vertebral bodies is common. Ischaemic necrosis of the femoral head can also occur.

7. **Growth retardation** in children is more common with dexamethasone and betamethasone.

8. **Eye**: Glaucoma and cataract may occur on prolonged therapy.

9. **Central nervous system**: Behavioural disturbances like nervousness, insomnia, mood changes can occur; psychosis may be precipitated.

10. **Long-term therapy** with steroids leads to immunosuppression, which makes the patient more vulnerable to various infections like fungal (candidiasis, cryptococcosis), viral (herpes, viral hepatitis), bacterial (reactivation of latent tuberculosis), etc.
11. **Hypothalamic pituitary adrenal (HPA) axis suppression**: The most dangerous side effect of longterm steroid therapy is HPA-axis suppression. Therefore, the important precautions to be taken

- **Whenever possible, topical use of steroids is preferred.**
- **Short- or intermediate-acting steroids** (e.g. hydrocortisone, prednisolone) should be preferred.
- Give steroids as a single morning dose at 8 a.m.; **if the daily dose is high, two-third of the dose in the morning and one-third in the evening**, which will mimic the endogenous hormone levels and minimize the chances of HPA axis suppression.
- Try **alternate-day steroid therapy in chronic conditions** like bronchial asthma, nephrotic syndrome,
- **Withdrawal of steroids after long-term (2 weeks) treatment** should be very slow to allow recovery of normal adrenocortical function.
- **The doses of steroid should be tapered gradually.**

**Abrupt stoppage of glucocorticoid therapy** following prolonged use leads to:

- **flaring up of the underlying disease** being treated.
- withdrawal symptoms **like fever, myalgia, arthralgia**, malaise, etc.
- **acute adrenal insufficiency** on exposure to stress, which manifests as anorexia, nausea, vomiting,
- **abdominal pain, hypotension**, dehydration, hyponatraemia, hyperkalaemia, etc.

**Relative contraindications for the use of corticosteroids**

- Hypertension
- Diabetes mellitus 3. Peptic ulcer
- Tuberculosis
- Herpes simplex keratitis
- Osteoporosis
- Epilepsy
- Psychosis
- Congestive cardiac failure
- Renal failure
- Glaucoma
Insulin Preparations

Conventional insulin preparations

- **Bovine (beef) insulin**: It differs from human insulin by three amino acid residues and is antigenic to man.
- **Porcine (pig) insulin**: It differs from human insulin by only one amino acid residue and is less immunogenic.

Monocomponent insulins

- Monocomponent insulins are **purified insulins**.
- They are less antigenic than conventional preparations, cause less insulin resistance and lipodystrophy at injection site.

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Onset</th>
<th>Peak effect (h)</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Ultra-short-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Insulin lispro</td>
<td>0.25 (15 min)</td>
<td>1–1.5</td>
<td>3–4</td>
</tr>
<tr>
<td></td>
<td>2. Insulin aspart</td>
<td>0.25 (15 min)</td>
<td>1–1.5</td>
<td>3–4</td>
</tr>
<tr>
<td></td>
<td>3. Insulin glulisine</td>
<td>5–15 min</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>II.</td>
<td>Short-acting insulin</td>
<td>Regular soluble insulin (crystalline)</td>
<td>0.5–1 h</td>
<td>2–4</td>
</tr>
<tr>
<td>III.</td>
<td>Intermediate acting insulin</td>
<td>NPH* (isophane)</td>
<td>1–2 h</td>
<td>6–10</td>
</tr>
<tr>
<td>IV.</td>
<td>Long-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Insulin glargine</td>
<td>2–5 h</td>
<td>-*</td>
<td>20–24</td>
</tr>
<tr>
<td></td>
<td>2. Insulin detemir</td>
<td>1–4 h</td>
<td>-*</td>
<td>20–24</td>
</tr>
</tbody>
</table>

* NPH, neutral protamine Hagedorn.
* Peak is minimal.

