Drugs of calcium and bone metabolism

- Ca in the body: ~99% as hydroxyapatite (Ca-phosphate) of the inorganic component of the bone matrix
- Imbalance between osteoclasts and osteoblasts may lead to osteoporosis.
- Regulators: parathyroid hormone, calcitonin, growth factor IL-6

Calcitonin

- 32 amino acid polypeptide hormone of the thyroid glands.
- Manufacturing: extraction from salmon glands.
- Decreases osteoclast activity in bones.
- Decreasing Ca²⁺ and phosphate reabsorption by the kidney tubules.
- Inhibits calcium resorption from the bones → hypocalcemia.
- Parathyroid hormone acts oppositely, normalises the Ca²⁺ level in tissues.

Bisphosphonates

- Very stable complex chelates with Ca²⁺ → strong absorption on the bones → inhibition of osteoclasts, prevention of the dissolution of hydroxylapatite.
- Use: treatment of osteoporosis, different conditions that feature bone fragility, to prevent bone loss due to steroid use, etc.

Bisphosphonates structure:

- Pyrophosphoric acid
- Bisphosphonic acid

Calcitonin structure:

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Calcium and bone metabolism:

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Thyroid hormones and antithyroid drugs

Action of thyronines:
- Increase of basic metabolic rate, increase sensitivity to catecholamines, affect protein synthesis.
- Essential to proper development and differentiation of all cells.

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Hyperthyroidism:
- weight loss, intolerance to heat, fatigue, weakness, hyperactivity, irritability, apathy, depression etc.
- eyelid retraction, bulging eyes.

Hyperthyroidism:
- Iodine deficiency (environmental)
- Hashimoto's thyroiditis (autoimmune disease)
- fatigue, slow speed, weight gain, goiter (struma)

Drugs of hypothyreodism

Levothyroxine sodium
Levothyroxinum naticum

Kendall (1915)

Thyroid-stimulating hormone (TSH or thyrotropin, anterior pituitary gland)

Antithyroid drugs

Potassium perchlorate
Kali perchloras

Interferes with iodide uptake into the thyroid gland.

Na or K iodide

Iodine Recommended Daily Allowance (RDA) is 150 µg/day

Natural sources: kelp and certain seafood, plants from iodine rich soil.

Iodized salt: NaCl fortified with NaI or KI.
Thiouracil derivatives

Propylthiouracil
Propylthiouracilum

Thioureia derivatives prevent the iodination step during the biosynthesis. Thiourea itself is too toxic.

Sexual hormones and their analogs

- Classification:
  - Androgens
  - Oestrogens
  - Progestogens
  - Gonadotropines - peptide hormones

Basic structures:

Sexual hormones and their analogs

Thiamazole
Thiamazolum

1,4-Dihydro-1-methyl-2H-imidazol-2-thione

Biosynthesis of steroid hormones

Cholesterol

Pregnenolone

Progesterone

Fetal testosterone

Hydrocortisone

Aldosterone

Androstenedione

Estrone

Testosterone

Estradiol

Regulation

GnRH (Gonadotropin releasing Hormone), FSH (Follicle-Stimulating Hormone) and LH (Luteinizing Hormone) – peptide hormones

Control feedback →

Male and female steroid hormones

Regulation of ovulation, pregnancy, spermatogenesis, sex organs, etc.
General modifications of steroids to alter pharmacokinetics or metabolism

Androgens and antiandrogens

- Butenandt, 1932

Antiandrogens

- Mesterolone
- Fluoxymesterone

Mesterolone

Fluoxymesterone

Testosterone

Butenandt, 1932

Strong masculinizing effect (up to psychology and behaviour)

Cyproterone acetate

Androgen receptor antagonist.
- For the treatment of hypersexuality, severe hirsutism, or for the treatment of male-to-female transsexuals.
- Treatment of metastatic prostate cancer.
- Side effects: liver toxicity
Anabolic steroids

- **Stanozolol**
- **Stanozololum**
- **Nandrolone**
- **Nandrolonum**

- They increase protein synthesis → buildup of cellular tissue, muscle mass.
- Also possess androgenic and virilizing properties.
- Abuse is very dangerous.

Effects of estrogens

- Promote the formation of female secondary sex characteristics,
- Stimulate endometrial growth,
- Increase uterine growth,
- Proliferation of breath ductile system,
- Reduce bone resorption, increase bone formation,
- Accelerate height growth,
- Accelerate metabolism (burn fat),
- Reduce muscle mass,
- Maintenance of vessel and skin.

Estrogens

- Isolated by Butenandt and Doisy (1929)
- Produced by female ovaries (follicles), placenta and the adrenal glands
- Nowadays steroid drugs are synthetized starting from cholesterol, stigmasterol, sitosterol or plant steroids using microbiological and chemical procedures

Uses of estrogens

- Hormone replacement therapy: in postmenopausal women to prevent osteoporosis;
- Inhibition of ovulation, birth control in combination with progesteron;
- Treatment of estrogen deficiency, ovarian disorders;
- Cancer treatment.

Estrogens

- **Estrone**
- **Estronum**
- **Estradiol** R = -H
- **Estradiol**
- **Estriol** R = -OH
- **Estriol**

- 3- and 17ß-esters (benzoate, valerate) with high lipid solubility are used in oily injections or transdermal formations.