Human insulins

- They are produced by recombinant DNA technology using E.coli or yeast.
- They are least immunogenic; insulin resistance and lipodystrophy at the site of injection are rare, e.g. **human regular insulin**, **human neutral protamine hagedorn (NPH) insulin**, etc.
- Purified human insulins are the commonly used insulin preparations.

Regular (soluble insulin):

- Short acting, soluble, crystalline zinc insulin.
- Forms hexamers; after s.c. injection, it is slowly absorbed.
onset of action is within 30 min; administered 30–45 min before meals.
Duration of action is 6–8 h.

**NPH (neutral protamine hagedorn) insulin or isophane insulin**
- **Intermediate acting insulin.**
- Insulin complexed with protamine and zinc; dissociates slowly on s.c. administration
- Onset of action is delayed and duration of action is 10–20 h.
- Given once or twice daily.

**Insulin analogues**
- They are produced by DNA recombinant technology. They are obtained following alteration of amino acid sequence of human insulin.

For example, **rapidly acting insulin analogues and long acting insulin analogues.**

**Rapidly acting insulin analogues (modification in the B chain):**
- insulin lispro,
- insulin aspart and
- insulin glulisine.

- They have **less tendency to form hexamers** (unlike regular insulin).
- On s.c. administration: **quickly dissociate into monomers**
- rapidly absorbed and **rapid onset of action within 5–15 min**; peak effect in 1 h.
- They are administered just before meals
- Duration of action is about **4 h**; lower risk of **late postprandial hypoglycemia.**
- Immunogenicity and binding to insulin receptor is similar to human regular insulin.

**Long-acting insulin analogues, e.g. insulin glargine and insulin detemir.**

**Insulin glargine**
- On s.c. administration: **slowly absorbed delayed onset of action with ‘peakless’ plasma concentration.**
- Administered **once daily.**
- **Cannot be mixed with other human insulins** because of its acidic pH.
- Fasting blood glucose levels are **better controlled** than NPH insulin.
Should be avoided in pregnant diabetics.

Insulin detemir
- On s.c. injection: binds to albumin in blood prolonged duration of action.
- Minimal peak level.
- Usually given twice daily.

Insulin therapy
- The main goal of insulin therapy is to maintain the fasting blood glucose concentration between 90 and 120 mg/dL.
- Postprandial glucose level below 150 mg/dL.

Indications for insulin
1. Type 1 diabetes mellitus.
2. Diabetic ketoacidosis.
4. Stress of surgery, infections and trauma (temporarily to tide over trauma, infection, surgery, etc.).
5. Patients with type 2 DM unresponsive to oral antidiabetic drugs.

Site of administration
Insulin is usually administered subcutaneously in the abdomen, buttock, anterior thigh or dorsal arm.

Complications of insulin therapy
1. Hypoglycaemia is the most common and dangerous complication.
2. Allergic reactions are rare; local skin reactions (swelling, redness) at the site of injection can occur, which may be due to minor contaminants.
3. Lipodystrophy
   - It may be avoided by using purified insulin preparations and changing the injection site by rotation.
4. Insulin resistance:
   - It is a state in which patient requires more than 200 U of insulin/day.
   - It is common among obese type-2 diabetics.
5. Oedema due to salt and water retention.
Diabetic ketoacidosis

Diabetic ketoacidosis is a complication of Type 1 diabetes mellitus.

- It is very rare in Type 2 DM.

The common precipitating factors are infection, trauma, severe stress, etc.

The clinical features are

- anorexia, nausea, vomiting
- polyuria, abdominal pain
- hypotension, tachycardia, hyperventilation,
- altered consciousness or coma in untreated cases.

Diabetic ketoacidosis is a medical emergency.

It is treated with

- Regular insulin (i.v.) Bolus than infusion and S.C
- correction of fluid and electrolyte imbalance is essential – Normal saline initially and then 5% glucose in normal saline when glucose fall below 250 mg/dl
- Potassium – hypokalamia correction
- Sodium bicarbonate
- Phosphate
- Antibiotics
Oral Antidiabetic Drugs

1. Sulfonylureas
   - **First generation**: Tolbutamide, chlorpropamide.
   - **Second generation**: glibenclamide, glipizide, gliclazide, glimepiride.