Uses of estrogens

- Ethynylestradiol

- Very strong effector of the estrogen receptor
- Most common use in the estrogen-progestin combination preparations of oral contraceptives.
**Nonsteroid stilben analogues**

Stilbene

**Chlorotrianisene**

**Chlorotrianisenum**

This and similar derivatives (clomifene, tamoxifen, selective antiestrogens) are mainly used in the anticancer chemotherapy (discussed there).

**Progestogens**

**Progesterone**

Progesteron (luteal hormone) is produced by the adrenal glands, gonads, corpus luteum and the placenta.

„Hormone of pregnancy“: prepares the uterus for implantation, decreases contractility of the uterine smooth muscle, inhibits lactation during pregnancy.

**Synthetic progestogen derivatives**

**19-Nortestosterone derivatives**

Norethisterone

Used mainly in case of menstrual disorders, premenstrual syndrome, painful periods.

**Specific uses:**
- To support pregnancy (recurrent pregnancy loss, habitual abortion, to inhibit preterm birth, etc.);
- Menstrual irregularities, amenorrhea;
- Birth control (components of e-pills);
- Therapy of breast or endometrial carcinoma.
Drugs acting on hemostasis

- Hemostasis: the physiologic process whereby bleeding is staunched.
- When a blood vessel is wounded:
  - Vasoconstriction constricts the blood vessel to slow bleeding;
  - Primary hemostasis: platelets bind to collagen in the exposed walls of the blood vessel to form a hemostatic plug;
  - Secondary hemostasis or coagulation: transformation of fibrinogen to polymerized fibrin to form a clot;
  - Beginning of the repair process.

Drugs acting on hemostasis

- Anticoagulants
- Inhibitors of thrombocyte aggregation
- Thrombolytic drugs
- Inhibitors of thrombocyte aggregation
- Hemostatic drugs

17-Acetoxyprogesterones

Medroxyprogesterone acetate

Hemostasis

Main steps of blood coagulation

Heparine

Strongly ionic linear polysaccharide of 60-100kD (glycosaminoglycan family)
Heparin Na or Ca
Heparinum natricum, ~ calcicum
- Heparin (6-20 kD fractions) in the form of Na+, Ca²⁺ or Mg²⁺ salts
- Heparinoids (depolymerized smaller fractions of ~5 kD) better bioavailability
- Uses: retardation of clotting during surgery, blood transfusion, to lessen the propagation of clots in the coronary arteries, etc.
- Mode of action: forms inactive complexes with protease enzymes, decreases the rate of coagulation.

Coumarin derivatives

- Coumarin and derivatives are often found in plants.
- Pleasant odour (scent of newly-mown hay) → used in tobacco products and perfumes, as food additive etc., now banned.
- Consumption of certain plants → haemophilic bleeding of cattle → development of oral anticoagulants.
- Coumarin is a slow acting potent rodenticide.

Coumarin derivatives

- Coumarin is a slow acting potent rodenticide.
- Coumarins inhibit the synthesis of biologically active forms of the vitamin K-dependent clotting factors II, VII, IX and X, as well as the regulatory factors protein C, protein S, and protein Z.

Warfarin Na
Warfarinum natricum

Use: to control the increased tendency for thrombosis, prophylaxis in formation blood clot (thrombus) to reduce the risk of embolism.

Acenocoumarol

Coumarins inhibits the synthesis of biologically active forms of the vitamin K–dependent clotting factors II, VII, IX and X, as well as the regulatory factors protein C, protein S, and protein Z.
Inhibitors of thrombocyte aggregation

**Acetylsalicylic acid, Aspirin**

Prophylactically ~100 mg/die dose to prevent clogging (platelet aggregation) after myocardial infarction, heart attacks.

**Ticlopidine**

5-((2-Chlorophenyl)methyl) 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine

Thrombolytic drugs

**Urokinase**

Urokinase

**Streptokinase**

Streptokinase - extracellular metallo-enzyme produced by beta-haemolytic streptococci.

**Alteplase**

- Urokinase – from tissue cultures of human kidneys.
- Streptokinase - extracellular metallo-enzyme produced by beta-haemolytic streptococci.
- Alteplase – a serine protease occurring in many endothelial cells, now produced by recombinant DNA technique.

Antifibrinolytic drugs

**Tranexamic acid**

Competitively inhibits the activation of plasminogen to plasmin. Used as firstline nonhormonal treatment of dysfunctional uterine bleeding.

Hemostatic drugs

**Gelaspon** gelatin sponge (Chauvin-Ankerpharm)

**Haemocomplettan** powder for infusion (Centeon)
Increases capillary endothelial resistance and promotes platelet adhesion (capillary bleeding)

2,5-Dihydroxybenzenesulfonic acid

Hydroxyethyl starch is used to prevent shock following severe blood loss caused by trauma, surgery, etc.

**Blood substitutes**

**Dextran**
- Produced by fermentation (*Leuconostoc mesenteroides* and *Streptococcus mutans*).
- Branched polysaccharide (20-115 kD) made of glucose molecules.
  - Main chain: $\alpha$-1,6 glycosidic linkages, branches: $\alpha$-1,4 and some $\alpha$-1,3 and $\alpha$-1,2 linkages.
- Uses:
  - To replace lost blood in emergency situations;
  - In eye drops as a lubricant;
  - In microsurgery as anticoagulant.
- Slowly metabolized to glucose (depending on mol. weight)

Hydroxyethyl starch

Dextran