2. Biguanides: Metformin.


5. Thiazolidinediones: Pioglitazone.


Newer antidiabetic agents
   - **GLP-1 receptor agonist**: Exenatide.
   - **DPP-4 inhibitors**: Sitagliptin.

**Sulfonylureas**

Sulfonylureas are divided into two generations.
   - All these drugs have the same mechanism of action, but differ in potency and duration of action.
   - The second-generation drugs are more potent than first generation drugs.

**Mechanism of action**

1. Sulfonylureas stimulate insulin secretion from β cells of pancreas

   **It is an insulin secretagogue.**

![Sulfonylureas Mechanism of Action Diagram]

   - Bind to specific receptors on β cells of islets of pancreas
   - Block the ATP-sensitive potassium channels
   - Depolarization and influx of Ca\(^{2+}\) ions into β cells
   - Degranulation and increased release of stored insulin from β cells
For successful therapy with sulfonylureas, at least 30% functioning \( \beta \) cells are necessary. Sulfonylureas are ineffective in type-1 DM because of absence of functioning \( \beta \) cells in the islets of pancreas.

2. Sulfonylureas increase the sensitivity of peripheral tissues to insulin by increasing the number of insulin receptors.
3. They reduce the release of glucagon.

**Pharmacokinetics**
- Sulfonylureas are well absorbed after oral administration, highly bound to plasma proteins and have low volume of distribution.
- They are metabolized in liver and excreted mainly in urine.

**Adverse effects**
1. Hypoglycaemia is common, particularly with glibenclamide and chlorpropamide due to their long duration of action.
   - Glibenclamide is best avoided in elderly patients because of the high risk of hypoglycaemia.
2. GI disturbances like nausea, vomiting, diarrhoea and flatulence.
3. **Weight gain** is due to stimulation of appetite.
4. **Allergic reactions**: Skin rashes, itching and photosensitivity.
5. **Teratogenicity**: Sulfonylureas are not safe during pregnancy.

**Use**
Sulfonylureas are useful in patients with type 2 diabetes mellitus.
Biguanides

Metformin is the only biguanide used clinically.

**Mechanism of action**
The mechanism of action of biguanide
It is as follows. Biguanides:
1. inhibit hepatic gluconeogenesis.
2. inhibit alimentary absorption of glucose.
3. increase peripheral utilization of glucose and decrease lipogenesis in adipose tissue.

**Biguanides do not affect insulin release. It does not cause weight gain.**

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**Pharmacokinetics**
- Metformin is taken orally, well absorbed through GI tract and is excreted mostly unchanged in urine.

**Adverse effects**
- Adverse effects are **metallic taste**, anorexia, nausea, vomiting, diarrhoea and skin rashes.
- **Lactic acidosis** is the most serious complication, but is rare with metformin.
- Prolonged use can cause vitamin B12 deficiency due to **malabsorption**. **Metformin usually does not cause hypoglycaemia even in large doses**.

**Use**
- Metformin is a commonly used **first-line drug for the treatment of type 2 DM**.
- It can be used alone or in combination with other antidiabetic agents.
Meglitinide Analogue (Repaglinide) and d-Phenylalanine Derivative (Nateglinide)

Repaglinide and nateglinide are structurally unrelated to sulfonylureas, but their mechanism of action is similar to sulfonylureas.

- They stimulate insulin release by closure of ATP-sensitive potassium channels in β cells of islets of pancreas - depolarization - insulin release.

- Repaglinide and nateglinide are well absorbed from GI tract, metabolized mainly in the liver and should be avoided in patients with hepatic failure.

They have rapid onset but short duration of action. They are less potent than sulfonylureas.

- They are used only in type-2 DM to control postprandial hyperglycaemia.

The main side effects

- repaglinide are weight gain and hypoglycaemia, but the episodes are less frequent;
- meglitinide causes nausea and flu like symptoms.

Thiazolidinediones

They increase sensitivity of peripheral tissues to insulin.

Selective agonist of PPAR-γ

Other actions: Pioglitazone reduces serum triglyceride and increases HDL levels.

Use

- Pioglitazone is used alone or in combination with sulfonylureas/metformin in patients with type-2 diabetes mellitus.

Adverse effects

- Nausea, vomiting, anaemia, weight gain, oedema and
- precipitation of heart failure in patients with low cardiac reserve
Glucosidase Inhibitors

These drugs should be given just before food.

Acarbose, miglitol and voglibose
- They reduce intestinal absorption of carbohydrates by inhibiting the enzyme α- glucosidase in the brush border of the small intestine and reduce postprandial hyperglycaemia.
- They are mainly used in obese type-2 DM patients.
- Side effects are mainly on GI tract flatulence, fullness and diarrhoea.

Newer Drugs

GLP-1 receptor agonists, e.g. exenatide
- Glucagon like peptide-1 (GLP-1) is released from the gut after meals.
- It stimulates insulin secretion, suppresses glucagon release and slows gastric emptying.
- It is degraded by dipeptidyl peptidase 4 (DPP- 4)
- its plasma half-life is 1–2 minutes. GLP-1 receptor agonists, e.g. exenatide, are resistant to DPP-4.
Their actions are similar to GLP-1. It is used in patients with type-2 diabetes mellitus.

DPP-4 (dipeptidyl peptidase 4) inhibitors, e.g. sitagliptin, saxagliptin
- They inhibit the enzyme DPP-4
- prevent inactivation of GLP-1 increase plasma concentration of GLP-1
- Increases insulin secretion, suppresses glucagon release, slows gastric emptying and improves control of postprandial hyperglycemia.
- They are administered orally in patients with type 2 diabetes mellitus.
- Allergic reactions can occur with sitagliptin.
- Respiratory and urinary tract infection may be seen with saxagliptin.
Bisphosphonates

Bisphosphonates are analogues of pyrophosphate.
- They are etidronate (oral, i.v.),
- alendronate (oral),
- pamidronate (i.v. infusion),
- zoledronate (i.v. infusion),
- risedronate (oral), etc.

Mechanism of action
Bisphosphonates exert antiresorptive effect.
- They have high affinity for calcium in the bone
- accumulate in areas of bone resorption taken up by osteoclasts
- promote their apoptosis.
- interfere with mevalonate pathway of cholesterol synthesis, which is required for normal function of osteoclasts.

Pharmacokinetics
- Bisphosphonates are highly polar and, hence, poorly absorbed through GI tract; a part of the absorbed drug is incorporated into bone and remains for long from months to years.
- The free drug is excreted unchanged in urine.

Uses
1. Paget’s disease of bone: Bisphosphonates are the treatment of choice for Paget’s disease. They reduce bone pain and decrease alkaline phosphatase level.
2. For prevention and treatment of postmenopausal osteoporosis: These drugs improve bone mineral density and reduce incidence of vertebral fracture.
3. To prevent corticosteroid induced osteoporosis along with oral calcium carbonate.
   - Zoledronate is the most potent and is the drug of choice for malignant hypercalcaemia.
5. Bisphosphonates are also useful to control hypercalcaemia of hyperparathyroidism.
6. To relieve the pain of lytic bone lesions.
Adverse effects
- They include nausea, vomiting, diarrhoea, **heartburn, oesophagitis, peptic ulcer**, fever, myalgia
- **hypocalcaemia**, headache and skin rashes.
- **Oral bisphosphonates should be taken with plenty of water** and the patient should remain upright for at least 30 minutes to prevent oesophagitis.
- Flu-like symptoms can occur on parenteral administration.

- **Drugs useful in hypercalcemia: Bisphosphonates and mithramycin** (inhibits bone resorption)
- Glucocorticoids (decrease Ca2+ absorption and increase its excretion).